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Arrestins in Apoptosis

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Abstract

Programmed cell death (apoptosis) is a coordinated set of events eventually leading to the massive activation of specialized proteases (caspases) that cleave numerous substrates, orchestrating fairly uniform biochemical changes than culminate in cellular suicide. Apoptosis can be triggered by a variety of stimuli, from external signals or growth factor withdrawal to intracellular conditions, such as DNA damage or ER stress. Arrestins regulate many signaling cascades involved in life-or-death decisions in the cell, so it is hardly surprising that numerous reports document the effects of ubiquitous nonvisual arrestins on apoptosis under various conditions. Although these findings hardly constitute a coherent picture, with the same arrestin subtypes, sometimes via the same signaling pathways, reported to promote or inhibit cell death, this might reflect real differences in pro- and antiapoptotic signaling in different cells under a variety of conditions. Recent finding suggests that one of the nonvisual subtypes, arrestin-2, is specifically cleaved by caspases. Generated fragment actively participates in the core mechanism of apoptosis: it assists another product of caspase activity, tBID, in releasing cytochrome C from mitochondria. This is the point of no return in committing vertebrate cells to death, and the aspartate where caspases cleave arrestin-2 is evolutionary conserved in vertebrate, but not in invertebrate arrestins. In contrast to wild-type arrestin-2, its caspase-resistant mutant does not facilitate cell death.

Keywords

Arrestin; Cell death; Apoptosis; Cell signaling; Cytochrome C; Caspases; JNKs

1 Apoptotic Pathways

Apoptosis is a form of programmed cell death (Vaux et al. 1994; Steller 1995) involving the activation of caspases (Thornberry and Lazebnik 1998; Crawford and Wells 2011). Caspases concentrate on key pathways, producing stereotypic morphological and biochemical changes in apoptotic cells (Dix et al. 2008; Mahrus et al. 2008; Chipuk et al. 2010). Apoptosis can be triggered by a number of factors including signaling via death receptors (DR); DNA damage by UV, γ -irradiation, or genotoxic drugs; load on endoplasmic reticulum (ER); withdrawal of growth or trophic factors; oxidative stress; and a large number of other factors.

The apoptotic pathway initiated by DR activation is known as extrinsic pathway (Fig. 1). Eight members of the DR family have been described, including the best-studied tumor

necrosis factor receptor alpha 1 (TNFR1), Fas (also known as CD95), TNF-related apoptosis-inducing ligand receptor 1 (TRAILR1), and TRAILR2 (Lavrik et al. 2005). The activation of DR by corresponding ligands leads to the formation of signaling complexes assembled at the intracellular surface of the receptor. Fas and TRAILR1/2 recruit what is known as death-inducing signaling complexes (DISC) containing FADD (Fas-Associated Death Domain), pro-caspase-8, and the long and short forms of the cellular FLICE inhibitory protein (FLIP_{L/S}) as main components (Lavrik et al. 2005; Guicciardi and Gores 2009). The formation and internalization of DISC result in the activation of initiator caspase-8 that cleaves and activates effector caspase-3, caspase-6, and caspase-7, triggering apoptotic cell death (Lavrik et al. 2005; Guicciardi and Gores 2009). In cell type I, DISC is effectively internalized, resulting in massive caspase-8 activation sufficient to activate downstream caspases (Scaffidi et al. 1998, 1999; Fulda et al. 2001). In cell type II, lower level of DISC formation results in weak caspase-8 activation that requires amplification to trigger apoptosis. The amplification cascade includes caspase-8-mediated cleavage of the member of the BCL-2 family BID to yield truncated BID (tBID) that translocates to the mitochondria inducing the cytochrome C release (Li et al. 1998; Luo et al. 1998) via a still poorly understood mechanism (Chipuk and Green 2008). The cytochrome C release results in the formation of the apoptosome and the activation of caspase-9, which in turn cleaves and activates the effector caspases (Danial and Korsmeyer 2004; Bratton and Salvesen 2010). In type II cells, Fas-induced apoptosis could be blocked by antiapoptotic BCL family members such as BCL-2 and BCL-XL (Scaffidi et al. 1998, 1999; Fulda et al. 2001). Therefore, tBID serves as a mediator of the positive feedback, or amplification, loop involving the mitochondria-dependent apoptotic signaling.

Stimulation of TNFR1 and similar DR results in the formation of two signaling complexes. Complex I assembled at the membrane includes TRADD (TNFR-associated death domain protein), RIPK1 (receptor-interacting serine/threonine-protein kinase 1), and TRAF2/5 (TNFR-associated factor) as main components (Micheau and Tschopp 2003; Lavrik et al. 2005). Complex I mediates TNFR1-induced activation of the NFκB and JNK pathways (Dempsey et al. 2003; Lavrik et al. 2005). The NFκB pathway is activated via recruitment of the IKK complex in the TRADD-dependent manner with participation of RIPK1 and TRAF2/5/6 through a series of K63 “nondestructive” ubiquitination events (Micheau and Tschopp 2003; Ea et al. 2006; O'Donnell and Ting 2010; Pobezinskaya and Liu 2012). Recruitment of the IKK complex leads to the phosphorylation of the NFκB inhibitory protein IκBα, with its subsequent degradation, and activation of NFκB-dependent transcription of antiapoptotic genes such as cFLIP, cIAP1, cIAP2, BCL-XL, and XIAP (Kreuz et al. 2001; Micheau et al. 2001; Dempsey et al. 2003; Chipuk et al. 2010). JNK activation by TNFR1 is TRAF2 dependent (Natoli et al. 1997; Reinhard et al. 1997; Yuasa et al. 1998; Habelhah et al. 2004). TNFR1 also activates the p38 pathway in a TRAF2- and RIPK1-dependent manner (Yuasa et al. 1998; Lee et al. 2003). The MAP kinase pathways are activated via recruitment and activation of upstream kinases MEKK1, ASK1, or TPL2 to TRAF2 (Nishitoh et al. 1998; Yuasa et al. 1998; Das et al. 2005) (see also chapters “Arrestin-Dependent Activation of ERK and Src Family Kinases,” “Arrestin-Dependent Activation of JNK Family Kinases,” and “Arrestin-Mediated Activation of p38 MAPK: Molecular Mechanisms and Behavioral Consequences”).

Complex I is internalized and transformed in the cytosol into complex II by exchange of signaling proteins associated with TNFR1. FADD and pro-caspase-8 are recruited, leading to caspase-8 activation and initiation of apoptosis (Micheau and Tschopp 2003; Schneider-Brachert et al. 2004). Unlike Fas and TRAIL receptors, TNFR1 is mostly involved in mediating inflammation and not cell death, and the outcome of the TNFR1 stimulation is cell type dependent. Inhibition of RNA or protein synthesis resulting in the blockade of complex I-mediated pro-survival NF κ B-mediated signaling is required to induce apoptosis via TNFR1 stimulation in most cell types. Blockade of NF κ B signaling promotes TNFR1-induced apoptosis mostly by blocking the synthesis of cFLIP that inhibits caspase-8 activation (Kreuz et al. 2001; Micheau et al. 2001). Alternatively, TNFR1 signaling could be switched from pro-survival to pro-apoptotic mode by Smac, also known as Diablo (or its mimetics). Smac is a protein released from the mitochondria together with cytochrome C that interacts with and inhibits apoptotic inhibitors XIAP, cIAP1, and cIAP2 (Chai et al. 2000; Du et al. 2000). Smac can also trigger RIPK1-dependent mode of caspase-8 activation by promoting degeneration of IAPs (Wang et al. 2008). The positive regulation of TNFR1 apoptotic signaling by Smac/Diablo released from the mitochondria is another mitochondria-based amplification pro-apoptotic mechanism.

The apoptotic pathway mediated by the release of pro-apoptotic factors from the mitochondria followed by the formation of apoptosome, activation of initiator caspase-9, and subsequent activation of effector caspases is referred to as the intrinsic pathway (Danial and Korsmeyer 2004) (Fig. 1). The intrinsic apoptotic pathway is triggered by a large variety of stimuli including DNA damage, withdrawal of growth factors, hypoxia, or endoplasmic reticulum stress. The signaling converges on the mitochondria where the interplay of pro- and anti-apoptotic BCL family members regulates cytochrome C release, although the exact biochemical mechanism of this process has not been elucidated (Danial and Korsmeyer 2004; Youle and Strasser 2008). Effectors BAK and BAX oligomerize and form pores in the outer mitochondrial membrane (Wei et al. 2000), allowing cytochrome C (and other mitochondrial proteins such as Smac/Diablo) to escape to the cytoplasm (Lindsten et al. 2000; Wei et al. 2001). The biochemical nature of this pore and the number of BAK or BAX proteins necessary to create it remain unknown (Youle and Strasser 2008). BCL-2 homology 3 (BH3)-only members of the BCL-2 family either directly activate BAX and BAK and induce cytochrome C release or do so indirectly via antagonistic interaction with antiapoptotic members of the same family. It is still unclear how exactly the interactions of pro- or anti-apoptotic BCL-2 proteins with BAK and BAX affect the pore formation process (Chipuk and Green 2008; Youle and Strasser 2008). Truncated BID (tBID) cleaved by caspase-8 activated in the extrinsic apoptotic pathway is the most potent cytochrome C releaser among BH3 proteins (Korsmeyer et al. 2000; Wei et al. 2000; Lovell et al. 2008), providing a strong amplification signal for apoptosis induced by DR activation. The release of cytochrome C from mitochondria promotes the formation of a structure known as apoptosome composed of cytochrome C, pro-caspase-9, and apoptotic protease activation factor 1 (Apaf 1) that results in caspase-9 activation (Danial and Korsmeyer 2004; Bratton and Salvesen 2010). Active caspase-9 cleaves and activates effector caspases. Thus, the apoptosome serves a function analogous to that of DISC, i.e., activation of an initiator caspase, albeit achieved via a different molecular mechanism. The apoptosome formation

that promotes massive activation of executioner caspase-3/caspase-6/caspase-7 is the key checkpoint in cell commitment to death (Youle and Strasser 2008). Stressful stimuli capable of engaging the intrinsic apoptotic pathway do so by increasing the expression of pro-apoptotic proteins or via direct inactivation of antiapoptotic proteins. Thus, DNA damage caused by UV, γ -irradiation, or genotoxic drugs results in stabilization of the transcription factor p53 that translocates to the nucleus promoting the expression of multiple pro-apoptotic genes and subsequent cell death (Oda et al. 2000; Nakano and Vousden 2001; Yu et al. 2001; Villunger et al. 2003; Naik et al. 2007; Michalak et al. 2008). Growth factors such as NGF and BDNF can induce neuronal death acting via p75 receptor, which is a member of the death receptor superfamily that includes Fas and TNFR1 (Chao 1994; Sessler et al. 2013). The mechanisms of this apoptosis are poorly understood but appear to involve JNK activation and downstream engagement of the mitochondrial pathway (Harrington et al. 2002; Salehi et al. 2002; Nykjaer et al. 2005; Ichim et al. 2012; Sessler et al. 2013). Some trophic factor receptors seem to function as so-called dependence receptors that induce positive apoptotic signaling in the absence of ligands. The survival of certain types of cells in culture is strictly dependent on the presence of specific trophic factors, and apoptosis of many cultured cell lines can be induced by serum withdrawal. Apoptosis mediated by dependence receptors involves caspase interaction and caspase-mediated cleavage of the receptor cytoplasmic domain yielding a pro-apoptotic peptide that mediates downstream signaling including transcriptional activation of pro-apoptotic genes (Rabizadeh and Bredeisen 2003; Bredeisen et al. 2005; Goldschneider and Mehlen 2010; Ichim et al. 2012). Thus, multiple cellular signaling pathways impact the core apoptotic machinery, thereby affecting cell death and survival.

2 Signaling Mechanisms in Apoptosis

Given the irreversible nature of apoptosis, it is not surprising that large number of checks and balances is incorporated into the core apoptotic mechanisms. Furthermore, multiple cellular signaling pathways impact the function of most proteins involved in apoptosis. A good example is TNFR1: its activation triggers anti- and pro-apoptotic mechanisms, such as activation of the NF κ B and JNK pathways. The NF κ B pathway suppresses apoptosis via transcriptional upregulation of antiapoptotic genes (Dempsey et al. 2003; Lavrik et al. 2005; Chipuk et al. 2010). The activity of the NF κ B pathway is regulated by inhibitory protein I κ B α that keeps NF κ B inactive in the cytoplasm. I κ B α is phosphorylated by the IKK complex, which induces its polyubiquitination and proteasomal degradation (Chen et al. 1996; Roff et al. 1996; Napetschnig and Wu 2013). NF κ B, thus released, translocates to the nucleus and activates transcription (Napetschnig and Wu 2013). The IKK complex is composed of two related catalytic subunits, IKK α and IKK β , and an important although catalytically inactive component NEMO/IKK γ (Chen et al. 1996; DiDonato et al. 1997; Mercurio et al. 1997; Yamaoka et al. 1998). IKK β phosphorylation is required for the NF κ B activation via so-called canonical pathway (turned on by TNF α), and it appears that TAK1, which also serves as an MAPKKK in the JNK pathway, can phosphorylate IKK β in the activation loop (Ninomiya-Tsuji et al. 1999; Wang et al. 2001; Sato et al. 2005). MEKK3, another upstream MAP kinase, has also been implicated in TNF α -induced IKK activation (Yang et al. 2001). NEMO specifically binds to linear and K63 polyubiquitin chains, which

is critical for the activation of the TNF α -induced IKK recruitment and NF κ B activation (see Napetschnig and Wu (2013) and references therein). The IKK complex could be activated by receptor belonging to Toll-like-interleukin-1 receptor superfamily involved in the innate immunity responses via recruitment of TRAF6 (Bradley and Pober 2001).

2.1 The JNK Pathway

Active NF κ B leads to a rapid quenching of TNFR1-induced JNK activation. The proposed mechanisms of NF κ B-induced suppression of JNK activity include upregulation of Gadd45 beta factor that inhibits MKK7, an upstream kinase activating JNK (De Smaele et al. 2001; Papa et al. 2004), and upregulation of XIAP (Tang et al. 2001). However, cells lacking Gadd45 beta or XIAP showed TNFR1-induced JNK activation similar to that of wild type (Amanullah et al. 2003; Kucharczak et al. 2003). An alternative mechanism involves TNF α -generated reactive oxygen species that inhibit JNK phosphatases (Kamata et al. 2005), which normally ensure low level of JNK activity (Cavigelli et al. 1996). Several studies reported that sustained JNK activation augments TNFR1-induced death in cells with deficient NF κ B pathway (De Smaele et al. 2001; Tang et al. 2001). Therefore, JNK activity could play a decisive role in the outcome of the TNFR1 activation if the function of the NF κ B pathway is compromised due to genetic defects or drug action. JNK activation plays the key role in apoptosis induced by UV irradiation and genotoxic drugs mediated by the intrinsic apoptotic pathway (Zanke et al. 1996; Tournier et al. 2000). JNK3, a JNK isoform selectively expressed in neurons, has been shown to be involved in apoptosis caused by excitotoxic (Yang et al. 1997) or other toxic (Namgung and Xia 2000) agents and by growth factor deprivation (Bruckner et al. 2001; Eilers et al. 2001; Coffey et al. 2002; Barone et al. 2008; Ambacher et al. 2012). JNK activation plays an important role in neuronal apoptosis following focal ischemia (Okuno et al. 2004; Gao et al. 2005) and in beta-amyloid-induced neuronal apoptosis (Morishima et al. 2001; Yao et al. 2005).

It appears that sustained JNK activation is required to promote apoptosis, whereas transient JNK activity is involved in cell proliferation and survival (Sánchez-Perez et al. 1998; Chen and Tan 2000; Dhanasekaran and Reddy 2008). The pro-apoptotic action of JNK is in many cases transcriptional, mediated by JNK-dependent phosphorylation and transactivation of the transcription factor c-jun and subsequent expression of pro-apoptotic genes (Behrens et al. 1999; Coffey et al. 2002; Barone et al. 2008; Dhanasekaran and Reddy 2008). Ironically, the nature of genes induced by JNK activation has never been extensively defined. One gene proposed to be transcriptionally activated by JNK and involved in apoptosis was Fas ligand (Le-Niculescu et al. 1999; Mansouri et al. 2003; Wang et al. 2004). Sustained JNK activation may promote TNF α -induced apoptosis via JNK-mediated activation of E3 ubiquitin ligase Itch that ubiquitinates cFLIP, leading to its proteasomal degradation and, subsequently, enhanced caspase-8 activation (Chang et al. 2006). JNK activation can also lead to caspase-8-independent cleavage of BID at a different site, and the cleaved product, jBId, translocated to the mitochondria, inducing preferential release of Smac/Diablo; this, in its turn, promotes TNF α -dependent apoptosis by disrupting the TRAF2-ciAP1 interaction inhibitory for caspase-8 activation (Deng et al. 2003). The JNK activity has been shown to affect the p53-dependent apoptosis in different cell types via p53 phosphorylation that alters the activity or stability (Fogarty et al. 2003; Oleinik et al. 2007). JNK is also known to

phosphorylate members of the BCL-2 family, thus directly affecting their function (Yamamoto et al. 1999; Donovan et al. 2002; Lei and Davis 2003; Putcha et al. 2003; Okuno et al. 2004). JNK can also alter their functions indirectly by phosphorylating interacting proteins. The best known such effect is translocation of BAX to the mitochondria promoted by JNK-dependent phosphorylation of BAX cytoplasmic anchoring protein 14-3-3 (Tsuruta et al. 2004; Gao et al. 2005). The function of neuron-specific JNK3 isoform in neuronal apoptosis caused by ischemia/hypoxia is believed to be mediated by induction of BIM and other pro-apoptotic genes (Kuan et al. 2003; Zhang et al. 2006; Zhao et al. 2007).

2.2 The p53 Pathway

The tumor suppressor protein p53 is a transcription factor that mediates apoptosis caused by multiple stressors, including DNA damaging agents such as UV, γ -irradiation, or genotoxic drugs (e.g., topoisomerase inhibitor etoposide) (Vousden and Lane 2007; Delbridge et al. 2012). As mentioned above, p53 promotes cell death by increasing the expression of pro-apoptotic genes such as BAX, PUMA, and NOXA (Oda et al. 2000; Nakano and Vousden 2001; Yu et al. 2001), with PUMA and, to a lesser degree, NOXA being the main culprits (Villunger et al. 2003; Naik et al. 2007; Michalak et al. 2008). The level of p53 in cells is tightly controlled to keep the balance between cell death and tumor development that occurs when p53 function is compromised (Delbridge et al. 2012). Oncoprotein RING finger E3 ubiquitin ligase Mdm2 is the main negative regulator of p53 that ubiquitinates p53, promoting its proteasomal degradation (Fang et al. 2000; Honda and Yasuda 2000). Apparently, Mdm2 requires collaboration with MdmX, a related protein without intrinsic E3 ligase activity, to polyubiquitinate p53 (Parant et al. 2001; Wang et al. 2011). In its turn, p53 stimulates Mdm2 transcription. Thus, Mdm2 and p53 form a regulatory feedback loop that is strongly impacted by cellular stress, resulting in inactivation of Mdm2 and activation of p53 (Stommel and Wahl 2005). The key importance of p53 for survival and Mdm2 for its regulation is strongly supported by the fact that mice lacking Mdm2 die in early embryogenesis, whereas mice lacking both Mdm2 and p53 are grossly normal (Jones et al. 1995; Montes de Oca Luna et al. 1995). Recent data demonstrate that, in addition to its transcriptional role, p53 regulates the mitochondrial apoptotic pathway in a transcription-independent manner via direct interaction with BCL-2 proteins at the mitochondria (Chipuk et al. 2003, 2004, 2005).

3 Arrestins Regulate Apoptosis via Signaling Mechanisms

The canonical mode of arrestin function in homologous desensitization of GPCRs involves arrestin binding to phosphorylated activated receptors that terminates G protein activation by blocking its access to the receptor cytoplasmic surface (Wilden 1995; Krupnick et al. 1997). Ubiquitous arrestin-2 and arrestin-3¹ regulate most GPCRs, suppressing G protein activation (Attramadal et al. 1992; Lohse et al. 1992). Arrestins also bind numerous non-receptor partners, thus regulating multiple cellular signaling pathways (Lefkowitz and Shenoy 2005; Gurevich and Gurevich 2006). Since many of these pathways are involved in “life-or-death”

¹Different systems of arrestin names are used in the field and in this book. We use systematic names of arrestin proteins: arrestin-1 (historic names S-antigen, 48-kDa protein, visual or rod arrestin), arrestin-2 (β -arrestin or β -arrestin-1), arrestin-3 (β -arrestin-2 or hTHY-ARRX), and arrestin-4 (cone or X-arrestin; for unclear reasons its gene is called “*arrestin-3*” in the HUGO database).

decisions in the cell, arrestins have been reported to influence cell death and survival via signaling mechanisms (Fig. 1). Indeed, considering a wide variety of signaling pathways regulated by arrestins (Gurevich and Gurevich 2006; Luttrell and Miller 2013), it would have been surprising if arrestins did not affect apoptosis. However, the data on the exact mechanisms involved are remarkably fragmentary.

GPCR stimulation followed by G protein activation can induce pro-apoptotic signaling, and arrestins would counteract that signaling simply by virtue of desensitizing the offending receptors. One example of such situation is apoptosis induced by stimulation of various GPCRs in arrestin-2/arrestin-3 DKO MEFs, with expression of either arrestin protecting these cells (Revankar et al. 2004). The molecular mechanism of GPCR-induced apoptosis, which occurs via the intrinsic pathway, includes the activation of p38, JNK, phosphatidylinositol 3-kinase (PI3K), and Gi/o-dependent signaling. Interestingly, excessive signaling due to defective receptor desensitization in the absence of arrestins does not seem to be the culprit. At least in case of the N-formyl peptide receptor, which is internalized in arrestin-independent manner but requires arrestins for recycling (Vines et al. 2003), receptor phosphorylation and internalization were required to induce apoptosis. Arrestin interaction with adaptor protein-2 (AP-2) participating in post-endocytotic receptor trafficking (see chapter “ β -Arrestins and G Protein-Coupled Receptor Trafficking”) was involved in the protection from GPCR-induced apoptosis by arrestins (Wagener et al. 2009).

In an alternative case scenario, arrestins could be involved in apoptosis-related signaling by various receptors, and as recent studies indicate, their role is not limited to GPCRs. Whether the outcome of arrestin-dependent signaling is pro-survival or pro-apoptotic depends on the specific configuration of the signaling system in which they act. When arrestin-mediated signaling results in the activation of pro-survival pathways such as ERK or Akt, arrestins provide cytoprotection. In the opposite case, when the arrestin action leads to the suppression of pro-survival or induction of pro-apoptotic signaling, arrestins serve to facilitate cell death. Thus, arrestin-2 protected cells from apoptosis caused by serum deprivation via NK1 receptor and arrestin-dependent ERK1/2 activation (DeFea et al. 2000). Similarly, arrestin-2-dependent ERK activation mediated protective effect of glutamate acting via metabotropic glutamate receptor 1 (mGluR1) against serum-deprivation-induced apoptosis (Emery et al. 2010). Both arrestin-2 and arrestin-3 mediate transactivation of the epidermal growth factor (EGF) receptor by the Gq-coupled receptor of neuropeptide urotensin II (Esposito et al. 2011). Urotensin II, which is expressed in the nervous, cardiovascular, and urogenital systems, and its receptor are upregulated in the pathological heart (Zhu et al. 2006), and this increase seems to be protective, since treatment with urotensin II antagonist exacerbates heart pathology and promotes apoptosis of cardiomyocytes, the effect linked to reduced EGF receptor transactivation and resulting ERK activity (Esposito et al. 2011). Arrestin-3 mediated the protection conferred by the angiotensin II receptor 1A to primary rat vascular smooth muscle or to HEK293 cells against hydrogen peroxide (H₂O₂)- or etoposide-induced apoptosis (Ahn et al. 2009). Arrestin-3-dependent ERK activation followed by activation of the P90 ribosomal S6 kinase (P90RSK) and activation of Akt was required for its antiapoptotic activity. P90RSK and Akt in their turn phosphorylated pro-apoptotic BCL-2 protein Bad at Ser¹¹² and Ser¹³⁶, respectively, thus inhibiting its pro-apoptotic activity. A similar mechanism was described

for the arrestin-2 role in the protection against glucose deprivation-induced apoptosis afforded by stimulation of the glucagon-like peptide-1 Gs-coupled receptor (GLP-1) to pancreatic beta cells (Quoyer et al. 2010). Arrestin-2-mediated ERK activation resulted in the activation of the P90RSK, leading to phosphorylation of Bad at Ser¹¹². Apparently, in some cases arrestin-dependent ERK activation could be harmful to cells. Thus, dopamine at high concentration acting at the D1 dopamine receptor has been reported to cause apoptotic death of primary and cultured neuronal cells via sustained arrestin-2-dependent ERK activation in the cytosol (Chen et al. 2004, 2009).

Arrestins are known to be involved in the regulation of the pro-survival Akt pathway. Previously, arrestin-3 (and to a lesser extent arrestin-2) has been shown to reduce the activity of the Akt pathway by scaffolding Akt with protein phosphatase 2 at the D2 dopamine receptor, which resulted in dephosphorylation of Akt at its main activating residue Thr⁴⁰⁸ (Manning and Cantley 2007). It has not been examined whether this regulatory effect of arrestin-3 on the Akt pathway activity plays any role in apoptosis, which appears likely. Arrestin-2 is protecting from serum deprivation-induced apoptosis by coupling the insulin-like growth factor 1 receptor to the activation of PI3K and subsequent activation of the Akt pathway (Povsic et al. 2003). This signaling process occurs independently of the tyrosine kinase activity of the receptor, Gi, or ERK activity. Platelet-activating factor acting at its receptor induces apoptosis in colon cancer cells by promoting dephosphorylation of Akt at Ser⁴⁷³ via assembly at the receptor of arrestin-2 and PH domain and leucine-rich repeat protein phosphatase 2 that dephosphorylates Akt at this residue (Crotty et al. 2013; Xu et al. 2013). This is a novel mode of arrestin-dependent inhibition of the Akt pathway that may play a role in apoptosis via suppression of the pro-survival Akt signaling. The glycogen synthase kinase-3 (GSK3) is the main substrate of Akt. This kinase is constitutively active, and it is inhibited by Akt phosphorylation (Manning and Cantley 2007). GSK3 β isoform is known to potentiate mitochondrial apoptotic signaling (Hetman et al. 2000; Beurel and Jope 2006; Eom et al. 2007; Mishra et al. 2007; Watcharasit et al. 2008). The pro-survival effect of the PI3K/Akt activation is largely mediated by inhibition of GSK3 β . Arrestins, particularly arrestin-3, by modulating the activity of PI3K and/or Akt, could impact the GSK3 β -dependent apoptosis. This notion is supported by the fact that MEFs lacking arrestin-3 demonstrate higher level of GSK3 β activity (lower phosphorylation) coupled with increased apoptotic death (Li et al. 2010).

Arrestins turned out to be involved in the regulation of the pro-survival NF κ B pathway. Arrestin-3 has been reported to inhibit NF κ B activation induced by TNF α (Gao et al. 2004). The mechanism of the inhibition involves direct interaction of arrestin-3 with the inhibitor of NF κ B I κ B α , which prevents phosphorylation and degradation of the latter, thus precluding the activation of NF κ B. In this study, arrestin-3 was shown to significantly inhibit TNF α -induced translocation of NF κ B p65 subunit into the nucleus and transcription of NF κ B-dependent genes. Importantly, arrestin-3 association with I κ B α , as well as its effect on the NF κ B activation, was significantly increased by stimulation of β 2-adrenergic receptor (b2AR). Thus, arrestin-3 mediates the effect of b2AR on the NF κ B activity, which may play a role in the sympathetic regulation of TNF α immune responses. In this study, the TNF α -induced apoptosis was not directly examined, although arrestin-3-dependent inhibition of the pro-survival signaling induced by TNFR1 should be expected to favor cell death.

Interestingly, arrestin-2 was reported to be unable to stabilize I κ B α and affect the p65 translocation or the expression of NF κ B target genes. Another group, however, demonstrated that both arrestin isoforms interacted with I κ B α , significantly inhibiting the NF κ B activity induced by various stimuli (Witherow et al. 2004). Moreover, knockdown of arrestin-2 and not arrestin-3 resulted in significant increase in the TNF α -induced activation of NF κ B, suggesting that arrestin-2 isoform is the prime regulator of the NF κ B activation in response to TNF α . The NF κ B is also activated by UV irradiation, and arrestin-3 was shown to suppress that activation via interaction with I κ B α facilitating apoptotic cell death (Luan et al. 2005). The ability of arrestin-3 to interact with I κ B α was blocked by its phosphorylation by casein kinase II, and stimulation of b2AR in epidermal cells promoted arrestin-3 dephosphorylation together with arrestin-3-dependent suppression of NF κ B activity. Therefore, arrestin-3 facilitated UV-induced apoptosis in the b2AR-dependent manner via inhibition of the NF κ B pathway. An alternative mechanism of arrestin-dependent regulation of the NF κ B activity was demonstrated in the immune system. Arrestin-3 was shown to interact with TRAF6 and inhibit TRAF6 autoubiquitination and oligomerization after stimulation of interleukin receptors, leading to suppression of the NF κ B activation and immunological response to endotoxin challenge (Wang et al. 2006). Since TRAF6 is also involved in the TNFR1-induced NF κ B activation, suppression of this effect may also favor apoptosis instead of cell survival.

An alternative mechanism of arrestin contribution to apoptosis caused by DNA damage is through its modulation of the p53 pathway. Arrestin-3 has been shown to bind E3 ubiquitin ligase, Mdm2, but not MdmX (Wang et al. 2003b), the key regulator of p53-dependent apoptosis mediated by the intrinsic pathway. Arrestin-3 binding to Mdm2 inhibited Mdm2 self-ubiquitination and Mdm2-dependent p53 ubiquitination, thus suppressing p53 degradation and promoting apoptosis. It appears somewhat inconsistent that arrestin-3 stabilizes both Mdm2 and p53, although normally high level of Mdm2 leads to a reduction in p53, and Mdm2 needs to be destabilized to allow the p53 level to rise (Stommel and Wahl 2005; Vousden and Lane 2007). Importantly, arrestin-3 binding to Mdm2 was reported to be strongly promoted by the activation of GPCRs such as δ -opioid, bradykinin, or b2AR. In this situation, arrestin-3 acted as a pro-apoptotic agent facilitating DNA damage-induced apoptosis. Conversely, arrestin-2, but not arrestin-3, recruited to active b2AR has been reported to facilitate Akt-mediated activation of Mdm2 promoting Mdm2-dependent degradation of p53 (Hara et al. 2011). Reduced level of p53 leads to the accumulation of stress-induced DNA damage in cultured cells and in the thymus in vivo, presumably due to defective p53-dependent apoptosis of damaged cells. Similarly, behavioral restrained stress leads to a reduction in the p53 level and accumulation of DNA damage in the mouse frontal cortex in the b2AR- and arrestin-2-dependent manner (Hara et al. 2013). Thus, arrestin-2 appears to play the antiapoptotic role via its activation of Mdm2. It remains unclear whether the opposite functions ascribed to arrestins in these studies could be explained away by the difference in arrestin isoforms, arrestin-3 versus arrestin-2, acting via different mechanism, direct interaction with Mdm2 versus indirect activation by Akt-dependent phosphorylation. Importantly, in these studies the mode of apoptosis, DNA damage induced, was the same, and the stimulating factor such as b2AR activation was also similar.

Although the role of JNK pathway in apoptosis is reasonably well established, and arrestin-3 is known to activate JNK3 (McDonald et al. 2000; Miller et al. 2001; Song et al. 2009a; Seo et al. 2011; Zhan et al. 2011, 2013; Breitman et al. 2012), this function of arrestins in apoptosis received surprisingly little attention. This is possibly because JNK3 expression is largely limited to the nervous system, with lower levels in the heart and testes (Gupta et al. 1996; Martin et al. 1996). Both arrestin isoforms attenuated H₂O₂-induced apoptosis by suppressing the JNK activation via direct interaction with apoptosis signal-regulated kinase-1 (ASK1), the upstream kinase (MAPKKK) in the JNK pathway (Zhang et al. 2009). Arrestin-ASK1 interaction, which was increased by H₂O₂, promoted ASK1 ubiquitination, via recruitment of E3 ligase CHIP, and subsequent proteasomal degradation, resulting in reduced JNK activation and increased cell survival without apparent contribution from receptors. Ironically, this is the opposite paradigm to the classic arrestin-mediated JNK3 activation based on scaffolding by arrestin-3 of JNK3 upstream kinases, leading to enhanced JNK3 activation (McDonald et al. 2000). In the study by Zhang et al., the authors claim that arrestin-3-dependent JNK3 activation facilitated neuronal apoptosis following ischemia (Zhang et al. 2012). However, no evidence of role of arrestin-3-dependent JNK3 activation was presented. Instead, the experiments demonstrated reduced JNK3 activation by angiotensin II type 1 receptor antagonist losartan accompanied by protection against ischemia/reperfusion-induced neuronal death.

Arrestin-3 has been shown to mediate endocytosis of the type III transforming in the serum starvation condition growth factor-beta (TGFβ) receptor (TGFβRIII) in complex with TGFβRII and to reduce TGF-beta signaling (Chen et al. 2003). The loss of arrestin-3 has been shown to increase the rate of TGFβ-induced apoptosis, but the effect was mediated by enhanced TGFβ-dependent activation of p38 MAP kinase and not by Smad activation (McLean et al. 2013). The arrestin-3 effect on the p38 activity is likely mediated by its effect on the trafficking of TGFβ receptors, since the surface expression of the receptors increases upon the loss of arrestin-3. Arrestin function in apoptosis could be mediated by interactions with proteins outside of canonical pro- or antiapoptotic pathways. For example, arrestin-2 has been shown to protect human urothelial cells from staurosporine-induced apoptosis in b2AR-dependent manner via interaction with 27-kDa heat shock protein (Rojanathammanee et al. 2009).

Arrestins mostly regulate apoptosis via signaling mechanisms in the cytosol, although both are known to shuttle between the cytosol in the nucleus (Scott et al. 2002; Wang et al. 2003a; Song et al. 2006). Arrestin-3, but not arrestin-2, possesses a strong nuclear export signal and is able to relocalize nuclear proteins such as JNK and Mdm2 from the nucleus to the cytosol (Scott et al. 2002; Wang et al. 2003b; Song et al. 2006). Arrestin-2, on the other hand, has a single amino acid difference with arrestin-3 in the corresponding region, and unless the nuclear export signal is engineered, it is unable to relocalize its binding partners from the nucleus (Wang et al. 2003a; Song et al. 2006). Arrestin-2 possesses nuclear localization signal (Hoepfner et al. 2012) and has been reported to localize to the nucleus in some cell types (Hoepfner et al. 2012) and perform nuclear functions (Kang et al. 2005). Therefore, arrestins, arrestin-2 in particular, could interfere with apoptosis via signaling in the nucleus. Indeed, arrestin-2 has been shown to confer cytoprotection by stimulating transcription of antiapoptotic BCL-2 and thus promoting the survival of CD4+ native and

activated T cells (Shi et al. 2007). Nuclear arrestin-2 also interacts with p53, acting in a somewhat poorly defined role of E3 ligase “adaptor” required for Mdm2 to ubiquitinate p53 and promote its degradation, although cytoplasmic arrestin-2 is sufficient to activate Mdm2 via the Akt pathway upon b2AR stimulation (Hara et al. 2011).

The ability of arrestins to engage the survival mechanisms via arrestin-dependent signaling could be taken advantage of via so-called biased ligands that are able to stimulate arrestin recruitment upon binding to GPCRs without inducing G protein activation (see chapter “Quantifying Biased β -Arrestin Signaling”). In some pathological conditions, the activity of select GPCRs is harmful, and in such cases antagonists are used as therapeutic agents. However, arrestin-dependent signaling, which might be beneficial, is also abolished by such drugs. The use of biased ligands achieves both ends: suppresses G protein-mediated and engages arrestin-mediated signaling. Thus, arrestin-biased ligand of angiotensin II type 1 receptor confers protection against cardiac injury induced by ischemia reperfusion injury or mechanical stretch, which is superior to that provided by angiotensin II antagonist losartan, a commonly used therapeutic agent. The protection was arrestin dependent, since it was absent in mice lacking arrestin-3 (Kim et al. 2012a).

4 Arrestins Regulate Apoptosis via Direct Interference in the Core Apoptotic Machinery

Thus, arrestins can affect cell survival in many ways via signaling, but direct pro-apoptotic action of arrestins at the core of cell death machinery was only recently reported (Kook et al. 2013). The signaling in the intrinsic apoptotic pathway involves cytochrome C release from the mitochondria that is orchestrated by the complex interplay of pro- and antiapoptotic members of the BCL-2 family of proteins (Chipuk and Green 2008, 2009). However, the exact mechanism of the process remains elusive. The involvement of additional players that do not belong to BCL family is one of the emerging ideas (Chipuk and Green 2008). Proteomic surveys suggest that caspase cleavage might supply regulators of apoptosis (Dix et al. 2008; Mahrus et al. 2008), but specific functional roles of cleavage products are rarely established. Active caspases are a notable example of caspase cleavage products playing critical role in cell death (Wolan et al. 2009). Another well-known example is BID: the product of its cleavage by caspases tBID translocates to mitochondria and promotes cytochrome C release. Possibly, some of the so-called dependence receptors require caspase-mediated cleavage for their death domains to be revealed or released (Bredesen et al. 2005). However, the full signaling potential of caspase cleavage products to affect this crucial step in the apoptotic pathway has not yet been explored.

As it turned out, arrestin-2 is cleaved by caspases at evolutionarily conserved Asp380 yielding an Arr2-(1-380) fragment (Kook et al. 2013). Apoptosis initiated via extrinsic (stimulation with TNF α combined with inhibition of protein synthesis by cycloheximide) or intrinsic (genotoxic drug etoposide) pathway resulted in the appearance of the same arrestin-2 fragment. A secondary cleavage site in arrestin-2, at Asp406 that is conserved only in mammals, was identified. When both aspartates were mutated to glutamates, the mutant (DblE) was resistant to caspases in all cell types (Kook et al. 2013). The presence of Asp380 in homologous positions in arrestin-2 from multiple species indicates that this

mechanism is conserved in vertebrate evolution. Unlike many substrates, arrestin-2 is not just an “innocent victim” of caspases. 1-380 translocated to the mitochondria and enhanced cytochrome C release by “assisting” another product of caspase-8 activity, tBID. Since virtually every mammalian cell expresses both arrestin-2 and arrestin-3 (Gurevich and Gurevich 2006), specific functions of individual subtypes can only be dissected in cells lacking one or the other. Arrestin-2 (A2KO) and arrestin-3 (A3KO) knockout mouse embryonic fibroblasts (MEFs), as well as arrestin-2/arrestin-3 double-knockout (DKO) MEFs, established more than a decade ago (Kohout et al. 2001), proved to be extremely useful tools in this regard. Increased cytochrome C release due to 1-380 significantly accelerated the progression of apoptosis. The rate of caspase activation and cell death in A3KO MEFs expressing only arrestin-2 was two- to threefold higher as compared to DKO MEFs lacking both arrestins. The ectopic expression of 1-380 in DKO MEFs facilitated TNF- α -induced apoptosis to the level observed in A3KO MEFs. WT arrestin-2 but not its uncleavable mutant also rescued vulnerability of DKO MEFs to cell death (Kook et al. 2013). Arrestin-2 does not have an identifiable mitochondrial localization signal, and mitochondria contain very little full-length arrestin-2, but large proportion of 1-380 localizes to mitochondria. Direct binding of purified 1-380 to isolated mitochondria and mitochondrial localization of expressed 1-380 even in non-apoptotic cells shows that, in contrast to full-length arrestin-2, it has an increased affinity for protein(s) residing in this compartment. 1-380 did not induce cytochrome C release by itself in cells or isolated mitochondria. Instead, it directly interacted with tBID and specifically facilitated cytochrome C release induced by tBID. The absence of BID completely abrogated pro-apoptotic effect of 1-380. Thus, caspase cleavage of arrestin-2 is a gain-of-function event resulting in a stronger interaction with tBID and the ability to enhance tBID-induced cytochrome C release that uncleaved arrestin-2 does not possess (Kook et al. 2013) (Fig. 1).

Both 1-380 and tBID are effectively generated by caspase-8, suggesting that their convergence at mitochondria plays crucial role in the extrinsic apoptotic pathway. However, apoptosis, like most cellular processes, has multiple backup mechanisms (Slee et al. 2000; Crawford and Wells 2011). Although the canonical way for caspase-8 activation is via death receptors, caspase-8 can also be activated in death receptor-independent manner, as seen, for example, in genotoxic drug-induced apoptosis (von Haefen et al. 2003; de Vries et al. 2007). Such activation occurs downstream of the mitochondria, cytochrome C release, and activation of effector caspases. Furthermore, in the absence of caspase-8, 1-380 could be generated by other caspases such as caspase-9 or caspase-6 (Kook et al. 2013).

Caspase activity in the cell is greatly increased by released cytochrome C via the apoptosome (Riedl and Salvesen 2007). Thus, cooperation of 1-380 and tBID in cytochrome C release creates a potent positive feedback loop, tipping the balance towards cell commitment to apoptotic death. This mechanism also sets a threshold for an irreversible cell “decision” to die: simultaneous generation of both fragments is necessary to maximize the death signal. The arrestin-2-dependent positive feedback loop greatly contributed to the mitochondrial apoptotic pathway, with magnitude of 1-380 effect on isolated mitochondria and intact cells comparable to that of tBID (Kook et al. 2013). The permeabilization of the outer mitochondrial membrane and the resulting cytochrome C release is usually the point of no return, committing the cell to death (Danial and Korsmeyer 2004). Extensive studies of

this step focusing on the interactions of pro- and antiapoptotic BCL family members with each other and pore-forming effectors BAK and BAX suggest that BID, BIM, and PUMA act as direct activators (Wei et al. 2000; Kim et al. 2009a; Ren et al. 2010). However, many molecular details necessary for mechanistic understanding of this process are missing (Chipuk and Green 2008; Youle and Strasser 2008). Our recent finding of the role of arrestin-2 cleavage product (Kook et al. 2013) supports the idea that direct involvement of additional players may explain inconsistencies between in vitro studies with BCL proteins and in vivo apoptosis (Chipuk and Green 2008). Our results suggest that tBID in complex with 1-380, rather than tBID alone, is the biologically relevant inducer of cytochrome C release (Kook et al. 2013). It is tempting to speculate that in cytochrome C release BIM and PUMA might also have their specific “helpers,” possibly generated by caspases.

Caspases often produce discrete stable cleavage products likely serving as functional effectors in apoptosis (Dix et al. 2008; Mahrus et al. 2008). However, the functions of caspase-generated fragments are rarely established. The functional consequences of the cleavage of most of the 777 caspase substrates in CASBAH database (Lüthi and Martin 2007) remain unknown. Caspase cleavage of several kinases unleashes or abrogates their pro-apoptotic or pro-survival functions, respectively, via changes in activity, subcellular localization, or substrate preferences (Kurokawa and Kornbluth 2009). Caspase cleavage products of diverse proteins contribute to the progression of apoptosis due to loss or gain of function or via dominant-negative action (Kim et al. 2009b; Crawford and Wells 2011; Oliver et al. 2011). Our experiments revealed a direct role of 1-380 in cytochrome C release, identifying it as an earlier unappreciated active participant in the core mechanism of apoptosis (Kook et al. 2013). This is the first example of direct cooperation of two caspase products, 1-380 and tBID, at the point where the cell makes a fateful decision to live or die. This cooperation likely contributes to making this decision irreversible and also effectively sets a threshold for cell commitment to apoptotic death.

5 Visual Arrestins in Apoptosis

Of the four vertebrate arrestin isoforms, two, arrestin-1 (a.k.a. visual or rod arrestin) and arrestin-4 (a.k.a. cone arrestin), are expressed in retinal photoreceptors. Arrestin-1 is expressed in both rods and cones, whereas arrestin-4 is found in cones (Gurevich and Gurevich 2009, 2010; Gurevich et al. 2011). Photoreceptors are highly specialized neurons adapted for their function. Both rods and cones have specialized compartment, the outer segment, where photopigment and proteins of the signaling cascade reside, largely separated from the rest of the cell (Pugh and Lamb 2000). Rods function in dim light and are exquisitely light sensitive, being capable of detecting one photon of light (Baylor et al. 1979). Such sensitivity is achieved, among other things, by high levels of expression of main signaling proteins such as photosensitive pigment rhodopsin (~3 mM) and arrestin-1 (>2 mM), an important component of the potent shutdown system ensuring almost zero background signaling (Pugh and Lamb 2000; Gurevich and Gurevich 2009; Gurevich et al. 2011). For comparison, the concentrations of higher expressed nonvisual arrestin isoform arrestin-2 in the adult rat central nervous system are ~200 nM and that of arrestin-3—almost 20-fold lower—~12 nM (Gurevich et al. 2004). Because of such high load of signaling proteins, the balance in rods is very precarious, and changes in the expression levels of

signaling proteins often lead to rod death. A well-known example is rhodopsin: an excellent correlation between the level of overexpression of this perfectly normal protein and the rate of photoreceptor degeneration was established (Tan et al. 2001). Transgenic overexpression of wild-type arrestin-1 did not undermine photoreceptor survival, although it somewhat compromised the health of their outer segments in older mice (Song et al. 2011). Conversely, the loss of arrestin-1 induced defect in signaling shutoff, excessive signaling, and light-dependent degeneration of rod outer segments and rod death by apoptosis (Xu et al. 1997; Song et al. 2009b, 2013). Even hemizygous mice with ~50 % level of arrestin-1 showed somewhat lower level of rod survival (Song et al. 2009b, 2013). Interestingly, the expression of arrestin-1 as low as 5 % of wild-type (WT) level was sufficient to maintain photoreceptor health and support their functional performance (Cleghorn et al. 2011; Song et al. 2011). Thus, the total loss of arrestin-1 function of quenching rhodopsin signaling is detrimental for rod survival and leads to rod death by apoptosis.

Arrestin interaction with phosphorylated rhodopsin that quenches phototransduction is required for rod survival. However, a very tight arrestin-rhodopsin interaction could be detrimental for rods, resulting in rod death. Such tight interaction is believed to cause retinal degeneration, a group of retinal degenerative diseases known as *retinitis pigmentosa* characterized by variable loss of rod photoreceptors across the retina followed by the death of cone photoreceptors (Mendes et al. 2005). Most of the cases are autosomal dominant and are caused by mutations in rhodopsin, leading to it being constitutively active or constitutively phosphorylated by rhodopsin kinase, with both conditions resulting in persistent arrestin-1 binding (Rim and Oprian 1995). Arrestin-1 mislocalizes rhodopsin from the outer segments to endosomes in inner segments and cell bodies, leading to rod death (Chuang et al. 2004; Chen et al. 2006). Recruitment of endocytic adapter protein-2 (AP-2) via arrestin-1 plays a role in rod death induced by arrestin-1 complex with constitutively active rhodopsin mutant (Moaven et al. 2013). A naturally occurring splice variant of arrestin-1 p44 lacking a part of the arrestin-1 C-tail and thus incapable of interacting with AP-2 but competent to quench phototransduction prevents the death of photoreceptors expressing constitutively active rhodopsin (Moaven et al. 2013). This pathway is evolutionarily conserved, since the same tight association of arrestin with activated rhodopsin induces apoptotic death of *Drosophila* photoreceptors (Alloway et al. 2000; Kiselev et al. 2000; Kristaponyte et al. 2012).

Arrestin-1 of several species has recently been shown to cooperatively form dimers and tetramers, with only a small fraction of it existing as monomer at physiological concentrations (Schubert et al. 1999; Imamoto et al. 2003; Hanson et al. 2007b, 2008b; Kim et al. 2011; Chen et al. 2013) (see chapter “Self-Association of Arrestin Family Members”). The physiological function of this phenomenon remained unclear. However, the mouse line expressing arrestin-1 mutant with reduced ability to form oligomers at ~240 % of WT arrestin-1 (which resulted in the monomer concentration exceeding that in WT mouse almost threefold) demonstrated rapid age-related apoptotic death of rod photoreceptors (Song et al. 2013). The mouse line expressing the same mutant at a much lower level (50 % of wild type, which yielded only ~20 % increase in monomer concentration) showed a very slow age-dependent degeneration. Importantly, mice overexpressing WT arrestin-1, which

robustly oligomerizes, so that overexpression leads to minimal increase in the monomer concentration, did not show photoreceptor death. Furthermore, co-expression of WT arrestin-1 with the mutant protected rods from the mutant-induced apoptosis, suggesting that previously demonstrated ability of WT to recruit mutant arrestin-1 into mixed oligomers (Hanson et al. 2007b, 2008b) may be responsible. These data suggest that monomeric arrestin-1 is toxic to rods and provides a functional explanation for the ability of arrestin-1 to oligomerize. Only monomeric arrestin-1 interacts with rhodopsin (Hanson et al. 2007b, 2008b), and it binds rhodopsin monomer with high affinity (Hanson et al. 2007a; Bayburt et al. 2011; Kim et al. 2012b; Singhal et al. 2013; Vishnivetskiy et al. 2013; Zhuang et al. 2013). Thus, arrestin-1 oligomers likely represent a nontoxic storage form not only in rods but also in cones. Arrestin-4, or cone arrestin, in spite of its name, is outnumbered in cone photoreceptors by arrestin-1 by ~50:1 (Nikonov et al. 2008). Since cone arrestin is unable to self-associate (Hanson et al. 2008a), and as monomer could be toxic to photoreceptors, cones simply cannot afford to express arrestin-4 at high level necessary to rapidly quench phototransduction in bright light in which they operate. Therefore, a certain amount of arrestin-4 might be produced for immediate use, but the main stock is kept as arrestin-1 oligomers to be employed when needed.

In retinal photoreceptors, rhodopsin is the main binding partner of visual arrestins, and the main function of arrestins in photoreceptors is to quench rhodopsin signaling (Gurevich et al. 2011). However, arrestin-1 is found not only in close proximity to its key binding partner rhodopsin, i.e., in the rod outer segments, but also in other rod compartments, specifically in synaptic terminals (Nair et al. 2005; Hanson et al. 2007a; Huang et al. 2010). Very little attention so far has been paid to possible rhodopsin-independent functions of arrestin-1 and their potential role in retinal photoreceptor death and survival. It has recently been shown that arrestin-1 interacts with N-ethylmaleimide-sensitive factor (NSF) (Huang et al. 2010). NSF is localized to photoreceptor synapses and functions to sustain high rate of neurotransmitter exocytosis. Arrestin-1 interaction with NSF was enhanced in the dark when rods were depolarized and neurotransmitter release was elevated. Mice lacking arrestin-1 displayed reduced levels of NSF and of other synaptic proteins, as well as reduced exocytosis, suggesting that arrestin-1 interaction with NSF was required for normal synaptic function in rods. Therefore, it is conceivable that arrestin-1 modulates rod survival via its interactions with proteins other than rhodopsin, such as synaptic proteins. It has been shown that arrestin-1 mutant with reduced ability to self-associate caused damage to synaptic terminals, which was detectable earlier than the loss of photoreceptors, suggesting that synapses might be the site of toxicity of arrestin-1 monomer (Song et al. 2013). Co-expression of WT arrestin-1 that protected photoreceptors from apoptosis conferred even more significant protection to synapses, again supporting the notion of synapses being the primary site of damage. These data indicate that the role of arrestin-1 in the photoreceptor death and survival could involve arrestin-1 interaction with proteins other than rhodopsin. Specifically, arrestin-1 function in photoreceptor synapses could be necessary to maintain photoreceptor health. Interestingly, the binding of arrestin-2 to NSF was described more than a decade ago (McDonald et al. 1999), suggesting that nonvisual subtypes might also be involved in synaptic functions, including neurotransmitter release.

6 Conclusions and Future Directions

Apoptotic cell death plays an important role in embryonic development, in homeostasis of multicell organisms, as well as in numerous pathological processes. Arrestins appear to be intimately involved in the regulation of a variety of signaling pathways involved in cell death and survival. Thus, reengineered signaling-biased arrestins with enhanced pro-apoptotic or pro-survival functions can be used as molecular tools to influence cell decision to live or die in desired direction (Gurevich and Gurevich 2012). Arrestin-3 mutants lacking the ability to activate JNK family kinases (chapter “Arrestin-Dependent Activation of JNK Family Kinases”) are obvious candidates to be tested in this regard. In addition, caspase cleavage product of arrestin-2 directly participates in the critical step in vertebrate apoptosis, assisting tBID in cytochrome C release (Kook et al. 2013). Importantly, caspase-resistant arrestin-2 mutant is lacking pro-apoptotic function (Kook et al. 2013), suggesting that it might be useful for cytoprotection. This finding also raises a question whether other arrestin subtypes, such as arrestin-1 and arrestin-3, are targeted by caspases and whether generated cleavage products acquire new functions, similar to that of arrestin-2. Visual arrestin-1, the functions of which were long believed to be limited to the shutoff of rhodopsin signaling (Gurevich et al. 2011), turned out to be an important regulator of photoreceptor health and survival acting at synaptic terminals (Song et al. 2013). Since the integrity of synapses is necessary for survival of all neurons, nonvisual arrestins might play a role in neuronal survival similar to that described for arrestin-1. Three out of four vertebrate arrestin subtypes self-associate forming distinct oligomers (Chen et al. 2013). Since arrestin-1 monomers appear to be cytotoxic, whereas oligomers are perfectly harmless (Song et al. 2013), self-association of nonvisual arrestins might also affect their role in cell survival (see chapter “Self-Association of Arrestin Family Members”). Considering that arrestins can impact cell death and survival via numerous mechanisms, every redesigned arrestin mutant, including those with enhanced ability to bind unphosphorylated receptors (chapter “Enhanced Phosphorylation-Independent Arrestins and Gene Therapy”), targeting individual GPCRs (chapter “Targeting Individual GPCRs with Redesigned Non-visual Arrestins”), and with modified trafficking properties (chapter “ β -Arrestins and G Protein-Coupled Receptor Trafficking”), changing interactions with ubiquitinating and deubiquitinating enzymes (chapter “Arrestin Interaction with E3 Ubiquitin Ligases and deubiquitinases: Functional and Therapeutic Implications”), must be specifically tested for its effect on apoptosis and cell survival.

References

- Ahn S, Kim J, Hara MR, Ren XR, Lefkowitz RJ. β -Arrestin-2 mediates anti-apoptotic signaling through regulation of BAD phosphorylation. *J Biol Chem*. 2009; 284:8855–8865. [PubMed: 19171933]
- Alloway PG, Howard L, Dolph PJ. The formation of stable rhodopsin-arrestin complexes induces apoptosis and photoreceptor cell degeneration. *Neuron*. 2000; 28:129–138. [PubMed: 11086989]
- Amanullah A, Azam N, Balliet A, Hollander C, Hoffman B, Fornace A, Liebermann D. Cell signalling: cell survival and a Gadd45-factor deficiency. *Nature*. 2003; 424:741–742. [PubMed: 12917673]
- Ambacher KK, Pitzul KB, Karajgikar M, Hamilton A, Ferguson SS, Cregan SP. The JNK- and AKT/ GSK3 β -signaling pathways converge to regulate Puma induction and neuronal apoptosis induced by trophic factor deprivation. *PLoS One*. 2012; 7:e46885. [PubMed: 23056511]

- Attramadal H, Arriza JL, Aoki C, Dawson TM, Codina J, Kwatra MM, Snyder SH, Caron MG, Lefkowitz RJ. Beta-arrestin2, a novel member of the arrestin/beta-arrestin gene family. *J Biol Chem.* 1992; 267:17882–17890. [PubMed: 1517224]
- Barone MC, Desouza LA, Freeman RS. Pin1 promotes cell death in NGF-dependent neurons through a mechanism requiring c-Jun activity. *J Neurochem.* 2008; 106:734–745. [PubMed: 18419764]
- Bayburt TH, Vishnivetskiy SA, McLean M, Morizumi T, Huang C-c, Tesmer JJ, Ernst OP, Sligar SG, Gurevich VV. Rhodopsin monomer is sufficient for normal rhodopsin kinase (GRK1) phosphorylation and arrestin-1 binding. *J Biol Chem.* 2011; 286:1420–1428. [PubMed: 20966068]
- Baylor DA, Lamb TD, Yau KW. Responses of retinal rods to single photons. *J Physiol.* 1979; 288:613–634. [PubMed: 112243]
- Behrens A, Sibilio M, Wagner EF. Amino-terminal phosphorylation of c-Jun regulates stress-induced apoptosis and cellular proliferation. *Nat Genet.* 1999; 21:326–329. [PubMed: 10080190]
- Beurel E, Jope RS. The paradoxical pro- and anti-apoptotic actions of GSK3 in the intrinsic and extrinsic apoptosis signaling pathways. *Prog Neurobiol.* 2006; 79:173–189. [PubMed: 16935409]
- Bradley JR, Pober JS. Tumor necrosis factor receptor-associated factors (TRAFs). *Onco-gene.* 2001; 20:6482–6491.
- Bratton SB, Salvesen GS. Regulation of the Apaf-1-caspase-9 apoptosome. *J Cell Sci.* 2010; 123:3209–3214. [PubMed: 20844150]
- Bredesen DE, Mehlen P, Rabizadeh S. Receptors that mediate cellular dependence. *Cell Death Differ.* 2005; 12:1031–1043. [PubMed: 16015380]
- Breitman M, Kook S, Gimenez LE, Lizama BN, Palazzo MC, Gurevich EV, Gurevich VV. Silent scaffolds: inhibition of c-Jun N-terminal kinase 3 activity in the cell by a dominant-negative arrestin-3 mutant. *J Biol Chem.* 2012; 287:19653–19664. [PubMed: 22523077]
- Bruckner SR, Tammariello SP, Kuan CY, Flavell RA, Rakic P, Estus S. JNK3 contributes to c-Jun activation and apoptosis but not oxidative stress in nerve growth factor-deprived sympathetic neurons. *J Neurochem.* 2001; 78:298–303. [PubMed: 11461965]
- Cavigelli M, Li W, Lin A, Su B, Yoshioka K, Karin M. The tumor promoter arsenite stimulates AP-1 activity by inhibiting a JNK phosphatase. *EMBO J.* 1996; 15:6269–6279. [PubMed: 8947050]
- Chai J, Du C, Wu JW, Kyin S, Wang X, Shi Y. Structural and biochemical basis of apoptotic activation by Smac/DIABLO. *Nature.* 2000; 406:855–862. [PubMed: 10972280]
- Chang L, Kamata H, Solinas G, Luo JL, Maeda S, Venuprasad K, Liu YC, Karin M. The E3 ubiquitin ligase itch couples JNK activation to TNF α -induced cell death by inducing c-FLIP(L) turnover. *Cell.* 2006; 124:601–613. [PubMed: 16469705]
- Chao MV. The p75 neurotrophin receptor. *J Neurobiol.* 1994; 25:1373–1385. [PubMed: 7852992]
- Chen YR, Tan TH. The c-Jun N-terminal kinase pathway and apoptotic signaling (Review). *Int J Oncol.* 2000; 16:651–662. [PubMed: 10717232]
- Chen ZJ, Parent L, Maniatis T. Site-specific phosphorylation of IkappaB α by a novel ubiquitination-dependent protein kinase activity. *Cell.* 1996; 84:853–862. [PubMed: 8601309]
- Chen W, Kirkbride KC, How T, Nelson CD, Mo J, Frederick JP, Wang XF, Lefkowitz RJ, Blobel GC. Beta-arrestin 2 mediates endocytosis of type III TGF- β receptor and down-regulation of its signaling. *Science.* 2003; 301:1394–1397. [PubMed: 12958365]
- Chen J, Rusnak M, Luedtke RR, Sidhu A. D1 dopamine receptor mediates dopamine-induced cytotoxicity via the ERK signal cascade. *J Biol Chem.* 2004; 279:39317–39330. [PubMed: 15247297]
- Chen J, Shi G, Concepcion FA, Xie G, Oprian D, Chen J. Stable rhodopsin/arrestin complex leads to retinal degeneration in a transgenic mouse model of autosomal dominant retinitis pigmentosa. *J Neurosci.* 2006; 26:11929–11937. [PubMed: 17108167]
- Chen J, Rusnak M, Lombroso PJ, Sidhu A. Dopamine promotes striatal neuronal apoptotic death via ERK signaling cascades. *Eur J Neurosci.* 2009; 29:287–306. [PubMed: 19200235]
- Chen Q, Zhuo Y, Francis DJ, Vishnivetskiy SA, Hanson SM, Zhan X, Brooks EK, Iverson TI, Altenbach C, Hubbell WL, Klug CS, Gurevich VV. The two non-visual arrestins form distinct oligomers. *J Biol Chem* (in revision). 2013

- Chipuk JE, Green DR. How do BCL-2 proteins induce mitochondrial outer membrane permeabilization? *Trends Cell Biol.* 2008; 18:157–164. [PubMed: 18314333]
- Chipuk JE, Green DR. PUMA cooperates with direct activator proteins to promote mitochondrial outer membrane permeabilization and apoptosis. *Cell Cycle.* 2009; 8:2692–2696. [PubMed: 19652530]
- Chipuk JE, Maurer U, Green DR, Schuler M. Pharmacologic activation of p53 elicits Bax-dependent apoptosis in the absence of transcription. *Cancer Cell.* 2003; 4:371–381. [PubMed: 14667504]
- Chipuk JE, Kuwana T, Bouchier-Hayes L, Droin NM, Newmeyer DD, Schuler M, Green DR. Direct activation of Bax by p53 mediates mitochondrial membrane permeabilization and apoptosis. *Science.* 2004; 303:1010–1014. [PubMed: 14963330]
- Chipuk JE, Bouchier-Hayes L, Kuwana T, Newmeyer DD, Green DR. PUMA couples the nuclear and cytoplasmic proapoptotic function of p53. *Science.* 2005; 309:1732–1735. [PubMed: 16151013]
- Chipuk JE, Moldoveanu T, Llambi F, Parsons MJ, Green DR. The BCL-2 family reunion. *Mol Cell.* 2010; 37:299–310. [PubMed: 20159550]
- Chuang JZ, Vega C, Jun W, Sung CH. Structural and functional impairment of endocytic pathways by retinitis pigmentosa mutant rhodopsin-arrestin complexes. *J Clin Invest.* 2004; 114:131–140. [PubMed: 15232620]
- Cleghorn WM, Tsakem EL, Song X, Vishnivetskiy SA, Seo J, Chen J, Gurevich EV, Gurevich VV. Progressive reduction of its expression in rods reveals two pools of arrestin-1 in the outer segment with different roles in photoresponse recovery. *PLoS One.* 2011; 6:e22797. [PubMed: 21818392]
- Coffey ET, Smiciene G, Hongisto V, Cao J, Brecht S, Herdegen T, Courtney MJ. c-Jun N-terminal protein kinase (JNK) 2/3 is specifically activated by stress, mediating c-Jun activation, in the presence of constitutive JNK1 activity in cerebellar neurons. *J Neurosci.* 2002; 22:4335–4345. [PubMed: 12040039]
- Crawford ED, Wells JA. Caspase substrates and cellular remodeling. *Annu Rev Biochem.* 2011; 80:1055–1087. [PubMed: 21456965]
- Crotty TM, Nakano T, Stafforini DM, Topham MK. Diacylglycerol kinase δ modulates Akt phosphorylation through pleckstrin homology domain leucine-rich repeat protein phosphatase 2 (PHLPP2). *J Biol Chem.* 2013; 288:1439–1447. [PubMed: 23184957]
- Danial NN, Korsmeyer SJ. Cell death: critical control points. *Cell.* 2004; 116:205–219. [PubMed: 14744432]
- Das S, Cho J, Lambert I, Kelliher MA, Eliopoulos AG, Du K, Tschlis PN. Tpl2/cot signals activate ERK, JNK, and NF-kappaB in a cell-type and stimulus-specific manner. *J Biol Chem.* 2005; 280:23748–23757. [PubMed: 15833743]
- De Smaele E, Zazzeroni F, Papa S, Nguyen DU, Jin R, Jones J, Cong R, Franzoso G. Induction of gadd45beta by NF-kappaB downregulates pro-apoptotic JNK signalling. *Nature.* 2001; 414:308–313. [PubMed: 11713530]
- de Vries JF, Wammes LJ, Jedema I, van Dreunen L, Nijmeijer BA, Heemskerk MH, Willemze R, Falkenburg JH, Barge RM. Involvement of caspase-8 in chemotherapy-induced apoptosis of patient derived leukemia cell lines independent of the death receptor pathway and downstream from mitochondria. *Apoptosis.* 2007; 12:181–193. [PubMed: 17136321]
- DeFea KA, Vaughn ZD, O'Bryan EM, Nishijima D, Dery O, Bunnett NW. The proliferative and antiapoptotic effects of substance P are facilitated by formation of a beta-arrestin-dependent scaffolding complex. *Proc Natl Acad Sci USA.* 2000; 97:11086–11091. [PubMed: 10995467]
- Delbridge AR, Valente LJ, Strasser A. The role of the apoptotic machinery in tumor suppression. *Cold Spring Harb Perspect Biol.* 2012; 4:a008789. [PubMed: 23125015]
- Dempsey PW, Doyle SE, He JQ, Cheng G. The signaling adaptors and pathways activated by TNF superfamily. *Cytokine Growth Factor Rev.* 2003; 14:193–209. [PubMed: 12787559]
- Deng Y, Ren X, Yang L, Lin Y, Wu X. A JNK-dependent pathway is required for TNFalpha-induced apoptosis. *Cell.* 2003; 115:61–70. [PubMed: 14532003]
- Dhanasekaran DN, Reddy EP. JNK signaling in apoptosis. *Oncogene.* 2008; 27:6245–6251. [PubMed: 18931691]
- DiDonato JA, Hayakawa M, Rothwarf DM, Zandi E, Karin M. A cytokine-responsive IkappaB kinase that activates the transcription factor NF-kappaB. *Nature.* 1997; 388:548–554. [PubMed: 9252186]

- Dix MM, Simon GM, Cravatt BF. Global mapping of the topography and magnitude of proteolytic events in apoptosis. *Cell*. 2008; 134:679–691. [PubMed: 18724940]
- Donovan N, Becker EB, Konishi Y, Bonni A. JNK phosphorylation and activation of BAD couples the stress-activated signaling pathway to the cell death machinery. *J Biol Chem*. 2002; 277:40944–40949. [PubMed: 12189144]
- Du C, Fang M, Li Y, Li L, Wang X. Smac, a mitochondrial protein that promotes cytochrome c-dependent caspase activation by eliminating IAP inhibition. *Cell*. 2000; 102:33–42. [PubMed: 10929711]
- Ea CK, Deng L, Xia ZP, Pineda G, Chen ZJ. Activation of IKK by TNF α requires site-specific ubiquitination of RIP1 and polyubiquitin binding by NEMO. *Mol Cell*. 2006; 22:245–257. [PubMed: 16603398]
- Eilers A, Whitfield J, Shah B, Spadoni C, Desmond H, Ham J. Direct inhibition of c-Jun N-terminal kinase in sympathetic neurones prevents c-jun promoter activation and NGF withdrawal-induced death. *J Neurochem*. 2001; 76:1439–1454. [PubMed: 11238729]
- Emery AC, Pshenichkin S, Takoudjou GR, Grajkowska E, Wolfe BB, Wroblewski JT. The protective signaling of metabotropic glutamate receptor 1 is mediated by sustained, beta-arrestin-1-dependent ERK phosphorylation. *J Biol Chem*. 2010; 285:26041–26048. [PubMed: 20566651]
- Eom TY, Roth KA, Jope RS. Neural precursor cells are protected from apoptosis induced by trophic factor withdrawal or genotoxic stress by inhibitors of glycogen synthase kinase 3. *J Biol Chem*. 2007; 282:22856–22864. [PubMed: 17548347]
- Esposito G, Perrino C, Cannavo A, Schiattarella GG, Borgia F, Sannino A, Pironti G, Gargiulo G, Di Serafino L, Franzone A, Scudiero L, Grieco P, Indolfi C, Chiariello M. EGFR trans-activation by urotensin II receptor is mediated by β -arrestin recruitment and confers cardioprotection in pressure overload-induced cardiac hypertrophy. *Basic Res Cardiol*. 2011; 106:577–589. [PubMed: 21369867]
- Fang S, Jensen JP, Ludwig RL, Vousden KH, Weissman AM. Mdm2 is a RING finger-dependent ubiquitin protein ligase for itself and p53. *J Biol Chem*. 2000; 275:8945–8951. [PubMed: 10722742]
- Fogarty MP, Downer EJ, Campbell V. A role for c-Jun N-terminal kinase 1 (JNK1), but not JNK2, in the beta-amyloid-mediated stabilization of protein p53 and induction of the apoptotic cascade in cultured cortical neurons. *Biochem J*. 2003; 371:789–798. [PubMed: 12534344]
- Fulda S, Meyer E, Friesen C, Susin SA, Kroemer G, Debatin KM. Cell type specific involvement of death receptor and mitochondrial pathways in drug-induced apoptosis. *Oncogene*. 2001; 20:1063–1075. [PubMed: 11314043]
- Gao H, Sun Y, Wu Y, Luan B, Wang Y, Qu B, Pei G. Identification of beta-arrestin2 as a G protein-coupled receptor-stimulated regulator of NF-kappaB pathways. *Mol Cell*. 2004; 14:303–317. [PubMed: 15125834]
- Gao Y, Signore AP, Yin W, Cao G, Yin XM, Sun F, Luo Y, Graham SH, Chen J. Neuroprotection against focal ischemic brain injury by inhibition of c-Jun N-terminal kinase and attenuation of the mitochondrial apoptosis-signaling pathway. *J Cereb Blood Flow Metab*. 2005; 25:694–712. [PubMed: 15716857]
- Goldschneider D, Mehlen P. Dependence receptors: a new paradigm in cell signaling and cancer therapy. *Oncogene*. 2010; 29:1865–1882. [PubMed: 20173780]
- Guicciardi ME, Gores GJ. Life and death by death receptors. *FASEB J*. 2009; 23:1625–1637. [PubMed: 19141537]
- Gupta S, Barrett T, Whitmarsh AJ, Cavanagh J, Sluss HK, Dérjard B, Davis RJ. Selective interaction of JNK protein kinase isoforms with transcription factors. *EMBO J*. 1996; 15:2760–2770. [PubMed: 8654373]
- Gurevich EV, Gurevich VV. Arrestins are ubiquitous regulators of cellular signaling pathways. *Genome Biol*. 2006; 7:236. [PubMed: 17020596]
- Gurevich, VV.; Gurevich, EV. Phototransduction: inactivation in rods. In: Dart, D., editor. *Encyclopedia of the eye*. Academic; Oxford: 2009. p. 375-380.
- Gurevich, VV.; Gurevich, EV. Phototransduction: inactivation in cones. In: Dartt, DA., editor. *Encyclopedia of the eye*. Academic; Oxford: 2010. p. 370-374.

- Gurevich VV, Gurevich EV. Synthetic biology with surgical precision: targeted reengineering of signaling proteins. *Cell Signal.* 2012; 24:1899–1908. [PubMed: 22664341]
- Gurevich EV, Benovic JL, Gurevich VV. Arrestin2 expression selectively increases during neural differentiation. *J Neurochem.* 2004; 91:1404–1416. [PubMed: 15584917]
- Gurevich VV, Hanson SM, Song X, Vishnivetskiy SA, Gurevich EV. The functional cycle of visual arrestins in photoreceptor cells. *Prog Retin Eye Res.* 2011; 30:405–430. [PubMed: 21824527]
- Habelhah H, Takahashi S, Cho SG, Kadoya T, Watanabe T, Ronai Z. Ubiquitination and translocation of TRAF2 is required for activation of JNK but not of p38 or NF-kappaB. *EMBO J.* 2004; 23:322–332. [PubMed: 14713952]
- Hanson SM, Gurevich EV, Vishnivetskiy SA, Ahmed MR, Song X, Gurevich VV. Each rhodopsin molecule binds its own arrestin. *Proc Natl Acad Sci USA.* 2007a; 104:3125–3128. [PubMed: 17360618]
- Hanson SM, Van Eps N, Francis DJ, Altenbach C, Vishnivetskiy SA, Klug CS, Hubbell WL, Gurevich VV. Structure and function of the visual arrestin oligomer. *EMBO J.* 2007b; 26:1726–1736. [PubMed: 17332750]
- Hanson SM, Vishnivetskiy SA, Hubbell WL, Gurevich VV. Opposing effects of inositol hexakisphosphate on rod arrestin and arrestin2 self-association. *Biochemistry.* 2008a; 47:1070–1075. [PubMed: 18161994]
- Hanson SM, Dawson ES, Francis DJ, Van Eps N, Klug CS, Hubbell WL, Meiler J, Gurevich VV. A model for the solution structure of the rod arrestin tetramer. *Structure.* 2008b; 16:924–934. [PubMed: 18547524]
- Hara MR, Kovacs JJ, Whalen EJ, Rajagopal S, Strachan RT, Grant W, Towers AJ, Williams B, Lam CM, Xiao K, Shenoy SK, Gregory SG, Ahn S, Duckett DR, Lefkowitz RJ. A stress response pathway regulates DNA damage through β 2-adrenoreceptors and β -arrestin-1. *Nature.* 2011; 477:349–353. [PubMed: 21857681]
- Hara MR, Sachs BD, Caron MG, Lefkowitz RJ. Pharmacological blockade of a β (2) AR- β -arrestin-1 signaling cascade prevents the accumulation of DNA damage in a behavioral stress model. *Cell Cycle.* 2013; 12:219–224. [PubMed: 23287463]
- Harrington AW, Kim JY, Yoon SO. Activation of Rac GTPase by p75 is necessary for c-jun N-terminal kinase-mediated apoptosis. *J Neurosci.* 2002; 22:156–166. [PubMed: 11756498]
- Hetman M, Cavanaugh JE, Kimelman D, Xia Z. Role of glycogen synthase kinase-3 β in neuronal apoptosis induced by trophic withdrawal. *J Neurosci.* 2000; 20:2567–2574. [PubMed: 10729337]
- Hoepfner CZ, Cheng N, Ye RD. Identification of a nuclear localization sequence in β -arrestin-1 and its functional implications. *J Biol Chem.* 2012; 287:8932–8943. [PubMed: 22267743]
- Honda R, Yasuda H. Activity of MDM2, a ubiquitin ligase, toward p53 or itself is dependent on the RING finger domain of the ligase. *Oncogene.* 2000; 19:1473–1476. [PubMed: 10723139]
- Huang SP, Brown BM, Craft CM. Visual arrestin 1 acts as a modulator for N-ethylmaleimide-sensitive factor in the photoreceptor synapse. *J Neurosci.* 2010; 30:9381–9391. [PubMed: 20631167]
- Ichim G, Tauszig-Delamasure S, Mehlen P. Neurotrophins and cell death. *Exp Cell Res.* 2012; 318:1221–1228. [PubMed: 22465479]
- Imamoto Y, Tamura C, Kamikubo H, Kataoka M. Concentration-dependent tetramerization of bovine visual arrestin. *Biophys J.* 2003; 85:1186–1195. [PubMed: 12885662]
- Jones SN, Roe AE, Donehower LA, Bradley A. Rescue of embryonic lethality in Mdm2-deficient mice by absence of p53. *Nature.* 1995; 378:206–208. [PubMed: 7477327]
- Kamata H, Honda S, Maeda S, Chang L, Hirata H, Karin M. Reactive oxygen species promote TNF α -induced death and sustained JNK activation by inhibiting MAP kinase phosphatases. *Cell.* 2005; 120:649–661. [PubMed: 15766528]
- Kang J, Shi Y, Xiang B, Qu B, Su W, Zhu M, Zhang M, Bao G, Wang F, Zhang X, Yang R, Fan F, Chen X, Pei G, Ma L. A nuclear function of β -arrestin1 in GPCR signaling: regulation of histone acetylation and gene transcription. *Cell.* 2005; 123:833–847. [PubMed: 16325578]
- Kim H, Tu HC, Ren D, Takeuchi O, Jeffers JR, Zambetti GP, Hsieh JJ, Cheng EH. Stepwise activation of BAX and BAK by tBID, BIM, and PUMA initiates mitochondrial apoptosis. *Mol Cell.* 2009a; 36:487–499. [PubMed: 19917256]

- Kim HJ, Lee HJ, Jun JI, Oh Y, Choi SG, Kim H, Chung CW, Kim IK, Park IS, Chae HJ, Kim HR, Jung YK. Intracellular cleavage of osteopontin by caspase-8 modulates hypoxia/reoxygenation cell death through p53. *Proc Natl Acad Sci USA*. 2009b; 106:15326–15331. [PubMed: 19706414]
- Kim M, Hanson SM, Vishnivetskiy SA, Song X, Cleghorn WM, Hubbell WL, Gurevich VV. Robust self-association is a common feature of mammalian visual arrestin-1. *Biochemistry*. 2011; 50:2235–2242. [PubMed: 21288033]
- Kim KS, Abraham D, Williams B, Violin JD, Mao L, Rockman HA. β -Arrestin-biased AT1R stimulation promotes cell survival during acute cardiac injury. *Am J Physiol Heart Circ Physiol*. 2012a; 303:H1001–H1010. [PubMed: 22886417]
- Kim M, Vishnivetskiy SA, Van Eps N, Alexander NS, Cleghorn WM, Zhan X, Hanson SM, Morizumi T, Ernst OP, Meiler J, Gurevich VV, Hubbell WL. Conformation of receptor-bound visual arrestin. *Proc Natl Acad Sci USA*. 2012b; 109:18407–18412. [PubMed: 23091036]
- Kiselev A, Socolich M, Vinos J, Hardy RW, Zuker CS, Ranganathan R. A molecular pathway for light-dependent photoreceptor apoptosis in *Drosophila*. *Neuron*. 2000; 28:139–152. [PubMed: 11086990]
- Kohout TA, Lin FS, Perry SJ, Conner DA, Lefkowitz RJ. beta-Arrestin 1 and 2 differentially regulate heptahelical receptor signaling and trafficking. *Proc Natl Acad Sci USA*. 2001; 98:1601–1606. [PubMed: 11171997]
- Kook S, Zhan X, Cleghorn WM, Benovic JL, Gurevich VV, Gurevich EV. Caspase-cleaved arrestin-2 and BID cooperatively facilitate cytochrome C release and cell death. *Cell Death Differ*. 2013 In Press.
- Korsmeyer SJ, Wei MC, Saito M, Weiler S, Oh KJ, Schlesinger PH. Pro-apoptotic cascade activates BID, which oligomerizes BAK or BAX into pores that result in the release of cytochrome c. *Cell Death Differ*. 2000; 7:1166–1173. [PubMed: 11175253]
- Kreuz S, Siegmund D, Scheurich P, Wajant H. NF-kappaB inducers upregulate cFLIP, a cycloheximide-sensitive inhibitor of death receptor signaling. *Mol Cell Biol*. 2001; 21(12):3964–3973. [PubMed: 11359904]
- Kristaponyte I, Hong Y, Lu H, Shieh BH. Role of rhodopsin and arrestin phosphorylation in retinal degeneration of *Drosophila*. *J Neurosci*. 2012; 32:10758–10766. [PubMed: 22855823]
- Krupnick JG, Gurevich VV, Benovic JL. Mechanism of quenching of phototransduction: binding competition between arrestin and transducin for phosphorhodopsin. *J Biol Chem*. 1997; 272:18125–18131. [PubMed: 9218446]
- Kuan CY, Whitmarsh AJ, Yang DD, Liao G, Schloemer AJ, Dong C, Bao J, Banasiak KJ, Haddad GG, Flavell RA, Davis RJ, Rakic P. A critical role of neural-specific JNK3 for ischemic apoptosis. *Proc Natl Acad Sci USA*. 2003; 100:15184–15189. [PubMed: 14657393]
- Kucharczak J, Simmons MJ, Fan Y, Gelinac C. To be, or not to be: NF- κ B is the answer—role of Rel/NF- κ B in the regulation of apoptosis. *Oncogene*. 2003; 22:8961–8982. [PubMed: 14663476]
- Kurokawa M, Kornbluth S. Caspases and kinases in a death grip. *Cell*. 2009; 138:838–854. [PubMed: 19737514]
- Lavrik I, Golks A, Krammer PH. Death receptor signaling. *J Cell Sci*. 2005; 118:265–267. [PubMed: 15654015]
- Lee TH, Huang Q, Oikemus S, Shank J, Ventura JJ, Cusson N, Vaillancourt RR, Su B, Davis RJ, Kelliher MA. The death domain kinase RIP1 is essential for tumor necrosis factor alpha signaling to p38 mitogen-activated protein kinase. *Mol Cell Biol*. 2003; 23:8377–8385. [PubMed: 14585994]
- Lefkowitz RJ, Shenoy SK. Transduction of receptor signals by beta-arrestins. *Science*. 2005; 308:512–517. [PubMed: 15845844]
- Lei K, Davis RJ. JNK phosphorylation of Bim-related members of the Bcl2 family induces Bax-dependent apoptosis. *Proc Natl Acad Sci USA*. 2003; 100:2432–2437. [PubMed: 12591950]
- Le-Niculescu H, Bonfoco E, Kasuya Y, Claret FX, Green DR, Karin M. Withdrawal of survival factors results in activation of the JNK pathway in neuronal cells leading to Fas ligand induction and cell death. *Mol Cell Biol*. 1999; 19:751–763. [PubMed: 9858598]
- Li H, Zhu H, Xu CJ, Yuan J. Cleavage of BID by caspase 8 mediates the mitochondrial damage in the Fas pathway of apoptosis. *Cell*. 1998; 94:491–501. [PubMed: 9727492]

- Li H, Sun X, LeSage G, Zhang Y, Liang Z, Chen J, Hanley G, He L, Sun S, Yin D. β -arrestin 2 regulates Toll-like receptor 4-mediated apoptotic signalling through glycogen synthase kinase-3 β . *Immunology*. 2010; 130:556–563. [PubMed: 20497256]
- Lindsten T, et al. The combined functions of proapoptotic Bcl-2 family members bak and bax are essential for normal development of multiple tissues. *Mol Cell*. 2000; 6:1389–1399. [PubMed: 11163212]
- Lohse MJ, Andexinger S, Pitcher J, Trukawinski S, Codina J, Faure JP, Caron MG, Lefkowitz RJ. Receptor-specific desensitization with purified proteins. Kinase dependence and receptor specificity of beta-arrestin and arrestin in the beta 2-adrenergic receptor and rhodopsin systems. *J Biol Chem*. 1992; 267:8558–8564. [PubMed: 1349018]
- Lovell JF, Billen LP, Bindner S, Shamas-Din A, Fradin C, Leber B, Andrews DW. Membrane binding by tBid initiates an ordered series of events culminating in membrane permeabilization by Bax. *Cell*. 2008; 135:1074–1084. [PubMed: 19062087]
- Luan B, Zhang Z, Wu Y, Kang J, Pei G. Beta-arrestin2 functions as a phosphorylation-regulated suppressor of UV-induced NF-kappaB activation. *EMBO J*. 2005; 24:4237–4246. [PubMed: 16308565]
- Luo X, Budihardjo I, Zou H, Slaughter C, Wang X. Bid, a Bcl2 interacting protein, mediates cytochrome c release from mitochondria in response to activation of cell surface death receptors. *Cell*. 1998; 94:481–490. [PubMed: 9727491]
- Lüthi AU, Martin SJ. The CASBAH: a searchable database of caspase substrates. *Cell Death Differ*. 2007; 14:641–650. [PubMed: 17273173]
- Luttrell LM, Miller WE. Arrestins as regulators of kinases and phosphatases. *Prog Mol Biol Transl Sci*. 2013; 118:115–147. [PubMed: 23764052]
- Mahrus S, Trinidad JC, Barkan DT, Sali A, Burlingame AL, Wells JA. Global sequencing of proteolytic cleavage sites in apoptosis by specific labeling of protein N termini. *Cell*. 2008; 134:866–876. [PubMed: 18722006]
- Manning BD, Cantley LC. AKT/PKB signaling: navigating downstream. *Cell*. 2007; 129:1261–1274. [PubMed: 17604717]
- Mansouri A, Ridgway LD, Korapati AL, Zhang Q, Tian L, Wang Y, Siddik ZH, Mills GB, Claret FX. Sustained activation of JNK/p38 MAPK pathways in response to cisplatin leads to Fas ligand induction and cell death in ovarian carcinoma cells. *J Biol Chem*. 2003; 278:19245–19256. [PubMed: 12637505]
- Martin JH, Mohit AA, Miller CA. Developmental expression in the mouse nervous system of the p493F12 SAP kinase. *Brain Res Mol Brain Res*. 1996; 35:47–57. [PubMed: 8717339]
- McDonald PH, Cote NL, Lin FT, Premont RT, Pitcher JA, Lefkowitz RJ. Identification of NSF as a beta-arrestin1-binding protein. Implications for beta2-adrenergic receptor regulation. *J Biol Chem*. 1999; 274:10677–10680. [PubMed: 10196135]
- McDonald PH, Chow CW, Miller WE, Laporte SA, Field ME, Lin FT, Davis RJ, Lefkowitz RJ. Beta-arrestin 2: a receptor-regulated MAPK scaffold for the activation of JNK3. *Science*. 2000; 290:1574–1577. [PubMed: 11090355]
- McLean S, Bhattacharya M, Di Guglielmo GM. β arrestin2 interacts with T β R2 to regulate Smad-dependent and Smad-independent signal transduction. *Cell Signal*. 2013; 25:319–331. [PubMed: 23069267]
- Mendes HF, van der Spuy J, Chapple JP, Cheetham ME. Mechanisms of cell death in rhodopsin retinitis pigmentosa: implications for therapy. *Trends Mol Med*. 2005; 11:177–185. [PubMed: 15823756]
- Mercurio F, Zhu H, Murray BW, Shevchenko A, Bennett BL, Li J, Young DB, Barbosa M, Mann M, Manning A, Rao A. IKK-1 and IKK-2: cytokine-activated IkappaB kinases essential for NF-kappaB activation. *Science*. 1997; 278:860–866. [PubMed: 9346484]
- Michalak EM, Villunger A, Adams JM, Strasser A. In several cell types tumour suppressor p53 induces apoptosis largely via Puma but Noxa can contribute. *Cell Death Differ*. 2008; 15:1019–1029. [PubMed: 18259198]
- Micheau O, Tschopp J. Induction of TNF receptor I-mediated apoptosis via two sequential signaling complexes. *Cell*. 2003; 114:181–190. [PubMed: 12887920]

- Micheau O, Lens S, Gaide O, Alevizopoulos K, Tschopp J. NF-kappaB signals induce the expression of c-FLIP. *Mol Cell Biol*. 2001; 21:5299–5305. [PubMed: 11463813]
- Miller WE, McDonald PH, Cai SF, Field ME, Davis RJ, Lefkowitz RJ. Identification of a motif in the carboxyl terminus of beta-arrestin2 responsible for activation of JNK3. *J Biol Chem*. 2001; 276:27770–27777. [PubMed: 11356842]
- Mishra R, Barthwal MK, Sondarva G, Rana B, Wong L, Chatterjee M, Woodgett JR, Rana A. Glycogen synthase kinase-3beta induces neuronal cell death via direct phosphorylation of mixed lineage kinase 3. *J Biol Chem*. 2007; 282:30393–30405. [PubMed: 17711861]
- Moaven H, Koike Y, Jao CC, Gurevich VV, Langen R, Chen J. Visual arrestin interaction with clathrin adaptor AP-2 regulates photoreceptor survival in the vertebrate retina. *Proc Natl Acad Sci USA*. 2013; 110:9463–9468. [PubMed: 23690606]
- Montes de Oca Luna R, Wagner DS, Lozano G. Rescue of early embryonic lethality in mdm2-deficient mice by deletion of p53. *Nature*. 1995; 378:203–206. [PubMed: 7477326]
- Morishima Y, Gotoh Y, Zieg J, Barrett T, Takano H, Flavell R, Davis RJ, Shirasaki Y, Greenberg ME. Beta-amyloid induces neuronal apoptosis via a mechanism that involves the c-Jun N-terminal kinase pathway and the induction of Fas ligand. *J Neurosci*. 2001; 21:7551–7560. [PubMed: 11567045]
- Naik E, Michalak EM, Villunger A, Adams JM, Strasser A. Ultraviolet radiation triggers apoptosis of fibroblasts and skin keratinocytes mainly via the BH3-only protein Noxa. *J Cell Biol*. 2007; 176:415–424. [PubMed: 17283183]
- Nair KS, Hanson SM, Mendez A, Gurevich EV, Kennedy MJ, Shestopalov VI, Vishnivetskiy SA, Chen J, Hurley JB, Gurevich VV, Slepak VZ. Light-dependent redistribution of arrestin in vertebrate rods is an energy-independent process governed by protein-protein interactions. *Neuron*. 2005; 46:555–567. [PubMed: 15944125]
- Nakano K, Vousden KH. PUMA, a novel proapoptotic gene, is induced by p53. *Mol Cell*. 2001; 7:683–694. [PubMed: 11463392]
- Namgung U, Xia Z. Arsenite-induced apoptosis in cortical neurons is mediated by c-Jun N-terminal protein kinase 3 and p38 mitogen-activated protein kinase. *J Neurosci*. 2000; 20:6442–6451. [PubMed: 10964950]
- Napetschnig J, Wu H. Molecular basis of NF-kB signaling. *Annu Rev Biophys*. 2013; 42:443–468. [PubMed: 23495970]
- Natoli G, Costanzo A, Ianni A, Templeton DJ, Woodgett JR, Balsano C, Levrero M. Activation of SAPK/JNK by TNF receptor 1 through a noncytotoxic TRAF2-dependent pathway. *Science*. 1997; 275:200–203. [PubMed: 8985011]
- Nikonov SS, Brown BM, Davis JA, Zuniga FI, Bragin A, Pugh ENJ, Craft CM. Mouse cones require an arrestin for normal inactivation of phototransduction. *Neuron*. 2008; 59:462–474. [PubMed: 18701071]
- Ninomiya-Tsuji J, Kishimoto K, Hiyama A, Inoue J, Cao Z, Matsumoto K. The kinase TAK1 can activate the NIK-I kappaB as well as the MAP kinase cascade in the IL-1 signalling pathway. *Nature*. 1999; 398:252–256. [PubMed: 10094049]
- Nishitoh H, Saitoh M, Mochida Y, Takeda K, Nakano H, Rothe M, Miyazono K, Ichijo H. ASK1 is essential for JNK/SAPK activation by TRAF2. *Mol Cell*. 1998; 2:389–395. [PubMed: 9774977]
- Nykjaer A, Willnow TE, Petersen CM. p75NTR—live or let die. *Curr Opin Neurobiol*. 2005; 15:49–57. [PubMed: 15721744]
- O'Donnell MA, Ting AT. Chronicles of a death foretold: dual sequential cell death checkpoints in TNF signaling. *Cell Cycle*. 2010; 9:1065–1071. [PubMed: 20237426]
- Oda E, Ohki R, Murasawa H, Nemoto J, Shibue T, Yamashita T, Tokino T, Taniguchi T, Tanaka N. Noxa, a BH3-only member of the Bcl-2 family and candidate mediator of p53-induced apoptosis. *Science*. 2000; 288:1053–1058. [PubMed: 10807576]
- Okuno S, Saito A, Hayashi T, Chan PH. The c-Jun N-terminal protein kinase signaling pathway mediates Bax activation and subsequent neuronal apoptosis through interaction with Bim after transient focal cerebral ischemia. *J Neurosci*. 2004; 24:7879–7887. [PubMed: 15356200]
- Oleinik NV, Krupenko NI, Krupenko SA. Cooperation between JNK1 and JNK2 in activation of p53 apoptotic pathway. *Oncogene*. 2007; 26:7222–7230. [PubMed: 17525747]

- Oliver TG, Meylan E, Chang GP, Xue W, Burke JR, Humpton TJ, Hubbard D, Bhutkar A, Jacks T. Caspase-2-mediated cleavage of Mdm2 creates a p53-induced positive feedback loop. *Mol Cell*. 2011; 43:57–71. [PubMed: 21726810]
- Papa S, Zazzeroni F, Bubici C, Jayawardena S, Alvarez K, Matsuda S, Nguyen DU, Pham CG, Nelsbach AH, Melis T, De Smaele E, Tang WJ, D'Adamio L, Franzoso G. Gadd45 beta mediates the NF-kappa B suppression of JNK signalling by targeting MKK7/JNKK2. *Nat Cell Biol*. 2004; 6:146–153. [PubMed: 14743220]
- Parant J, Chavez-Reyes A, Little NA, Yan W, Reinke V, Jochemsen AG, Lozano G. Rescue of embryonic lethality in Mdm4-null mice by loss of Trp53 suggests a nonoverlapping pathway with MDM2 to regulate p53. *Nat Genet*. 2001; 29:92–95. [PubMed: 11528400]
- Pobezinskaya YL, Liu Z. The role of TRADD in death receptor signaling. *Cell Cycle*. 2012; 11:871–876. [PubMed: 22333735]
- Povsic TJ, Kohout TA, Lefkowitz RJ. Beta-arrestin1 mediates insulin-like growth factor 1 (IGF-1) activation of phosphatidylinositol 3-kinase (PI3K) and anti-apoptosis. *J Biol Chem*. 2003; 278:51334–51339. [PubMed: 14534298]
- Pugh, EN., Jr; Lamb, TD. Phototransduction in vertebrate rods and cones: molecular mechanisms of amplification, recovery and light adaptation. In: Stavenga, DG.; DeGrip, WJ.; Pugh, EN., Jr, editors. *Handbook of biological physics. Molecular mechanisms in visual transduction*. Elsevier; Amsterdam: 2000. p. 183-255.
- Putcha GV, Le S, Frank S, Besirli CG, Clark K, Chu B, Alix S, Youle RJ, LaMarche A, Maroney AC, Johnson EMJ. JNK-mediated BIM phosphorylation potentiates BAX-dependent apoptosis. *Neuron*. 2003; 38:899–914. [PubMed: 12818176]
- Quoyer J, Longuet C, Broca C, Linck N, Costes S, Varin E, Bockaert J, Bertrand G, Dalle S. GLP-1 mediates antiapoptotic effect by phosphorylating Bad through a beta-arrestin 1-mediated ERK1/2 activation in pancreatic beta-cells. *J Biol Chem*. 2010; 285:1989–2002. [PubMed: 19915011]
- Rabizadeh S, Bredesen DE. Ten years on: mediation of cell death by the common neurotrophin receptor p75(NTR). *Cytokine Growth Factor Rev*. 2003; 14:225–239. [PubMed: 12787561]
- Reinhard C, Shamon B, Shyamala V, Williams LT. Tumor necrosis factor alpha-induced activation of c-jun N-terminal kinase is mediated by TRAF2. *EMBO J*. 1997; 16:1080–1092. [PubMed: 9118946]
- Ren D, Tu HC, Kim H, Wang GX, Bean GR, Takeuchi O, Jeffers JR, Zambetti GP, Hsieh JJ, Cheng EH. BID, BIM, and PUMA are essential for activation of the BAX- and BAK-dependent cell death program. *Science*. 2010; 330:1390–1393. [PubMed: 21127253]
- Revankar CM, Vines CM, Cimino DF, Prossnitz ER. Arrestins block G protein-coupled receptor-mediated apoptosis. *J Biol Chem*. 2004; 279:24578–24584. [PubMed: 15051714]
- Riedl SJ, Salvesen GS. The apoptosome: signalling platform of cell death. *Nat Rev Mol Cell Biol*. 2007; 8:405–413. [PubMed: 17377525]
- Rim J, Oprian DD. Constitutive activation of opsin: interaction of mutants with rhodopsin kinase and arrestin. *Biochemistry*. 1995; 34:11938–11945. [PubMed: 7547930]
- Roff M, Thompson J, Rodriguez MS, Jacques JM, Baleux F, Arenzana-Seisdedos F, Hay RT. Role of IkappaBalpha ubiquitination in signal-induced activation of NFkappaB in vivo. *J Biol Chem*. 1996; 271:7844–7850. [PubMed: 8631829]
- Rojanathammanee L, Harmon EB, Grisanti LA, Govitrapong P, Ebadi M, Grove BD, Miyagi M, Porter JE. The 27-kDa heat shock protein confers cytoprotective effects through a beta 2-adrenergic receptor agonist-initiated complex with beta-arrestin. *Mol Pharmacol*. 2009; 75:855–865. [PubMed: 19176359]
- Salehi AH, Xanthoudakis S, Barker PA. NRAGE, a p75 neurotrophin receptor-interacting protein, induces caspase activation and cell death through a JNK-dependent mitochondrial pathway. *J Biol Chem*. 2002; 277:48043–48050. [PubMed: 12376548]
- Sánchez-Perez I, Murguía JR, Perona R. Cisplatin induces a persistent activation of JNK that is related to cell death. *Oncogene*. 1998; 16:533–540. [PubMed: 9484843]
- Sato S, Sanjo H, Takeda K, Ninomiya-Tsuji J, Yamamoto M, Kawai T, Matsumoto K, Takeuchi O, Akira S. Essential function for the kinase TAK1 in innate and adaptive immune responses. *Nat Immunol*. 2005; 6:1087–1095. [PubMed: 16186825]

- Scaffidi C, Fulda S, Srinivasan A, Friesen C, Li F, Tomaselli KJ, Debatin KM, Krammer PH, Peter ME. Two CD95 (APO-1/Fas) signaling pathways. *EMBO J*. 1998; 17:1675–1687. [PubMed: 9501089]
- Scaffidi C, Schmitz I, Zha J, Korsmeyer SJ, Krammer PH, Peter ME. Differential modulation of apoptosis sensitivity in CD95 type I and type II cells. *J Biol Chem*. 1999; 274:22532–22538. [PubMed: 10428830]
- Schneider-Brachert W, Tchikov V, Neumeyer J, Jakob M, Winoto-Morbach S, Held-Feindt J, Heinrich M, Merkel O, Ehrenschrwender M, Adam D, Mentlein R, Kabelitz D, Schütze S. Compartmentalization of TNF receptor 1 signaling: internalized TNF receptosomes as death signaling vesicles. *Immunity*. 2004; 21:415–428. [PubMed: 15357952]
- Schubert C, Hirsch JA, Gurevich VV, Engelman DM, Sigler PB, Fleming KG. Visual arrestin activity may be regulated by self-association. *J Biol Chem*. 1999; 274:21186–21190. [PubMed: 10409673]
- Scott MG, Le Rouzic E, Perianin A, Pierotti V, Enslen H, Benichou S, Marullo S, Benmerah A. Differential nucleocytoplasmic shuttling of beta-arrestins. Characterization of a leucine-rich nuclear export signal in beta-arrestin2. *J Biol Chem*. 2002; 277:37693–37701. [PubMed: 12167659]
- Seo J, Tsakem EL, Breitman M, Gurevich VV. Identification of arrestin-3-specific residues necessary for JNK3 kinase activation. *J Biol Chem*. 2011; 286:27894–27901. [PubMed: 21715332]
- Sessler T, Healy S, Samali A, Szegezdi E. Structural determinants of DISC function: new insights into death receptor-mediated apoptosis signalling. *Pharmacol Ther*. 2013 in press.
- Shi Y, Feng Y, Kang J, Liu C, Li Z, Li D, Cao W, Qiu J, Guo Z, Bi E, Zang L, Lu C, Zhang JZ, Pei G. Critical regulation of CD4(+) T cell survival and autoimmunity by beta-arrestin 1. *Nat Immunol*. 2007; 8:817–824. [PubMed: 17618287]
- Singhal A, Ostermaier MK, Vishnivetskiy SA, Panneels V, Homan KT, Tesmer JJ, Veprintsev D, Deupi X, Gurevich VV, Schertler GF, Standfuss J. Insights into congenital night blindness based on the structure of G90D rhodopsin. *EMBO Rep*. 2013; 14:520–526. [PubMed: 23579341]
- Slee EA, Keogh SA, Martin SJ. Cleavage of BID during cytotoxic drug and UV radiation-induced apoptosis occurs downstream of the point of Bcl-2 action and is catalysed by caspase-3: a potential feedback loop for amplification of apoptosis-associated mitochondrial cytochrome c release. *Cell Death Differ*. 2000; 7:556–565. [PubMed: 10822279]
- Song X, Raman D, Gurevich EV, Vishnivetskiy SA, Gurevich VV. Visual and both non-visual arrestins in their “inactive” conformation bind JNK3 and Mdm2 and relocalize them from the nucleus to the cytoplasm. *J Biol Chem*. 2006; 281:21491–21499. [PubMed: 16737965]
- Song X, Coffa S, Fu H, Gurevich VV. How does arrestin assemble MAPKs into a signaling complex? *J Biol Chem*. 2009a; 284:685–695. [PubMed: 19001375]
- Song X, Vishnivetskiy SA, Gross OP, Emelianoff K, Mendez A, Chen J, Gurevich EV, Burns ME, Gurevich VV. Enhanced arrestin facilitates recovery and protects rod photoreceptors deficient in rhodopsin phosphorylation. *Curr Biol*. 2009b; 19:700–705. [PubMed: 19361994]
- Song X, Vishnivetskiy SA, Seo J, Chen J, Gurevich EV, Gurevich VV. Arrestin1 expression in rods: balancing functional performance and photoreceptor health. *Neuroscience*. 2011; 174:37–49. [PubMed: 21075174]
- Song X, Seo J, Baameur F, Vishnivetskiy SA, Chen Q, Kook S, Kim M, Brooks EK, Altenbach C, Hong Y, Hanson SM, Palazzo MC, Chen J, Hubbell WL, Gurevich EV, Gurevich VV. Rapid degeneration of rod photoreceptors expressing self-association-deficient arrestin-1 mutant. *Cell Signal*. 2013; 25:2613–2624. [PubMed: 24012956]
- Steller H. Mechanisms and genes of cellular suicide. *Science*. 1995; 267:1445–1449. [PubMed: 7878463]
- Stommel JM, Wahl GM. A new twist in the feedback loop: stress-activated MDM2 destabilization is required for p53 activation. *Cell Cycle*. 2005; 4:411–417. [PubMed: 15684615]
- Tan E, Wang Q, Quiambao AB, Xu X, Qtaishat NM, Peachey NS, Lem J, Fliesler SJ, Pepperberg DR, Naash MI, Al-Ubaidi MR. The relationship between opsin overexpression and photoreceptor degeneration. *Invest Ophthalmol Vis Sci*. 2001; 42:589–600. [PubMed: 11222515]

- Tang G, Minemoto Y, Dibling B, Purcell NH, Li Z-W, Karin M, Lin A. Inhibition of JNK activation through NF- κ B target genes. *Nature*. 2001; 414:313–317. [PubMed: 11713531]
- Thornberry NA, Lazebnik Y. Caspases: enemies within. *Science*. 1998; 281:1312–1316. [PubMed: 9721091]
- Tournier C, Hess P, Yang DD, Xu J, Turner TK, Nimnual A, Bar-Sagi D, Jones SN, Flavell RA, Davis RJ. Requirement of JNK for stress-induced activation of the cytochrome c-mediated death pathway. *Science*. 2000; 288:870–874. [PubMed: 10797012]
- Tsuruta F, Sunayama J, Mori Y, Hattori S, Shimizu S, Tsujimoto Y, Yoshioka K, Masuyama N, Gotoh Y. JNK promotes Bax translocation to mitochondria through phosphorylation of 14-3-3 proteins. *EMBO J*. 2004; 23:1889–1899. [PubMed: 15071501]
- Vaux DL, Haeccker G, Strasser A. An evolutionary perspective on apoptosis. *Cell*. 1994; 76:777–779. [PubMed: 8124715]
- Villunger A, Michalak EM, Coultas L, Müllauer F, Böck G, Ausserlechner MJ, Adams JM, Strasser A. p53- and drug-induced apoptotic responses mediated by BH3-only proteins puma and noxa. *Science*. 2003; 302:1036–1038. [PubMed: 14500851]
- Vines CM, Revankar CM, Maestas DC, LaRusch LL, Cimino DF, Kohout TA, Lefkowitz RJ, Prossnitz ER. N-formyl peptide receptors internalize but do not recycle in the absence of arrestins. *J Biol Chem*. 2003; 278:41581–41584. [PubMed: 12947104]
- Vishnivetskiy SA, Ostermaier MK, Singhal A, Panneels V, Homan KT, Glukhova A, Sligar SG, Tesmer JJ, Schertler GF, Standfuss J, Gurevich VV. Constitutively active rhodopsin mutants causing night blindness are effectively phosphorylated by GRKs but differ in arrestin-1 binding. *Cell Signal*. 2013; 25:2155–2162. [PubMed: 23872075]
- von Haefen C, Wieder T, Essmann F, Schulze-Osthoff K, Dörken B, Daniel PT. Paclitaxel-induced apoptosis in BJAB cells proceeds via a death receptor-independent, caspases-3/-8-driven mitochondrial amplification loop. *Oncogene*. 2003; 22:2236–2247. [PubMed: 12700660]
- Vousden KH, Lane DP. p53 in health and disease. *Nat Rev Mol Cell Biol*. 2007; 8:275–283. [PubMed: 17380161]
- Wagener BM, Marjon NA, Revankar CM, Prossnitz ER. Adaptor protein-2 interaction with arrestin regulates GPCR recycling and apoptosis. *Traffic*. 2009; 10:1286–1300. [PubMed: 19602204]
- Wang C, Deng L, Hong M, Akkaraju GR, Inoue J, Chen ZJ. TAK1 is a ubiquitin-dependent kinase of MKK and IKK. *Nature*. 2001; 412:346–351. [PubMed: 11460167]
- Wang P, Wu Y, Ge X, Ma L, Pei G. Subcellular localization of beta-arrestins is determined by their intact N domain and the nuclear export signal at the C terminus. *J Biol Chem*. 2003a; 278:11648–11653. [PubMed: 12538596]
- Wang P, Gao H, Ni Y, Wang B, Wu Y, Ji L, Qin L, Ma L, Pei G. Beta-arrestin 2 functions as a G-protein-coupled receptor-activated regulator of oncoprotein Mdm2. *J Biol Chem*. 2003b; 278:6363–6370. [PubMed: 12488444]
- Wang WH, Grégori G, Hullinger RL, Andrisani OM. Sustained activation of p38 mitogen-activated protein kinase and c-Jun N-terminal kinase pathways by hepatitis B virus X protein mediates apoptosis via induction of Fas/FasL and tumor necrosis factor (TNF) receptor 1/TNF-alpha expression. *Mol Cell Biol*. 2004; 24:10325–10365.
- Wang Y, Tang Y, Teng L, Wu Y, Zhao X, Pei G. Association of beta-arrestin and TRAF6 negatively regulates Toll-like receptor-interleukin 1 receptor signaling. *Nat Immunol*. 2006; 7:139–147. [PubMed: 16378096]
- Wang L, Du F, Wang X. TNF- α induces two distinct caspase-8 activation pathways. *Cell*. 2008; 133:693–703. [PubMed: 18485876]
- Wang X, Wang J, Jiang X. MdmX protein is essential for Mdm2 protein-mediated p53 polyubiquitination. *J Biol Chem*. 2011; 286:23725–23734. [PubMed: 21572037]
- Watcharasit P, Thiantanawat A, Satayavivad J. GSK3 promotes arsenite-induced apoptosis via facilitation of mitochondria disruption. *J Appl Toxicol*. 2008; 28:466–474. [PubMed: 17849503]
- Wei MC, Lindsten T, Mootha VK, Weiler S, Gross A, Ashiya M, Thompson CB, Korsmeyer SJ. tBID, a membrane-targeted death ligand, oligomerizes BAK to release cytochrome c. *Genes Dev*. 2000; 14:2060–2071. [PubMed: 10950869]

- Wei MC, Zong WX, Cheng EH, Lindsten T, Panoutsakopoulou V, Ross AJ, Roth KA, MacGregor GR, Thompson CB, Korsmeyer SJ. Proapoptotic BAX and BAK: a requisite gateway to mitochondrial dysfunction and death. *Science*. 2001; 292:727–730. [PubMed: 11326099]
- Wilden U. Duration and amplitude of the light-induced cGMP hydrolysis in vertebrate photoreceptors are regulated by multiple phosphorylation of rhodopsin and by arrestin binding. *Biochemistry*. 1995; 34:1446–1454. [PubMed: 7827093]
- Witherow DS, Garrison TR, Miller WE, Lefkowitz RJ. beta-Arrestin inhibits NF-kappaB activity by means of its interaction with the NF-kappaB inhibitor IkappaBalpha. *Proc Natl Acad Sci USA*. 2004; 101:8603–8607. [PubMed: 15173580]
- Wolan DW, Zorn JA, Gray DC, Wells JA. Small-molecule activators of a proenzyme. *Science*. 2009; 326:853–858. [PubMed: 19892984]
- Xu J, Dodd RL, Makino CL, Simon MI, Baylor DA, Chen J. Prolonged photoresponses in transgenic mouse rods lacking arrestin. *Nature*. 1997; 389:505–509. [PubMed: 9333241]
- Xu C, Reichert EC, Nakano T, Lohse M, Gardner AA, Revelo MP, Topham MK, Stafforini DM. Deficiency of phospholipase A2 group 7 decreases intestinal polyposis and colon tumorigenesis in Apc(Min/+) mice. *Cancer Res*. 2013; 73:2806–2816. [PubMed: 23361301]
- Yamamoto K, Ichijo H, Korsmeyer SJ. BCL-2 is phosphorylated and inactivated by an ASK1/Jun N-terminal protein kinase pathway normally activated at G(2)/M. *Mol Cell Biol*. 1999; 19:8469–8478. [PubMed: 10567572]
- Yamaoka S, Courtois G, Bessia C, Whiteside ST, Weil R, Agou F, Kirk HE, Kay RJ, Israël A. Complementation cloning of NEMO, a component of the IkappaB kinase complex essential for NF-kappaB activation. *Cell*. 1998; 93:1231–1240. [PubMed: 9657155]
- Yang DD, Kuan CY, Whitmarsh AJ, Rincón M, Zheng TS, Davis RJ, Rakic P, Flavell RA. Absence of excitotoxicity-induced apoptosis in the hippocampus of mice lacking the Jnk3 gene. *Nature*. 1997; 389:865–870. [PubMed: 9349820]
- Yang J, Lin Y, Guo Z, Cheng J, Huang J, Deng L, Liao W, Chen Z, Liu Z, Su B. The essential role of MEKK3 in TNF-induced NF-kappaB activation. *Nat Immunol*. 2001; 2:620–624. [PubMed: 11429546]
- Yao M, Nguyen TV, Pike CJ. Beta-amyloid-induced neuronal apoptosis involves c-Jun N-terminal kinase-dependent downregulation of Bcl-w. *J Neurosci*. 2005; 25:1149–1158. [PubMed: 15689551]
- Youle RJ, Strasser A. The BCL-2 protein family: opposing activities that mediate cell death. *Nat Rev Mol Cell Biol*. 2008; 9:47–59. [PubMed: 18097445]
- Yu J, Zhang L, Hwang PM, Kinzler KW, Vogelstein B. PUMA induces the rapid apoptosis of colorectal cancer cells. *Mol Cell*. 2001; 7:673–682. [PubMed: 11463391]
- Yuasa T, Ohno S, Kehrl JH, Kyriakis JM. Tumor necrosis factor signaling to stress-activated protein kinase (SAPK)/Jun NH2-terminal kinase (JNK) and p38. Germinal center kinase couples TRAF2 to mitogen-activated protein kinase/ERK kinase 1 and SAPK while receptor interacting protein associates with a mitogen-activated protein kinase kinase upstream of MKK6 and p38. *J Biol Chem*. 1998; 273:22681–22692. [PubMed: 9712898]
- Zanke BW, Boudreau K, Rubie E, Winnett E, Tibbles LA, Zon L, Kyriakis J, Liu FF, Woodgett JR. The stress-activated protein kinase pathway mediates cell death following injury induced by cis-platinum, UV irradiation or heat. *Curr Biol*. 1996; 6:606–613. [PubMed: 8805279]
- Zhan X, Kaoud TS, Dalby KN, Gurevich VV. Non-visual arrestins function as simple scaffolds assembling MKK4–JNK3α2 signaling complex. *Biochemistry*. 2011; 50:10520–10529. [PubMed: 22047447]
- Zhan X, Kaoud TS, Kook S, Dalby KN, Gurevich VV. JNK3 binding to arrestin-3 differentially affects the recruitment of upstream MAP kinase kinases. *J Biol Chem*. 2013; 288:28535–28547. [PubMed: 23960075]
- Zhang QG, Wang XT, Han D, Yin XH, Zhang GY, Xu TL. Akt inhibits MLK3/JNK3 signaling by inactivating Rac1: a protective mechanism against ischemic brain injury. *J Neurochem*. 2006; 98:1886–1898. [PubMed: 16831194]

- Zhang Z, Hao J, Zhao Z, Ben P, Fang F, Shi L, Gao Y, Liu J, Wen C, Luo L, Yin Z. beta-Arrestins facilitate ubiquitin-dependent degradation of apoptosis signal-regulating kinase 1 (ASK1) and attenuate H₂O₂-induced apoptosis. *Cell Signal*. 2009; 21:1195–1206. [PubMed: 19306926]
- Zhang TL, Fu JL, Geng Z, Yang JJ, Sun XJ. The neuroprotective effect of losartan through inhibiting AT1/ASK1/MKK4/JNK3 pathway following cerebral I/R in rat hippocampal CA1 region. *CNS Neurosci Ther*. 2012; 18:981–987. [PubMed: 23095236]
- Zhao J, Pei DS, Zhang QG, Zhang GY. Down-regulation Cdc42 attenuates neuronal apoptosis through inhibiting MLK3/JNK3 cascade during ischemic reperfusion in rat hippocampus. *Cell Signal*. 2007; 19:831–843. [PubMed: 17161586]
- Zhu YC, Zhu YZ, Moore PK. The role of urotensin II in cardiovascular and renal physiology and diseases. *Br J Pharmacol*. 2006; 148:884–901. [PubMed: 16783414]
- Zhuang T, Chen Q, Cho M-K, Vishnivetskiy SA, Iverson TI, Gurevich VV, Sanders CR. Involvement of distinct arrestin-1 elements in binding to different functional forms of rhodopsin. *Proc Natl Acad Sci USA*. 2013; 110:942–947. [PubMed: 23277586]

Fig. 1.

Numerous arrestin functions play a role in apoptosis and cell survival. The activation of the death receptor TNFR1 by TNF α results in the assembly of the multi-protein complex I that activates the NF κ B pathway along with JNK and p38 pathways. The NF κ B signaling is antiapoptotic, mostly via transcriptional activation of FLIP that inhibits caspase-8 activation. Activation of JNK and p38 promotes apoptosis via transcriptional as well as posttranscriptional mechanisms (see text). Signaling complex II formed following internalization and reshuffling of signaling proteins directly activates caspase-8 that cleaves and activates effector caspase-3, caspase-6, and caspase-7 initiating apoptosis. Apoptotic pathway induced via death receptor is known as the extrinsic pathway. Caspase-8 also cleaves BID, generating tBID that translocates to the mitochondria inducing BAX-BAK oligomerization and cytochrome C release. Cytochrome C organizes apoptosome, activating caspase-9, which then activates massive amounts of caspase-3. Apoptosis can also be initiated by a variety of stress stimuli that engage the mitochondria-based apoptotic pathway termed the intrinsic pathway. Specifically, genotoxic drugs and other stimuli causing DNA damage initiate the intrinsic pathway via transcription factor p53 that upregulates pro-apoptotic genes BAX, PUMA, and NOXA. Arrestins have been shown to promote activation of MAP kinases by scaffolding (Chapters 12–14). GPCR-dependent activation of ERK1/2 by both nonvisual arrestins has been shown to provide protection against apoptosis induced by various agents in many cell types. Arrestin-3, but not arrestin-2, is able to activate neuron-specific JNK3 isoform. Although JNK3 has been shown to play an important role in neuronal apoptosis, the evidence of the role of arrestin-3-dependent JNK3 activation in neuronal death is so far lacking. Both arrestin isoforms interact with I κ B α , an inhibitory protein that binds NF κ B and holds it in the cytosol, preventing NF κ B-dependent antiapoptotic transcription. Arrestins have been demonstrated to regulate the activity of the pro-survival Akt pathway. Arrestin-3 is able to reduce the Akt activity via scaffolding Akt together with PP2A that dephosphorylates Akt in response to D2 dopamine receptor stimulation. Arrestins have been shown to stabilize Mdm2 and promote its activation, as well as affect p53 degradation and level (see text for details). Arrestin-2 also interacts with

p53 in the nucleus, acting as important adaptor for Mdm2 required for Mdm2-dependent p53 degradation. Interestingly, caspase-8 that cleaves BID also cleaves arrestin-2 at the C-terminus generating Arr2-(1-380) fragment. Arr2-(1-380) translocates to the mitochondria, directly binds tBID, and greatly enhances its ability to induce cytochrome C release from mitochondria, thereby promoting apoptosis. *Black arrows* indicate direct or indirect posttranslational activation; *black bar*—inhibitory modification; *white arrows*—transcriptional upregulation; *dotted line*—translocation. *Abbreviations:* *TNFR1* TNF α receptor 1, *RIPK1* receptor-interacting serine/threonine-protein kinase 1, *FADD* Fas-associated death domain protein, *TRADD* TNF receptor-associated death domain (TRADD), *TRAF* TNF receptor-associated factor, *FLIP* FLICE-like inhibitory protein (a.k.a. CFLAR, CASP8, and FADD-like apoptosis regulator), *DD* death domain, *DED* death effector domain, *RTK* receptor tyrosine kinase, *GPCR* G protein-coupled receptor