Mitochondria: the indispensable players in innate immunity and guardians of the inflammatory response

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Abstract

Mitochondria, the dynamic organelles and power house of eukaryotic cells function as metabolic hubs of cells undergoing continuous cycles of fusion and fission. Recent findings have made it increasingly apparent that mitochondria essentially involved in energy production have evolved as principal intracellular signaling platforms regulating not only innate immunity but also inflammatory responses. Perturbations in mitochondrial dynamics, including fusion/fission, electron transport chain (ETC) architecture and cristae organization have now been actively correlated to modulate metabolic activity and immune function of innate and adaptive immune cells. Several newly identified mitochondrial proteins in mitochondrial outer membrane such as mitochondrial antiviral signaling protein (MAVS) and with mitochondrial DNA acting as danger-associated molecular pattern (DAMP) and mitochondrial ROS generated from mitochondrial sources have potentially established mitochondria as key signaling platforms in antiviral immunity in vertebrates and thereby orchestrating adaptive immune cell activations respectively. A thorough understanding of emerging and intervening role of mitochondria in toll-like receptor-mediated innate immune responses and NLRP3 inflammasome complex activation has gained lucidity in recent years that advocates the imposing functions of mitochondria in innate immunity. Fascinatingly, also how the signals stemming from the endoplasmic reticulum co-operate with the mitochondria to activate the NLRP3 inflammasome is now looked ahead as a stage to unravel as to how different mitochondrial and associated organelle stress responses co-operate to bring about inflammatory consequences. This has also opened avenues of research for revealing mitochondrial targets that could be exploited for development of novel therapeutics to treat various infectious, inflammatory, and autoimmune disorders. Thus, this review explores our current understanding of intricate interplay between mitochondria and other cellular processes like autophagy in controlling mitochondrial homeostasis and regulation of innate immunity and inflammatory responses.

Keywords Mitochondrial dynamics · Mitophagy · Inflammasome · NLRP3 · Innate immune response · Inflammation

Introduction

Mitochondria, the cellular powerhouses in all the eukaryotic organelles serve as energy storehouses to supply energy when energy needs have to be met. Mitochondria with their dynamic

behavior have now been well acclaimed to be predominantly the cellular entities with both biosynthetic and bioenergetics characteristics. These multi-faceted organelles are capable of executing a wide array of functions which include metabolism, cell proliferation, programmed cell death and in orchestration of the cellular differentiation process (Cheng and Ristow 2013). In addition to their well-appreciated roles in cellular metabolism and programmed cell death, mitochondria perform in eukaryotic cells as centrally positioned hubs in the innate immune system. The ability of these energetically active organelles to swap from their catabolic functions of generating ATP to anabolic activities like *de novo* synthesis of macromolecules, critical for cellular homeostasis and life sustenance enables them to achieve the metabolic demands of different immune cells. Over the last decade, it has been observed that a cellular metabolic shift from catabolic state to an anabolic program essentially drives the transformation of

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immune cells from metabolically quiescent stage to a highly active metabolic state during early or active phase of an immune response (Pearce and Pearce 2013). Thus, metabolic remodelling centrally coordinated by mitochondria has made it one of the evolving organelles controlling the maintenance and establishment of innate and adaptive immune responses (Weinberg et al. 2015; Sandhir et al. 2017). A well orchestrated mitochondrial functioning apart from its role in energy generation is also critical to establish and maintain the both the phenotype and activity of immune cells (Mehta et al. 2017). Strikingly, changes in the mitochondrial shape, size and localisation determined by mitochondrial dynamics events including fusion, fission have now seen to have far reaching consequences in regulating the function of T cells (Liesa and Shrihail 2016). In fact, the mitochondrial morphological changes which are metabolically controlled are also influenced by mitochondrial autophagy (mitophagy) and macroautophagy, critical for mitochondrial turn over and for maintaining both cellular function and intracellular homeostasis (Haroon and Vermulst 2016; Youle and van der Bliek 2012).

Moreover, latest fascinating evidences pinpoint towards active involvement of mitochondria in parallel cellular functions such as inflammatory signalling and generation of pro-inflammatory responses through the interconnection of mitochondrial homeostasis with the latter. Mitochondrial dysfunctions amounting to mitochondrial reactive oxygen species (mROS) production and mitochondrial DNA(mtDNA) release have been enormously responsible for the activation of Nod-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome and subsequent amplification of inflammatory responses (Jo et al. 2016). Since the discovery of (MAVS) aiding in eliciting the type I interferon response during viral infection, this finding has catapulted the role of mitochondria into a regulatory organelle for both immune function and inflammation (Seth et al. 2005). Of late, it is assumed and also seen that there is increased signals stemming from different stressed organelles like endoplasmic reticulum especially targeting mitochondria to promote inflammation through NLRP3 inflammasome activation (Martinon 2017).

Hence, this review focuses on highlighting the emerging functions of mitochondrial dynamics, the mitochondrial signaling components /proteins and mROS and mtDNA leaking out of damaged mitochondria or mitochondrial dysfunctions as players assigning mitochondria as key scaffolds for modulating innate immunity and inflammatory responses. A close functional interplay between mitochondrial dysfunction, insufficient quality control and mitochondrial turn over mechanisms driving mitophagy and their association with many inflammatory pathologies will be discussed in this review, especially with mitochondrial targeted therapeutics holding a great prospective in treatment of diverse pathological conditions.

Mitochondria mediated activation of 'inflammasome': effector of innate immunity and escalator of inflammation

The innate immune response serves as the first line of defense against invading pathogens or any tissue injury by sensing or getting activated by a range of intracellular or surface expressed pattern recognition receptors (PRRs) on the inflammatory cells like macrophages, dendritic cells and neutrophils. The immunity receptors known as the PRRs mediating in turn the inflammatory signaling pathways recognize ligands such as the pathogen-associated molecular patterns (PAMPs) like microbial nucleic acids, lipoproteins, carbohydrates, or the host-derived cellular stress signals known as the damage-associated molecular patterns (DAMPs) which are released by the cells of the host in response to injury or necrotic cell death (e.g., mtDNA, cardiolipin, ATP, and formyl peptides (Brubaker et al. 2015; Mills et al. 2017). Amongst the PRRs well documented, the membrane bound Toll-like receptors (TLRs), the interleukin receptors (ILRs) and the tumor necrosis factor receptors 1 (TNF-R1) and 2 (TNF-R2) majorly activate immune response. These PRRs initiate intracellular signaling cascades such as activation of nuclear factor NF- κ B or cellular kinase, c-Jun amino-terminal kinase (JNK) (Nguyen et al. 2005) upon binding of extracellular ligands like PAMPs & DAMPs to the immune receptors leading to the release of pro-inflammatory cytokines IL-1 β and IL-18 and thereby hastening the inflammatory response (Garlanda et al. 2013). However, unlike the TLR's, the cytoplasmic PRRs categorized as nucleotide-binding domain leucine-rich repeat-containing receptors (NLRs) sense a spectra of intracellular stimuli and are classified into 4 classes (NLRP1, NLRP3, NLRC4 & AIM2) with demonstrated caspase-dependent cytokine activation or inflammatory activity (Franchi et al. 2009).

The NLRP3 inflammasome has been the most well defined and named owing to its caspase-activating multifactor scaffolding assembly and thus holding the center stage of pro-inflammatory responses. NLRP3 or the NACHT, LRR & PYD containing protein, a principal activator of caspase-1, interacts with a caspase recruitment domain (CARD) motif containing adaptor, the apoptosis-associated speck-like protein (ASC) which aids in oligomerization and associates with pro-caspase-1, to form the final NLRP3 inflammasome in macrophages (Fernandes-Alnemri et al. 2007). The binding of caspase-1 to NLRP3 inflammasome leads to autocatalytic cleavage of inactive pro-caspase-1 forming the caspase-1 heterodimer which then subsequently activates inflammatory cytokines IL-1 β and IL-18 from their pro-forms (Gu et al. 1997; Thornberry et al. 1992; Wilson et al. 1994). Although, diverse forms of endogenous and exogenous stimuli like microbial infection, bacterial pore forming toxins, monosodium urate, extracellular ATP etc. activate the NLRP3 inflammasome (Tschopp and Schroder 2010), the exact mechanisms of its

activation by such divergent stimuli of cellular stress remains to be thoroughly investigated and understood.

Moreover, emerging literature precedence now pinpoint towards mitochondrial components encompassing a multitude of factors interacting and activating the NLRP3 inflammasome thereby justifiably crediting mitochondria as a significant contributor to innate immune signaling in macrophages (Zhou et al. 2011).

Mitochondria: a central hub for NLRP3 inflammasome signaling

The role of mitochondria in NLRP3 inflammasome signaling gained prominence when mitochondria as a whole was shown to be recruited in a microtubule dependent manner to the inflammasome within cytoplasm of the macrophages, thus involving yet another host of mitochondrial factors suggestively in inflammasome mediated signaling (Misawa et al. 2013). Furthermore, role of mitochondria in inflammasome signaling got cemented with the observation which saw the co-localization of mitochondria with the NLRP3/ASC/Caspase-1 scaffold assembly upon induction of inflammation. The criticality of mitochondria in orchestrating inflammatory cell death or 'pyroptosis', mediated through the NLRP3 inflammasome reinforces mitochondria as key effector of innate immunity (Jo et al. 2016; Zhou et al. 2011). The first evidence highlighting the mtDNA facilitated induction of an inflammatory response comes from the work by Collins elucidating that ectopic administration of isolated mtDNA can induce arthritis (Collins et al. 2004). Subsequently, it was shown that mitochondrial DAMPs, including formyl peptides and mtDNA, activate human neutrophils via the formyl peptide receptor and TLR9, respectively (Zhang et al. 2010).

The mitochondrial dysfunctions ending in the release of toxic mitochondrial reactive oxygen species (mROS) and the mitochondrial DNA (mtDNA) have been found to be key signals for NLRP3 inflammasome activity (Martinon 2010). For instance, the robust ROS production arising out of the inhibition of ETC complexes, complex I by rotenone or complex II by antimycin A results in activation of the NLRP3 inflammasome (Chen et al. 2003; Won et al. 2015). To add on, inhibition of mitochondrial voltage dependent anion channel (VDAC) abolishes both intracellular ROS generation & inflammasome activity thus indicating a straightforward regulation of NLRP3 inflammasome by mROS production in macrophages (Heid et al. 2013). Interestingly, mtDNA if oxidized and released from mitochondrial matrix into cytoplasm either during apoptosis or as a consequence of accumulation of mitochondrial ROS directly activates the NLRP3 inflammasome and this activation is also under feedback inhibition competitively, by the levels of oxidized dG (8-OHdG) (Shimada et al. 2012). Notwithstanding later studies have put forth that oxidized mtDNA could bind to the NLRP3

inflammasome in apoptotic macrophages, inducing IL-1 β production (Shimada et al. 2012; Nakahira et al. 2011).

These observations are also corroborated by NLRP3^{-/-}, ASC^{-/-} macrophage knockout models where cytosolic translocation of mtDNA is not seen indicating a plausible inflammation induced cytosolic translocation of mtDNA (Nakahira et al. 2011). Although, how such a highly packaged compact circular DNA crosses a double layered membranous organelle into the cytosolic compartment is still elusive and future work by mitochondrial biologists needs to be done to throw some light on this unexplored event. Another immune response, type I interferon response mediated by heightened expression of interferon-stimulated genes (ISGs) is brought about by the cytosolic release of mtDNA that is sensed by DNA sensor cGAS(sensor cytosolic cyclic GMP-AMP synthase), activating the STING (stimulator of interferon genes protein)-IRF3 signaling for generating this response (West et al. 2015). Thus, mtDNA (in the form of DAMPs) apart from triggering TLR-9 mediated inflammatory myocarditis and dilated cardiomyopathy (Oka et al. 2012), has been very recently reported to exert an antiviral function post its release into the circulation mainly due to injury or septic shock ending in pathological endothelial permeability (Sun et al. 2013). Similarly mitochondrial transcription factor A (TFAM) prime mtDNA packaging protein is also reported to facilitate inflammation in hemorrhagic shock (Chaung et al. 2012).

Consequently mitochondrial ROS and mitochondrial DNA release have been vehemently associated with the inflammatory consequences leading to cytokine secretions like IL-1 β as comprehended in the case of an enhanced IL-1 β synthesis observed in the post succinate oxidation triggered ROS production that is attributable to HIF-1 α stabilization (Mills et al. 2016). In continuation, a late report pinpoints towards the translocation of inner mitochondrial membrane lipid, cardiolipin (otherwise thought to be a remnant of cell membrane of prokaryotic cell) to outer mitochondrial membrane due to both ROS-dependent and independent induction of NLRP3 inflammasome where it interacts with NLRP3 inflammasome assembly en route to IL-1 β secretion (Iyer et al. 2013). Thus, mROS and mtDNA cytosolic translocation have proven to be long standing amplifiers of the dangerous inflammatory signals in controlling the innate immune regulation and the inflammatory responses. Very recently, a proactive role of a selective cellular expulsion of damaged mtDNA in response to sustained and mild oxidative stress in pulmonary epithelial cells has been reported by viable (non-necrotic/non-apoptotic) epithelial cells in vitro (Szczeny et al. 2018). The entry of the damaged mtDNA into the cytoplasm is followed by its interaction with ZBP1 leading to triggering of the inflammatory signaling via activation of the TBK1/IRF3 signaling pathway. Adding on, even the extracellular extrusion of damaged mtDNA via exosomes is seen where it triggers inflammation in neighboring unstressed,

naive cells. These processes occur in fully viable cells that are subjected to survivable levels of mtDNA-specific damage. However, the biochemical trait of the extruded damaged mtDNA remains to be explored and defined in addition to mechanisms regulating its cytoplasmic release which need further analysis. So, much still remains to be understood about these dynamic events as to how these mitochondrial factors acting as key inflammatory messengers get dynamically recruited to NLRP3 inflammasome and exact details still eludes the inflammation researchers across the globe.

Pathways and mechanisms checking the organelle integrity such as the mitochondria, the endoplasmic reticulum (ER) and the nuclear envelope are emerging as central component of immune responses to cellular stress and inflammation. Many of the initial work on ER-associated NLRP3 inflammasome activation have provided substantial evidences that NLRP3 inflammasome might be involved in caspase-1 activation with respect to ER-stress. Later, treating the macrophages with compounds that disrupt ER function such as thapsigargin and tunicamycin was found to trigger inflammasome-dependent IL-1 β secretion with the NLRP3 inflammasome responding to ER stress downstream of a previously uncharacterized ER stress response signaling pathway distinct from the UPR (Menu et al. 2012). Two more reassuring studies have advocated that ER-stress may encourage inflammasome activation by mediating the up-regulation of the NLRP3 binding protein TXNIP in insulin-producing β -cells (Lerner et al. 2016; Osowski et al. 2012) although the mechanistic insights awaits further studies. In a study involving microbial infection with the *Brucella abortus* vaccine strain RB51, it was established that ER-stress mediated IRE1 activation engages NLRP3 at the mitochondria eliciting an amplification-loop that amplifies the release of mitochondrial signals such as mROS, further increasing NLRP3 activation (Bronner et al. 2015). Hence, such findings recommend that ER-stress may target the mitochondria to promote inflammasome activation justifying organelle co-operativity in generating inflammatory response via such sharing of inflammatory signals.

Mitochondrial antiviral signaling protein (MAVS): the harbinger of innate immune signaling cascade

Mitochondrial antiviral signaling protein (MAVS), an outer mitochondrial membrane (OMM) protein (Seth et al. 2005), has been attributed to be the chief architect of innate immune signaling response upon viral infections since its discovery in the year 2005 as a novel retinoic acid-inducible gene I (RIG-I) - like receptor (RLR) adaptor protein (Seth et al. 2005; Kawai et al. 2005; Meylan et al. 2005; Xu et al. 2005). MAVS is also known as IFN β promoter stimulator 1 (IPS1), as CARD adaptor inducing IFN β (CARDIF) or as virus-induced signaling adaptor (VISA). MAVS owing to its

OMM locale is suitably expressed for antiviral signaling positioning mitochondria centrally in innate immune response against viral pathogens. MAVS mediated induction of antiviral and inflammatory pathways via activation of pro-inflammatory cytokines, NF- κ B and IRF-3 in an immune response to RNA viruses has been well documented in the past (Seth et al. 2005; Belgnaoui et al. 2011). MAVS, a 540 amino acid protein comprises of three functional domains, a N-terminal CARD domain, a proline rich domain and a trans-membrane (TM) C terminal domain which resembles TM domain containing tail anchored mitochondrial proteins like the Bcl-2 family proteins (Seth et al. 2005). The oligomerization of MAVS could be driven by augmented levels of mROS aiding in type I Interferon (IFN) release that is independent of RNA sensing. This event clearly indicates the pivotal role of MAVS in being a principal sensor of mROS mediated inflammation (Buskiewicz et al. 2016). Furthermore, the association of MAVS with NLRP3 augments its oligomerization leading to caspase-1 activation (Park et al. 2013). Strikingly, MAVS protein is also known to contribute importantly towards the pathophysiologic activity of the NLRP3 inflammasome in vivo and subsequent IL-1 β production by intermediating NLRP3 recruitment to mitochondria (Subramanian et al. 2013). Besides regulating antiviral type I IFN responses, the MAVS protein also elicited the double stranded or dsRNA-induced apoptosis via its interaction with caspase-8 which was independent of the Bax/Bak pathway (El Maadidi et al. 2014). The signaling by MAVS is negatively regulated by the ubiquitin E3 ligases SMURF1, Gp78, and Mul1 (Jacobs et al. 2014; Jenkins et al. 2013; Wang et al. 2012a) as these E3 ligases show notable functional involvement in regulating the removal of mitochondria suggestive of an immunosuppressive role of mitophagy in response to toxic pathogenic stimuli and cellular debris (Fu et al. 2013; Orvedahl et al. 2011). The degradation of MAVS is mediated by ubiquitin ligase Smurf1 (Wang et al. 2012a) whereas signaling by MAVS is governed by inhibitory post-translational modification of RIG-I by Mul1 (Jenkins et al. 2013). Furthermore, MAVS was found to be regulated by GP78 via both ubiquitin-dependent and independent mechanisms. (Jacobs et al. 2014). The dual functions of Smurf1, Mul1 and GP78 in mitophagy and MAVS regulation are overlapping or not still remains mysterious and needs to be proven with documented evidences.

The literature evidences in last decade have begun to unravel the molecular mechanisms by which the MAVS supra-molecular assembly or 'MAVS signalosome' is organized to regulate antiviral responses. Previously, it was illustrated that a TRAF-interaction motif (TIM) within MAVS protein assisted in a direct interaction of MAVS with the signaling factor, TRAF-3 to activate the antiviral immune response (Saha et al. 2006). This finding was then superseded by a recent work that identified a tripartite 14 TRIM14 motif based

interaction with MAVS and NF- κ B within the MAVS signalosome, thus expediting the antiviral immune response (Zhou et al. 2014). Additionally, many TRAF proteins such as TRAF 2, TRAF 5 and TRAF 6 were recruited to MAVS polymers thereby activating IRF-3 signaling (Liu et al. 2013). Even the tyrosine kinase c-abl via its physical and functional interactions positively modulates MAVS protein function as validated by c-abl silencing mediated disruption of NF- κ B and IRF-3 signaling (Song et al. 2010). Intriguingly, the MAVS protein function associated antiviral response is abrogated by mitochondrion-resident E3 ligase MARCH5, via its binding to MAVS which promotes its proteasomal degradation too (Yoo et al. 2015). Not the least, yet another MAVS interacting adaptor protein TAX1BP1 has been identified that helps in recruiting the E3 ligase Itch to MAVS protein signalosome prompting the ubiquitination and degradation of MAVS and blocking viral RNA mediated apoptosis (Choi et al. 2017). Latest work on the NS3 protein of dengue virus has highlighted the binding of this MAVS protein also to 14-3-3 ϵ , an essential cellular protein mediating the cytosol-to-mitochondrial membrane translocation of RIG-I, subsequently averting the translocation of RIG-I to the MAVS protein, which would inhibit antiviral immunity (Chan and Gack 2016). Put together, a plethora of positive and negative regulators via their interaction and post translational modification of MAVS protein coordinate the antiviral immune responses.

Mitochondrial dynamics: watchdogs of OXPHOS, inflammation and innate immunity

The mitochondrial network in eukaryotic cells being highly dynamic engages both fusion and fission events which fluctuate and show reciprocity in their occurrence regularly to modulate the changes in mitochondrial shape, size and localization along with mitochondrial activity. Mitochondria due to such dynamic behavior essentially participate not only in governing mitochondrial integrity and network but also mammalian development, neurodegenerative disorders and apoptosis (Chan 2006; Detmer and Chan 2007). The mitochondrial fusion players or mitofusion proteins, MFN1 and MFN2 are the best characterized outer mitochondrial membrane (OMM) fusion proteins with MFN2 primarily proposed to be associated with tethering between endoplasmic reticulum (ER) and mitochondria (de Brito and Scorrano 2008). The optic atrophy 1 (OPA1) takes care of the inner mitochondrial membrane (IMM) fusion, while the mitochondrial fission is guarded by the fission players such as the fission GTPase, dynamin-related protein 1 (DRP1), mitochondrial fission protein (FIS1) and the mitochondrial fission factor (MFF) (Chan 2006).

Mitochondrial dynamics seems to regulate immune-cell function by orchestrating the functional activities of T cells as evident from the occurrence of both fusion and fission

processes in these cells. The naïve T cells exhibit a fission phenotype with fragmented mitochondria (Ron-Harel et al. 2016). Nonetheless, the memory T cells (T_m cells) display fused and elongated mitochondria with tight cristae which facilitate efficient ETC supercomplex formation and OXPHOS (Fig. 1) in contrast to the effector T cells (T_{eff} cells) which due to increased fission show fragmented mitochondria, have loose cristae organization and therefore less efficient ETC super complex formation and OXPHOS with increased dependency on glycolysis (Buck et al. 2016). However, forcing a mitochondrial fusion supports a phenotype that of memory T cell exhibiting increased OXPHOS and high respiratory capacity (Cassidy-Stone et al. 2008; Wang et al. 2012b). Hence, such distinctively visible mitochondrial dynamics have proven to be pivotal to the function of T cells with OPA1 due to its role in fusion of the IMM and not MFN1 or MFN2, being primarily accountable for the fused morphology of memory T cells that is helpful for cell survival during times of stress (Buck et al. 2016; Mishra et al. 2014). On the contrary, the fragmented or fission morphology is associated with increased ROS production which might contribute to T_{eff} cell activation and proliferation (Frank et al. 2012; Yu et al. 2006).

Recently, mitochondrial dynamics has been documented to be actively implicated in the regulation of RLR signaling bringing forth a new dimension to mitochondria mediated antiviral immune responses. Earlier work has illustrated that MFN2 inhibits RLR signaling through its constitutive interaction with MAVS in high molecular mass complexes (Yasukawa et al. 2009). Furthermore, the overexpression of MFN2 completely abrogated NF- κ B and IRF-3 activation downstream of RIG-I, MDA5 and MAVS whereas loss of endogenous MFN2 as seen in *mf2^{-/-}* murine embryonic fibroblasts (MEFs) show heightened MAVS signaling followed by an increased production of interferon- β (IFN- β) following viral infection (Yasukawa et al. 2009). Strikingly, manipulating only MFN1 expression does not need lead to similar consequences suggestively pinpointing towards a unique role of MFN2 in regulating MAVS signaling independent of its function in mitochondrial fusion.

Nevertheless, with two more literature evidences an additional role of MFN1 was then implicated in RLR signaling. Interestingly, with the demonstrated interaction of MAVS with MFN1, the function of mitochondrial fusion for efficient RLR signaling became markedly strong and was supported by the finding that inhibiting fusion by knockdown of MFN1 or OPA1 attenuated virus induced abrogated NF- κ B and IRF-3 activation (Castanier et al. 2010). On the other hand, depletion of either DRP1 or FIS1 obviously leading to elongated mitochondrial network ended up in increased RLR signaling and supported the previous findings. To add on, it was confirmed that elongated mitochondria in fact promotes the endoplasmic reticulum (ER)-mitochondria interactions during viral

infection thereby augmenting the association of MAVS with stimulator of interferon genes (STING) to boost RLR signaling (Castanier et al. 2010).

Antagonistically, the overexpression of mitochondrial fusion promoting players leads to decrease in mitochondrial membrane potential ($\Delta\psi_m$) culminating in reduced signaling by NF- κ B and IRF-3 (Fig. 1). On the whole, the latest studies till date have argued about mitofusins (MFNs) playing quintessential roles in MAVS mediated antiviral signaling via their interaction with MAVS although much more work needs to be done to bring more lucidity in ascribing definitive functions to these proteins. Consequently, mitochondrial fusion serves as a conducive platform favoring mitochondria-MAM interactions thereby setting up a RLR-MAVS assembly or signalosome for an effective antiviral response post viral infection.

Notably important to mention is that MAVS has also been localized to peroxisomes with a very precise role in early but transient expression of antiviral genes called interferon-stimulated genes (ISGs) (Dixit et al. 2010). Interestingly, mitochondrial MAVS triggers both IFN- β and IFN- λ while peroxisomal MAVS induces IFN- λ in an interferon regulatory factor 1 (IRF1)-dependent manner (Odendall et al. 2014). However, coordination of both mitochondrial and peroxisomal MAVS is mandatory for getting a maximal antiviral response (Fig. 1).

Another noteworthy impact of mitochondrial morphology functionally affecting the CD4⁺ T cells comes from the studies highlighting a stark mitochondrial morphological alteration seen due to deficiency of mitochondrial transcription factor (TFAM) resulting in impaired cristae organization (Baixauli et al. 2015). It was observed that in these TFAM deficient cells (tfam^{-/-} cells) not only the ETC function is compromised owing to decreased amounts of typically the Complex I and Complex III but these cells are more inflammatory in nature with boosted secretion of IFN- γ and IL-6 but lower amounts of cytokine IL-10. The functional binding of TFAM to the mtDNA results in forming the TFAM-bound mtDNA which along with cell free mtDNA can both act as DAMPs and elicit a systemic inflammatory response (Caielli et al. 2016). The likelihood of oxidized TFAM both in the modulation of its binding to mtDNA and the inflammatory milieu of aging signifies an unexplored area of investigation worthy enough to get attention to decipher the precise functionality of TFAM-mtDNA interplay in inflammation and immunity.

Recently certain key players involved in mitochondrial dynamics have been also found to impact inflammation through the NLRP3 activation. It was observed that knockdown of dynamin-related protein 1 (DRP1) causing uncharacteristic mitochondrial elongation lead to a noticeable increase in NLRP3-dependent caspase-1 activation and interleukin-1-beta secretion in mouse bone marrow-derived macrophages (Park et al. 2015). On the other hand, carbonyl cyanide m-chlorophenyl hydrazine (CCCP), a chemical inducer of mitochondrial fission, evidently diminished NLRP3 inflammasome assembly and activation. Additionally, it has also been shown that mitofusin 2, (MFN2) is elaborately linked to NLRP3 inflammasome activation (Ichinohe et al. 2013). Of late, SESN2 (sestrin 2), known as stress-inducible protein has been found to reduce prolonged NLRP3 inflammasome activation probably by prompting mitophagy that removes the damaged mitochondria (Kim et al. 2016a). Taken together, these findings potentially direct towards the burgeoning importance of mitochondrial dynamics in potentiating NLRP3 inflammasome activation, leading to aberrant inflammation.

Hence, perturbations in mitochondrial dynamics, including fusion/fission, ETC architecture and cristae organization, control the metabolic activity and immune function of both innate

and adaptive immune cells and manage the inflammatory responses in mammalian cells.

Defects in mitochondrial autophagy or mitophagy: a by-pass to aberrant inflammation

Autophagy is the cellular self-eating phenomenon, principally involving the mediation of lysosome for degradation of intracellular components during periods of stress like nutrient deprivation as an adaption to survive (Bento et al. 2016). Accumulation of damaged mitochondria leads to heightened ROS production and is accompanied by an increase in cytoplasmic calcium levels followed by cytosolic release of mtDNA and consequently all these result in inflammasome activation (Escames et al. 2012; Ichimura et al. 2003; Maass et al. 2005). Therefore, elimination of damaged/dysfunctional mitochondria by degradation could prove to be detrimental in strategically addressing progressive inflammatory pathologies. Selective or non-selective autophagic removal of mitochondria (also known as mitophagy) prompted by loss of mitochondrial membrane potential ($\Delta\psi_m$) (Elmore et al. 2001) and aimed at controlling mROS production and mitochondrial quality and turnover has proven to be indispensable for sustenance of cellular homeostasis (Kurihara et al. 2012). This process is an extreme attempt by mitochondria to disperse damaged components before whole-sale organelle degradation is elicited and might impact the formation of inflammasome (Gottlieb and Carreira 2010) leading to aberrant inflammatory responses upon defective or inadequate mitophagy (Kim et al. 2016b; Shi et al. 2012). Removing the damaged mitochondria serves as anti-fusion mechanism preventing mitochondrial fusion into a healthy network and thereby stalling the accumulation of toxic mitochondrial products. Thus, lysosome delivery of autophagosome engulfing compromised mitochondria culminates the mitophagy process and when this autophagic clearance of damaged mitochondria is hampered or inadequate it triggers an aberrant inflammasome activation leading to variety of inflammatory, neurodegenerative, aging, myopathies, cardiac and autoimmune diseases (Okamoto and Kondo-Okamoto 2012).

Currently, several mitochondrial proteins either located in the OMM or in IMM have been identified to be mitophagy receptors in mammalian cells. The OMM localized receptors of mitophagy identified till date mainly include BCL2 interacting protein 3 (BNIP3), Nip3-like protein X (NIX) and the FUN14 domain-containing protein1 (FUNDC1) (Lazarou 2015). Fascinatingly, cardiolipin and prohibitin2 (PHB2) which are localized in the IMM have also been shown to serve as mitophagy receptors upon stressful stimuli (Chu et al. 2013; Shen et al. 2017; Wei et al. 2017). Especially, cardiolipin is now known to get externalized to OMM on the damaged mitochondria of neurons and neuronal-like cells

for selective degradation of mitochondria upon treatment of mitophagic stimuli where it has been shown to bind to LC3 to promote engulfment by autophagosome (Chu et al. 2013). Thus, the mitophagy receptors harbor (LC3-interacting region) LIR consensus sequences that are needed for direct binding of these receptors to LC3 and for mitophagy signaling processes (Ploumi et al. 2017). NIX is originally reported to be mediating the mitochondrial turnover and clearance during reticulocyte maturation through its expression (Novak et al. 2010). In addition to canonical LC3 binding NIX is now presumed to control mitophagy via a short cytoplasmic domain sequence known as minimal essential region, the binding elements to this region are yet to be identified and further work in this direction will unravel newer non-canonical mechanisms of NIX mediated regulation of mitophagy (Novak et al. 2010). Other well-known effectors of mitophagy which form an integral part of the mitochondrial surveillance systems monitoring the status of functional/dysfunctional mitochondria encompass the Parkinson's disease proteins PINK1, a serine/threonine kinase and Parkin, a ubiquitin E3 ligase (Geisler et al. 2010; Narendra et al. 2008; Ziviani et al. 2010) and the other ubiquitin ligases GP78, Smurf1 and Muf1 (Jenkins et al. 2013; Fu et al. 2013; Orvedahl et al. 2011). Recently, unconventional involvement of NIX-mediated mitochondrial turnover mechanism was documented in human fibroblasts lacking PINK1 and Parkin opening up a possibility of innovative therapeutic approach for getting rid of malformed mitochondria in Parkinson's disease via non-canonical routes of mitophagy (Koentjoro et al. 2017; Park et al. 2017). The receptor BNIP3 operates in regulating hypoxia-induced mitophagy to prevent detrimental ROS accumulation (Zhang et al. 2008) by increase in its own expression governed by the transcription factor HIF1 α and by phosphorylation of serine residues near its LIR to promote LC3 binding (Zhu et al. 2013). Another mitophagy receptor, FUNDC1 is also known to escalate the mitophagy process upon hypoxic conditions which also promote its LC3 binding too (Liu et al. 2012). FUNDC1 is constitutively expressed under normoxic conditions displaying perturbed LC3 binding due to phosphorylation of FUNDC1 at Ser13 and Tyr 18 by casein kinase II and Src kinase respectively (Liu et al. 2014). Thus phosphorylation and dephosphorylation events differentially modulate the LC3 binding activity of FUNDC1 thereby controlling mitophagy (Chen et al. 2014). Furthermore, the dephosphorylation dependent interaction of FUNDC1 with fission protein, DRP1 and fusion protein, OPA1 has been recently documented that helps FUNDC1 to coordinate mitochondrial dynamics through fission, fusion and mitochondrial quality control through mitophagy (Chen et al. 2016).

The role of two Parkinson's disease (PD)-associated proteins, the mitochondrial kinase PINK1 and the ubiquitin E3-ligase Parkin has become pivotal to ubiquitin mediated mitochondrial quality control, through the accumulation of PINK1

on defective mitochondria, triggering the translocation/phosphorylation of ubiquitin followed by activation of Parkin from the cytosol to mitochondria to mediate the clearance of damaged mitochondria via autophagy (mitophagy) (Kane et al. 2014; Koyano et al. 2014; Lazarou et al. 2013; Sha et al. 2010; Stolz et al. 2014). Thus, mitophagy or selective removal /autophagy of completely dysfunctional mitochondria linked to protein misfolding or depolarization (Narendra et al. 2008) is sequentially governed by post-translational modifications and the function and precise steps and sequence of PTMs in this cascade are only being appreciated lately. In this context, it seems the mitochondria need to deteriorate to an appropriate level to be cleared or to engage the selective autophagy/mitophagy pathway. The healthy mitochondria display sequential proteolysis of PINK1 by peptidase and PARL (Jin et al. 2010; Meissner et al. 2011) which is preceded by transport of PINK1 preprotein into the IMM (Jin et al. 2010; Greene et al. 2012). However, the damaged mitochondria with loss of mitochondrial integrity and membrane potential exhibit blockage of import of PINK1 onto the IMM preventing its proteolytic cleavage sequestering PINK on the OMM which is aided by its interaction with a subunit of the TOM complex, TOM7 (Hasson et al. 2013). This accumulation of PINK1 on the OMM is also triggered in response to the unfolded protein stress in the mitochondrial matrix (Jin et al. 2010). The PINK1 mediated recruitment of Parkin is influenced through the phosphorylation of both Parkin and ubiquitin (Kane et al. 2014; Koyano et al. 2014; Lazarou et al. 2013; Sha et al. 2010; Stolz et al. 2014) activating parkin. The activated parkin on damaged mitochondria orchestrates the polyubiquitination of many OMM proteins including the mitofusin 1 and 2 (MFN1/2), VDAC and TOM20 (Fivenson et al. 2017) thereby targeting some of these proteins like mitofusins to degradation (Chen and Dorn 2nd. 2013; Gegg et al. 2010) and hence blocking fusion and segregating damaged mitochondria from healthy mitochondrial network. As a response towards damage or loss of membrane potential smaller mitochondria are generated which can be simply engulfed by autophagosomal membranes. Thus, PINK1 acts as a molecular sensor for mitochondrial integrity and functionality tagging the dysfunctional mitochondria from the rest of healthy ones for Parkin-mediated degradation. So on and so forth ironically, the mechanistic details of Parkin signaling the recruitment of autophagic machinery still remains ambiguous. One possible hypothesis utilizes the binding of non-degradative ubiquitin chain linkages (e.g., K63) to autophagy adaptors to direct the selective clearance of mitochondria through LC3 and/or GABARAP recruitment. The translocation of the autophagy adaptor p62 to mitochondria upon activation of the PINK1/Parkin pathway promotes mitochondrial clustering, but is not indispensable for mitophagy (Geisler et al. 2010; Narendra et al. 2010). Multiple evidences suggest the contribution of autophagy adaptors to PINK1/Parkin

mediated mitophagy as supported by Parkin mediated ubiquitination of autophagy adaptors NBR1, TAX1BP1 and NDP52 (Sarraf et al. 2013) and increased levels of NBR1 on mitochondria following Parkin translocation (Chan et al. 2011). In light of this, it is intriguing to note the observations highlighting the TBK1-mediated phosphorylation of autophagy receptors like OPTN augmenting selective autophagy of damaged mitochondria that is Parkin independent but PINK1 driven suggesting a novel role of such phosphorylation in amplification of selective autophagy of mitochondria (Richter et al. 2016). Therefore, TBK1 kinase can efficiently target *M. tuberculosis* to autophagosomes (Watson et al. 2012) and possibly mirror PINK1 activity during bacterial infection/xenophagy. Owing to recent observations demonstrating that loss of PINK1 enhances inflammation by impeding the levels of pro- and anti-inflammatory cytokines leading subsequently to cell death, PINK1 of late has emerged to be dynamic regulator of innate immunity (Sun et al. 2018). Interestingly, PINK1-depleted nematodes are found to be sensitive to *P. aeruginosa* infection (Kirienko et al. 2015).

Selective autophagy/mitophagy is also found to be very critical in maintenance of a continuous and sustained mitochondrial function in tissue and organs of high energy demand such as the heart. Clearance of dysfunctional mitochondria in normal cardiomyocytes mitophagy supports the cell survival through removing long lived organelles and proteins (Vasquez-Trincado et al. 2016). The aberrations of the activity of the respiratory chain and ATP production may be considered as a core of mitochondrial dysfunction in cardiac pathological situations. Therefore, at lower level of cardiac stress, mitophagy removes impaired /dysfunctional mitochondria which otherwise results in the enhanced production of reactive oxygen species due to accumulated damaged mitochondria, in the depletion of cell ATP pool, extensive cell damage, and apoptosis of cardiomyocytes (Campos et al. 2016). Loss of a proper control of autophagy was shown to be involved in the pathogenesis of various cardiovascular diseases (CVDs), including ischemic heart disease, cardiac hypertrophy, heart failure, and dilated cardiomyopathy. Mitochondrial dysfunction being an inducer of oxidative stress also serves to be a definitive pro-atherogenic molecular mechanism (Chistiakov et al. 2018). Interestingly, damaging events such as acute cardiac ischemia-reperfusion injury lead to the reduction of the autophagy flux and pharmacological upregulation of autophagy prevents the onset of cell death following ischemia-reperfusion injury (Hamacher-Brady et al. 2006; Sala-Mercado et al. 2010; Yogalingam et al. 2013). In an animal model abrogating mitophagy in Parkin-deficient hearts accumulates dysfunctional mitochondria, leads to oxidative stress, apoptosis, left ventricular dysfunction, and pathological cardiac hypertrophy (Gong et al. 2015). Moreover, defective mitophagy exacerbates cardiac damage induced by myocardial infarction (Narendra et al. 2008). Such studies expose the

essentiality of an orchestrated process of elimination of damaged mitochondria during stress conditions (i.e., myocardial infarction or heart failure) in order to guard against oxidative stress and apoptosis and therefore, contributing to the maintenance of cardiac physiology.

Current literature evidences have also speculated the accumulation of ROS (reactive oxygen species) in aging mammalian cells due to mtDNA mutations or defective OXPHOS complex due to aging. It's now known that ROS generated due to faulty mitochondrial biogenesis leading to metabolic stress would be an amplifying signal for eliciting mitophagy or selective autophagy. Several studies have highlighted the immunogenic capabilities of defective mitochondria (Krysko et al. 2011) with impaired mitochondrial metabolism leading to increased mitochondrial ROS (mtROS) levels and defective ion homeostasis. Infections caused by pathogens are now known to impair mitochondrial homeostasis mediating mtDNA release, excessive mtROS production, and subsequently inflammasome stimulation as seen mainly in case of macrophages. Accordingly, several studies advocate that augmented mtROS levels are required for the bactericidal activity of macrophages (Hall et al. 2013; West et al. 2011). For instance, blocking autophagy in macrophages results in mROS production leading to mitochondrial damage and in turn inflammasome activation (Zhou et al. 2011; Rodgers et al. 2014). It has been strongly documented that there is contrasting influences on the macrophage activity governed by their reliance on the metabolic pathways they depend upon. For instance, M1 macrophages activity is mostly affected by glycolysis and PPP while mitochondrial OXPHOS and TCA capacities are decreased (Weinberg et al. 2015; Haschemi et al. 2012) while M2 macrophages activity relies more on FAO, mitochondrial OXPHOS, and TCA, but less in glycolysis and PPP fluxes (Van den Bossche et al. 2016). Notably, by products of mitochondrial metabolism, such as mtROS, have also been involved in innate immune responses and macrophages activity and mtROS production has been shown to mediate inflammatory cytokine secretion (Chandel et al. 2001). Taken together mitochondrial homeostasis and mitophagy have proven decisive for functional behavior of macrophages.

So on and so forth, it has been demonstrated that in LC3 or Beclin 1 deficient cells displaying marginal increase in optimum ROS levels and cytosolic leakage of mtDNA actually led to the induction of NLRP3 inflammasome supplemented with release of cytokine IL-1 β (Nakahira et al. 2011). Similarly, during RLR signaling autophagy flawed macrophages or autophagy deficient MEFs accumulated damaged mitochondria thereby amplifying the inflammatory signals and signaling pathways (Tal and Iwasaki 2011), possibly due to increase in MAVS due to damaged mitochondria and maintaining consistently high levels of mROS (Tal et al. 2009). Conversely, scavenging the mROS could prove

beneficiary in curbing inflammation where in, this kind of protective mitophagy generates pro-survival signals as evident in generation of memory NK cells (O'Sullivan et al. 2015). In another instance, initiating autophagy by FoxO1 has been shown to boost NK cell development and functionality leading to an effective antiviral immune response (Wang et al. 2016).

Thus, it is prevalent now that activation of autophagy and fine-tuning of mitophagy in particular is critical for maintenance of a fine balance between appropriate inductions of innate immune response via essentially ensuring mitochondrial homeostasis. A plethora of well-coordinated molecular mechanisms preserve cellular and organismal survival in a context and dose dependent fashion in response to internal/external stimuli to mediate the process of mitophagy and de-regulation of which eventually leads to systemic unsolved inflammation with tissue collapse. Moreover, it still remains to be worked out if potent therapeutic strategies for several pathologies such as immune disorders, cancer, and neurodegeneration could comprise of the pharmacological stimulation or inhibition of mitophagy. Mounting studies pinpoint that persistent cellular feedback responses mediated by mitophagy maintain a functional mitochondrial cohort inside the cells to regulate innate immunity.

Mitochondria targeted therapeutics: is it a great promise for treatment of diverse inflammatory disease pathologies?

Mitochondria are emerging as not only energy supplying machineries but also as a repertoire of various biological machines working in a communion or balance to maintain cellular homeostasis. Thus, a minute anomaly or asynchrony in such a delicate balance ends up in several abnormalities like perturbation in mitochondrial membrane potential ($\Delta\psi_m$), imbalance in TCA intermediates, mtDNA associated damage, mROS production etc. Most of these processes, either directly or indirectly impact the cellular immune response which subsequently manifest the consequences of various immune-cell dysfunctions and even inflammatory disorders. Numerous studies have indicated that such mitochondrial anomalies are associated with NLRP3 activation in disease conditions like Alzheimer's disease (AD) (Heneka et al. 2013), Parkinson's disease (PD) (Jha et al. 2010; Zhou et al. 2016), type 2 diabetes, atherosclerosis (Guo et al. 2015), gout, renal injury and cancer (Leemans et al. 2011). Mitochondrial dysfunction could occur upstream of NLRP3 activation by providing triggers for such activation in the neuro-pathological processes (Won et al. 2015) where in buildup of protein aggregates like Lewy bodies, senile plaques, or PrPsc can excite the activity of inflammasome induced production of pro-inflammatory cytokines in microglial cells (Gustin et al. 2015). Strikingly, in most of the demyelinating diseases like multiple sclerosis

(MS) and AD, deactivation of inflammasome complex has shown to be defensive in nature. Thus, inhibitors of NLRP-3 inflammasome has already shown great promise for developing interesting therapeutics for such diseases and therefore current efforts are directed towards therapeutics that target mitochondria mediated NLRP3 inflammasome activation or mitochondrial dysfunctions affecting immune cell function which may hold great promise in the treatment of diverse disease and pathological conditions.

In the pursuance of such therapeutic targets, interestingly treatment with Lithium chloride, a GSK3 β inhibitor, has been shown to prevent hippocampal neuronal apoptosis induction after radiation exposure (Yazlovitskaya et al. 2006) by abrogating GSK3 β mediated phosphorylation of VDAC in OMM and apoptotic induction. Also, many of the natural and artificial uncouplers (UCPs) like fatty acids, proteins, and carbonyl cyanide m-chlorophenylhydrazone (CCCP) work by lowering membrane potential and impeding mROS (Heinen et al. 2007) thereby being implicated potentially in pathogenesis of numerous disorders including obesity, type-2 diabetes (Gao et al. 2015), aging and tumor progression (Woyda-Ploszczyca and Jarmuszkiewicz 2008).

Accordingly, the newly discovered and identified mROS scavengers have now boomed to be novel potential therapeutic targets adopted for treatment in mitochondria related disorders like AD, PD, amyotrophic lateral sclerosis (ALS). For instance, NO scavengers like cPTIO (partial inhibitor of complex I) and FeTPPS and MnTBAP (complete blockers of complex I) have been identified as effective but now in experimental stages. In addition, MitoQ10 and MitoVit E (homologues of ubiquinone and vitamin E respectively) possess better ROS scavenging activity and enhanced ETC function (Li et al. 2013). CoQ10, a natural antioxidant which acting as a mobile electron carrier between complexes I and III or complexes II and III, shows great promise by impeding brain mitochondrial dysfunctions induced by A β neurotoxicity on brain mitochondria (Moreira et al. 2002). Yet another interesting therapeutic intervention which has surfaced over the years has been the switching of the pro-inflammatory macrophages M1 to the anti-inflammatory macrophages, M2 by the usage of anti-inflammatory agents like metformin and rotenone which decrease LPS-induced pro-IL-1 β and ROS while boosting IL-10 (Kelly et al. 2015). Metformin is predicted to target complex I of the ETC to decrease RET, ROS and pro-IL-1 β production (Jha et al. 2015). Since, its observed that mitochondrial involvement in the development of insulin resistance appears to occur via elevated mitochondrial ROS production, rather than decreased OXPHOS activity per se (Pospisilik et al. 2007), utilizing mROS scavenging drugs like metformin has thrown some light towards anti-diabetic therapeutics. Fascinatingly, the oxidized form of xanthine dehydrogenase, xanthine oxidase (XO) contribute to the formation of uric acid as well as mROS manifesting in the form of inflammatory

disease condition, gout. As a therapeutic strategy inhibition of XO was discovered to diminish inflammasome activation, signifying that drugs used in gout to target XO and lower uric acid levels, may also impact mitochondria-triggered inflammation (Ives et al. 2015).

In recent years, clinical therapies to combat leukemia, lymphomas and solid tumors involve T cell immunotherapies, including checkpoint-inhibitor blockade, engaging chimeric antigen receptor (CAR) T cells and adoptive cell transfer. With plethora of metabolic information available about the T cells implicated in anti-tumor responses, this has been of great advantage. Chronic infections along with cancer results in T cell exhaustion (Crawford et al. 2014; Wherry and Kurachi 2015) executed by co-inhibitory molecule PD-1 and is associated with reduced mitochondrial respiration and glycolysis, and the exhausted T cells have fused, depolarized mitochondria and increased ROS compared with effector T cells (T_{eff} cells). PD-1, known to orchestrate metabolic dysregulation negatively regulates the transcription coactivator PGC-1 α , thereby upsetting mitochondrial biogenesis. Overexpression of PGC-1 α in T cells transferred to mice with established tumors led to increased mitochondrial mass, rendering the T cells with antitumor immunity (Scharping et al. 2016). PGC-1 α may therefore represent a therapeutic target for reviving exhausted CD8 $^{+}$ T cells in diverse settings (Bengsch et al. 2016). Nonetheless, in patients with metastatic cancer, adoptive T cell transfer has shown great effectiveness in disease regression. Hence for this beneficial strategy, the choice of T cells with low mitochondrial membrane potential as an indicator of improved metabolic fitness, associated with better long-term in vivo persistence and an enhanced capacity to eradicate established tumor has been much easier. This metabolic sorting coupled procuring of the T cells with high survival capacity has been a real promising option to choose against the T cells with high mitochondrial membrane potential (Sukumar et al. 2016) and low survival rates. Additionally, several mutations in mtDNA are supposed to be responsible for nearly 120 syndromes involving mitochondrial proteins (Chinnery and Hudson 2013) have exposed open are of mitochondria based cellular therapy. With the recent work highlighting about reduction in cytosolic mtDNA leading to inhibition in IFN β induction in *Mycobacterium tuberculosis* infected macrophages post treatment with mitochondria specific MitoQ (Wiens and Ernst 2016), it has opened up new vistas for therapeutic interventions targeting mtDNA release. Even, carefully obstructing mutant mtDNA replication by peptide nucleic acid, allowing wild type mtDNA replication is predicted to be a potent remedy for many mitochondria associated inflammatory disorders (Taylor et al. 1997).

Excitingly, mitochondrial dysfunctions prominently resulting in activation of innate response have been implicated in diverse pathological conditions and efforts have been focused towards modulation of mitochondria mediated

inflammasome activation that eventually might provide novel therapeutic approaches to work on disease conditions with altered pathogenic axis involving mitochondria and inflammation. Thus, these therapies and the signaling cascades have cemented a path or horizon for looking forward to a tantalizing array of therapeutic possibilities for inflammatory diseases and cancer.

Conclusions

Mitochondria have gained attention now as a centrally positioned signaling hub for coordinating the signaling networks associated with innate immunity, autophagy and inflammation besides their ancestral and hierarchical function as cellular energy suppliers. The requirement of the innate immune activation for the cellular energy output and substantial metabolic reprogramming has bring forth the integration of mitochondria into this arm of immunity which has necessarily evolved to establish and enhance the cross talk between metabolism and innate immune pathways. Hence, the precise interactions of mitochondrial factors with innate inflammatory factors especially the NLRP3 and its inflammasome amalgamates two previously not much linked fields of cell biology, immunity and inflammation. These interactions essentially are of paramount medical importance considering the fact that increased inflammation is now emanating as a key contributory factor to the onset of a wide range of rapidly expanding pathological diseased conditions and disorders. Amongst the various mitochondrial factors, the MAVS protein as discussed in this review establishes itself as a key player in regulation of RLR signaling and antiviral immune responses with its set of positive and negative regulators of antiviral immune signaling pathways. Mitochondrial dynamics also with its fusion and fission players plays its significant part in regulating organelle cross talk mediated antiviral signaling as evident through ER-mitochondria mediated signaling at the shared membranes, the MAMs. However, with more details concerning the nucleation of RLR signaling at the interface between mitochondria and MAMs being added to existing literature, the future will undoubtedly identify new mitochondrial molecules that regulate MAVS signaling and explore other mitochondrial proteins that might be critical for RLR signaling. Emerging evidence pinpoints that both autophagy and mitophagy play definitive roles in the control of mitochondrial homeostasis and regulation of innate and inflammatory responses. The participation of mROS levels and status of mtDNA and its intracellular release cannot be neglected keeping in view about the consequences that these two factors have on the mitochondria mediated NLRP3 inflammasome activation.

With unraveling of the dynamics and bioenergetics of stress and inflammation in human disease, understanding the intrinsic mechanistic connections of inflammatory signaling

with mitochondrial biology will prove the vitality of such a connection to cellular homeostasis and human health. The future of mitochondria dependent inflammatory and immune signaling in mammals not only involves identifying ancillary relevant proteins but in addition provide a clear understanding of the signaling pathways regulating inflammatory and immune responses. Therefore, untying such complicated mitochondrial signaling networks will unambiguously increase the number of useful targets for therapies opening up new vistas for developing therapeutic strategies for acute and chronic pathological and inflammatory disorders.

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Compliance with ethical standards

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