Published in final edited form as:

Cell Mol Life Sci. 2012 February ; 69(4): 487–500. doi:10.1007/s00018-011-0760-0.

The biology of interleukin-1: emerging concepts in the regulation of the actin cytoskeleton and cell junction dynamics

Pearl P. Y. Lie, C. Yan Cheng, and Dolores D. Mruk

Center for Biomedical Research, Population Council, 1230 York Avenue, New York, NY 10065, USA

Dolores D. Mruk: d-mruk@popcbr.rockefeller.edu

Abstract

Interleukin (IL)-1 is a proinflammatory cytokine with important roles in innate immunity, as well as in normal tissue homeostasis. Interestingly, recent studies have also shown IL-1 to function in the dynamics of the actin cytoskeleton and cell junctions. For example, treatment of different epithelia with IL-1 α often results in the restructuring of the actin network and cell junctions, thereby leading to junction disassembly. In this review, we highlight new and interesting findings that show IL-1 to be a critical player of restructuring events in the seminiferous epithelium of the testis during spermatogenesis.

Keywords

Interleukin; Cytokine; Testis; Sertoli cell; Cell junction; Actin cytoskeleton

Introduction

Interleukin (IL)-1 is a potent proinflammatory cytokine capable of triggering multiple physiological processes such as activation of lymphocytes, induction of acute-phase hepatic proteins, infiltration of leukocytes at sites of infection, fever and anorexia [1, 2], clearly indicating that this cytokine is critical for innate immune response. Since the characterization of the IL-1 α and IL-1 β sequences more than two decades ago [3, 4], several new members have been added into the growing IL-1 family (e.g., IL-33 [5], also known as IL-1F11), and they have also been demonstrated to have roles in inflammation and host defense. In contrast to IL-2, which is a product of lymphocytes, IL-1 family members are products of macrophages. Furthermore, misregulation of IL-1 is known to underlie the pathogenesis of a myriad of auto-inflammatory diseases that are treatable by IL-1 receptor blockade [1, 6]. For example, in patients with familial cold autoinflammatory syndrome, the administration of IL-1 receptor antagonist prevented the onset of acute inflammatory symptoms, which were triggered by cold exposure [7]. Notwithstanding the proinflammatory nature of IL-1, the α subtype of this cytokine also has normal physiological roles, and it is known to participate in the regulation of cell proliferation and differentiation [8, 9], illustrating the breadth of IL-1 function. Interestingly, growing evidence has revealed that IL-1 signaling frequently targets the actin cytoskeleton during both inflammatory conditions and normal tissue homeostasis [10, 11]. In this review article, we highlight the emerging role of IL-1 in the restructuring of cell junctions and the cytoskeleton in epithelia and other tissues. In particular, we discuss the activities of IL-1 α in the seminiferous

epithelium, where it coordinates junction restructuring events at the blood–testis barrier (BTB) and Sertoli–germ cell adhesion throughout the seminiferous epithelial cycle of spermatogenesis [12, 13].

Overview of IL-1 properties and signaling

IL-1 is the founding member of the IL-1 family of ligands, which is currently constituted by 11 members including both agonist molecules that are capable of activating receptor-mediated signaling (e.g., IL-1 α , IL-1 β , IL-18 and IL-33) and antagonist molecules (e.g., IL-1 receptor antagonist [IL-1Ra]) [1]. In conventional terms, IL-1 α and IL-1 β are collectively referred to as IL-1, which was initially reported to be a fever-inducing proinflammatory substance but later shown to consist of two distinct gene products [14]. These two IL-1 subtypes, together with their physiological inhibitor IL-1Ra, are perhaps the most well studied members of the IL-1 family. In this section, we discuss the general properties and the signaling/non-signaling roles of IL-1. For additional background information, interested readers are referred to two recent reviews [1, 15].

The biogenesis of IL-1

IL-1 α and IL-1 β are both expressed as 31-kDa precursors (proIL-1), each of which is encoded by a distinct gene and are the products of macrophages [16]. While in vitro experiments using recombinant mature proteins have shown IL-1 α and IL-1 β to exhibit similar biological effects, in vivo, however, they have distinct physiological roles and regulatory mechanisms. For instance, IL-1 β must be processed into a mature protein for optimal activity, but its counterpart has activity as both a mature and a precursor protein which is partly due to proIL-1 α 's ability to bind IL-1 receptor type I (IL-1RI) [17]. These intracellular precursors are cleaved by cysteine proteases into a propeptide and a mature 17-kDa protein. Specifically, proIL-1 α is processed by calpain [18], whereas proIL-1 β is processed by caspase-1 (formerly known as IL-1 β -converting enzyme) [19]. Indeed, mice lacking caspase-1 are defective in the maturation of proIL-1 β and IL-18 [20, 21].

IL-1 secretion does not adhere to the classical endoplasmic reticulum–Golgi route given that both IL-1 subtypes lack a signal peptide [22]. Instead, IL-1 β maturation and secretion require the assembly of large (i.e., ~700 kDa) multi-protein complexes known as inflammasomes [23, 24]. In essence, the inflammasome is a molecular scaffold that directs caspase-1 activation for the cleavage of proIL-1 β . A similar mechanism exists for IL-18 as well [24]. The assembly and activation of inflammasomes can be triggered by infection, stress, reactive oxygen species and cell disruption; and their activation has been linked to such diseases as type II diabetes and gout [24, 25]. Several prototypical inflammasomes are known to exist, and each of them contains a distinct NOD-like receptor (NLR) such as NALP1 (NACHT, LRR and PYD-containing protein 1) [24, 26]. NLR proteins are intracellular pathogen sensors that facilitate the assembly of other inflammasome components, including the adaptor protein ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain), the effector procaspase-1, as well as other inflammatory caspases (e.g., caspase-5 and -11) [24, 26, 27]. In addition to the conformational change in procaspase-1 that is induced by its recruitment to inflammasomes, the activation of procaspase-1 requires a secondary stimulus that produces ionic perturbations in cells [26]. One example of such a stimulus is the activation of P2X₇ receptor, a member of the P2 family of nucleotide receptors, and an ATP-gated ion channel permeable to Na⁺, K⁺, and Ca²⁺ [28, 29]. P2X₇ receptor activation triggers the influx of Na⁺ and Ca²⁺ and the efflux of K⁺ from cells (e.g., macrophages), which in turn promotes caspase-1 activation, resulting in proIL-1 β cleavage [25, 30]. In fact, several findings have indicated that stimulation of the P2X₇ receptor can activate c-Jun N-terminal kinases (JNK) 1 and 2, extracellular signal-regulated kinases (ERK) 1 and 2, and p38 mitogen-activated

protein kinase (MAPK) [31–33]. Taken together, IL-1 β maturation is a tightly regulated process with complex underlying signaling pathways.

The release of mature IL-1 β from cells is mediated by at least two different secretory pathways. First, the exocytosis of IL-1 β characterized by Andrei et al. [34] involves the loading of proIL-1 β and procaspase-1 into secretory lysosomes, which eventually results in the externalization of mature IL-1 β and other lysosomal contents in a phospholipase-dependent manner [34]. Alternatively, IL-1 β is secreted by the budding of small plasma membrane blebs (i.e., microvesicles) [35]. This has been visualized by the live imaging of activated monocytes, in which bioactive IL-1 β -containing membrane blebs were rapidly shed from the plasma membrane shortly after exposure to 3'-O-(4-benzoylbenzoyl) ATP (BzATP), a synthetic P2X₇ receptor agonist [35]. On a final note, unlike IL-1 β , which is largely secreted by activated immune cells (e.g., monocytes, dendritic cells and neutrophils), IL-1 α is hardly ever detected in sera or in bodily fluids during inflammation, and its occasional presence may simply be due to IL-1 α being released from dying cells [36]. Instead, IL-1 α is generally believed to function intracellularly and/or at the cell surface where a membrane-bound myristoylated form of proIL-1 α has been reported to exist [37]. However, the testis appears to be an exception since secreted IL-1 α can be detected in the fluids within this organ such as in seminiferous tubular and rete testis fluids under normal circumstances [38], which will be discussed later.

Receptor-mediated IL-1 signaling

There are two types of receptors that bind IL-1, namely IL-1 receptor type I and type II (IL-1RI and IL-1RII, respectively) [1]. Of these, signaling is mediated exclusively by IL-1RI, a member of the interleukin-1 receptor (IL-1R)/Toll-like receptor (TLR) superfamily [39] (Fig. 1), whereas IL-1RII is a prototypical decoy receptor with regulatory functions [40, 41]. For both receptors, the IL-1/IL-1R complex recruits a co-receptor known as IL-1 receptor accessory protein (IL-1RAcP) [42, 43], thereby resulting in the formation of a heterodimeric receptor complex that is essential for IL-1RI-mediated signal transduction (Fig. 1). Signaling is initiated by the juxtaposition of Toll-IL-1 receptor (TIR) domains present within the cytoplasmic tails of IL-1RI and IL-1RAcP [44]. Basically, these events lead to the recruitment of myeloid differentiation primary response gene 88 (MyD88), an adaptor protein that in turn recruits IL-1 receptor associated kinases (IRAKs) [45, 46]. Four IRAKs are known to exist, IRAKs-1 through -4 [47–49]. Of these, IRAK-3 (or IRAK-M) lacks intrinsic kinase activity and is a negative regulator of TLR signaling, whereas IRAK-4 is indispensable for IL-1R/TLR signaling [46]. Within the IL-1RI signaling complex, IRAK-4 kinase activity promotes the phosphorylation and activation of IRAK-1, which in turn recruits tumor necrosis factor receptor-associated factor (Traf)-6 [39, 50]. The subsequent dissociation of these kinases from the receptor complex and the recruitment of downstream signaling molecules, ultimately result in the activation of nuclear factor- κ B (NF- κ B) and MAPK pathways [39, 50, 51] (Fig. 1). IL-1RII, on the other hand, does not possess a TIR domain, and the resulting heterodimeric receptor complex is non-signaling [44]. Hence, its sequestration of IL-1 and the co-receptor IL-1RAcP negatively regulates IL-1RI-mediated signaling. Adding to the intricacy, IL-1RII was also found to be required for proIL-1 α activity in the nucleus [52], illustrating its involvement in a wide range of biological processes within cells.

Non-receptor-mediated proIL-1 α signaling

There is evidence to suggest that intracellular IL-1 α , especially nuclear-localized proIL-1 α , also participates in signaling events that are beyond those of the classical IL-1RI-mediated pathway. First, proIL-1 α exhibited biological activity that was independent of IL-1 signaling mediated by cell surface receptors [53]. In endothelial cells for instance, overexpression of a

proIL-1 α fusion protein inhibited cell proliferation, and this effect was insensitive to the addition of exogenous IL-1Ra, which would have blocked cell surface receptors [53]. Second, proIL-1 α (but not proIL-1 β) can be actively imported into the nucleus due to the presence of a nuclear localization sequence residing in the precursor domain, unlike mature IL-1 α , which is largely restricted to the cytoplasm [54]. Nuclear translocation of proIL-1 α is regulated by a number of different proteins, including Ras-related nuclear protein (Ran; a small GTPase) [55, 56] and HS1-associated protein X-1 (HAX-1, a multi-functional protein with roles in apoptosis and cell migration [57] that binds to IL-1 α [58]). Third, nuclear-localized proIL-1 α participates in transcriptional regulation. For instance, the transcription of collagenase was up-regulated in endothelial cells that over-expressed proIL-1 α fusion protein [53]. On a final note, misregulation of proIL-1 α nuclear translocation is linked to the pathogenesis of diseases such as systemic sclerosis (SSc) [52]. Skin fibroblasts obtained from SSc patients showed an aberrant accumulation of proIL-1 α in the nucleus [59], which was suppressed by the knockdown of HAX-1 [52]. Equally important, this blockage of proIL-1 α nuclear entry was also accompanied by the relief of certain SSc phenotypes (e.g., excessive IL-6 production) [52], illustrating the significance of tightly regulating proIL-1 α localization.

Mechanisms of cytoskeletal and cell junctional remodeling by IL-1

IL-1 stimulation can result in profound changes in cellular behavior, which oftentimes involves remodeling of the cytoskeleton and changes in cell–cell adhesion. For instance, IL-1 is known to induce actin stress fiber formation in different cell types [60, 61], and to increase tight junction (TJ) permeability in the intestinal epithelium [62] and in the blood–brain barrier [63]. IL-1 is also involved in the non-inflammatory-related restructuring of cell junctions, which occurs during normal tissue homeostasis. For instance, IL-1 α was recently reported to affect the permeability of the blood–testis barrier (BTB) during spermatogenesis [12, 13], which we will discuss in detail later. In the following two sections, we highlight signaling events that underlie IL-1-induced cytoskeletal and cell junctional remodeling.

Regulation of cytoskeletal and junctional dynamics through Rho GTPases

The small GTPases RhoA and Rac1 are likely to be effectors in IL-1 signaling because a fusion protein of IL-1RI co-immunoprecipitated with RhoA and Rac1 in HeLa cell extracts [64]. These proteins are members of the Rho GTPase family (e.g., RhoA-C, Rac1-3 and Cdc42), which are molecular switches best known for their role in regulating the actin cytoskeleton, as well as cell polarity and vesicular transport [65, 66]. Two major types of Rho effectors are crucial for the induction of actin polymerization, namely diaphanous-related formins (DRFs) and WASP (Wiskott-Aldrich syndrome protein)/WAVE (WASP-family verprolin-homologous protein) [65, 67]. While both DRFs and WASP/WAVE proteins promote the nucleation of actin filaments, the resulting structures have distinct conformations. DRFs facilitate the polymerization of unbranched actin filaments upon activation by RhoA, B or C; whereas WASP/WAVE proteins, effectors of Cdc42 and Rac1 respectively, favor the formation of the dendritic actin network via the activity of the Arp (actin-related protein) 2/3 complex [65, 68, 69]. Furthermore, Rho is capable of activating another class of effectors that indirectly encourages actin polymerization, namely p160 Rho-associated coiled-coil-containing protein kinase (ROCK). This serine/threonine kinase phosphorylates and activates LIM kinase, which in turn targets cofilin. As a result, phosphorylated cofilin is incapable of severing and depolymerizing actin [65, 68, 69], thereby promoting actin polymerization.

RhoA and Rac1 have been reported to participate in IL-1 signaling. For instance, Rac1 activity appears to be required for the formation of lamellipodia in SH-SY5Y neuroblastoma cells that were grown on collagen and treated with IL-1 β [70]. This Rac1-dependent effect

may be mediated through the activation of WAVE proteins, which in turn activate the Arp2/3 complex for the nucleation of actin branches, thereby forming a dendritic network characteristic of lamellipodia [67, 68]. Nevertheless, additional studies are needed to substantiate the role of Rac1 as an IL-1 effector. In the case of Rho, evidence shows an association of Rho activity with IL-1 signaling particularly at focal adhesions. As mentioned previously, IL-1RI physically interacts with RhoA [64], a crucial regulator of focal adhesion assembly [71]. IL-1 β was also found to be clustered at cell–matrix adhesion sites that resembled focal adhesions [72], which implies that focal adhesions are key sites that harbor IL-1 receptors. Moreover, a number of studies indicate that IL-1 signaling relies on integrins and cell–matrix adhesion because the effects of IL-1 were abrogated after integrin-blocking antibodies were used or after cells were plated on non-integrin substrates [73–75]. Finally, and most importantly, IL-1-induced reorganization of the actin cytoskeleton into stress fibers is dependent on Rho activity since this phenotype is blocked by inhibitors of Rho (e.g., C3 transferase) and its effector ROCK (e.g., Y27632) [60, 74, 76]. In these studies, treatment with IL-1 (including both α and β subtypes) induced the formation of cytosolic stress fibers as visualized by phalloidin staining in cultured endothelial cell monolayers [60, 74] and isolated chondrocytes [76], and this effect was suppressed by pre-treating cells with Rho/ROCK inhibitors. Downstream of Rho-ROCK signaling, LIM kinase-mediated inactivation of cofilin, an actin severing and depolymerizing protein, would therefore encourage actin polymerization during stress fiber assembly [67, 68].

In summary, these results demonstrate that Rho activity participates in IL-1-induced stress fiber formation, which is important for focal adhesion and cell junction dynamics (Fig. 1). By definition, stress fibers are contractile structures comprised of actin filaments, crosslinking proteins and myosin II motors. They attach to focal adhesions, and their assembly is generally under the regulation of Rho [71, 77]. Moreover, this type of actin-based structure is especially prominent in fibroblasts in vitro where it functions in cell–matrix adhesion and in the transmission of tensile forces during cell movement. The formation of stress fibers in different epithelia and endothelia may also be connected to cell junctional integrity. For example, blocking Rho activity during treatment of endothelial cells with IL-1 not only prohibits the formation of stress fibers; it also prohibits TJ disruption and paracellular gap formation [74]. In another study, IL-1 β was found to up-regulate transforming growth factor (TGF)- β in a Rho-dependent manner [74]. Not surprisingly, this cytokine is also known to adversely affect TJ integrity [78, 79], suggesting that IL-1 may be working with other cytokines such as TGF- β and TNF to facilitate junction restructuring.

Regulation of cytoskeletal and junctional dynamics through nuclear factor- κ B

It is well known that IL-1 stimulation induces the activation of nuclear factor- κ B (NF- κ B) (Fig. 1), a major mediator of IL-1-induced genomic effects and whose misregulation is known to participate in the pathogenesis of many diseases such as cancer and diabetes [80, 81]. NF- κ B, a transcription factor comprised of proteins from the NF- κ B/Rel family, plays a key role during inflammation via the transcriptional regulation of proinflammatory genes such as cytokines, adhesion molecules and matrix metalloproteases [82]. NF- κ B is normally maintained in an inactive state within the cytoplasm of unstimulated or resting cells where it is sequestered by inhibitors (i.e., I κ Bs or the unprocessed forms of NF- κ B1 and NF- κ B2), until signaling is induced by stress factors such as IL-1, tumor necrosis factor (TNF)- α or lipopolysaccharides (LPS) [82, 83]. In brief, the canonical NF- κ B pathway is mediated through the activation of the I κ B kinase (IKK) complex, which in turn phosphorylates the inhibitor I κ B α . The resulting ubiquitination and degradation of I κ B α leads to a transient increase in unbound NF- κ B molecules that are free to translocate into the nucleus, thereby functioning in transcriptional regulation [82, 83] (Fig. 1).

Several reports have described the role of NF- κ B in IL-1 β -induced modulation of intestinal epithelial cell junctions. For example, treatment of Caco-2 cells with IL-1 β is known to increase the permeability of TJs [62], and this effect is mediated by the canonical NF- κ B pathway, which involves upstream regulation by MEKK-1 (MAP/Erk kinase kinase-1; a MAPK kinase kinase) [84]. These adverse effects of IL-1 β on TJ function are accompanied by a decrease in the mRNA level of occludin [62], but an increase in the protein level and kinase activity of myosin light chain kinase (MLCK) [85]. Moreover, these IL-1 β -mediated effects can be abrogated following NF- κ B inhibition/p65 knockdown [62, 85], MEKK-1 knockdown [84] or MLCK inhibition/knockdown [85], confirming the specificity of these effects. Notably, the ability of IL-1 to stimulate MLCK expression illustrates its dual role in regulating actin stress fiber assembly (see previous section) and contractility. MLCK is a serine/threonine protein kinase that phosphorylates the regulatory light chain of myosin II and stimulates its activity in actomyosin contraction [86, 87], thereby generating force during events such as cell migration. In epithelial and endothelial barriers, MLCK-induced contraction of the perijunctional actomyosin belt is also associated with weakened cell adhesion [87, 88]. Therefore, IL-1-induced barrier disruption is likely to be a combined effect involving changes in junctional protein expression, and the assembly and contraction of actomyosin structures, which are mediated through the activities of Rho and MLCK (Fig. 1).

IL-1 α as a regulator of normal tissue homeostasis

As discussed previously, IL-1 is a proinflammatory cytokine, and for this reason, many studies on IL-1 are set in the context of pathological inflammatory conditions such as acute lung injury [74], osteoarthritis [76] and autoimmune thyroid disease [61]. Still, other studies have shown constitutive expression of IL-1 α (but not IL-1 β) in a number of tissues such as the skin and the endothelium, where it functions as an autocrine growth factor or in normal tissue homeostasis [1, 16]. The interplay of IL-1 α with IL-1Ra regulates cell proliferation and differentiation in a number of different cell types. In skin fibroblasts and endothelial cells, for instance, the up-regulation of IL-1 α production in aging cells is associated with growth arrest and senescence [8, 89]. Indeed, the inhibition of IL-1 α by the use of antisense oligomers [8] or the addition of exogenous IL-1Ra [90] extended the proliferative lifespan and enhanced the replicative capacity of endothelial cells. On the other hand, IL-1 α influences keratinocytes in a different manner. Throughout keratinocyte maturation, the IL-1 α level remains constant, whereas IL-1Ra accumulates highly in large differentiated cells [9]. Moreover, IL-1 α secreted by keratinocytes stimulates the production of growth factors (e.g., keratinocyte growth factor) in skin fibroblasts, which in turn support keratinocyte proliferation [91]. These two observations suggest that IL-1 α signaling associates with the proliferation of keratinocytes, while its attenuation promotes cell differentiation instead. In addition to the regulation of keratinocyte growth, expression of IL-1 α in the epidermis was found to be important for the restoration of permeability barrier function after acute barrier disruption [92, 93]. Taken collectively, these findings illustrate important physiological roles for IL-1 α in the regulation of cell turnover and in promoting tissue repair, thereby maintaining normal tissue function. To further support IL-1 α 's role in homeostasis, we have recently demonstrated IL-1 α to be an important regulator of cytoskeletal and cell junctional dynamics in the seminiferous epithelium of the mammalian testis [12, 13]. In the following sections, we focus primarily on the non-inflammatory related functions of IL-1 α during spermatogenesis.

Role of IL-1 α in spermatogenesis

Introduction to spermatogenesis

In the seminiferous epithelium of the adult mammalian testis, spermatogenesis is the process in which germ cells undergo cell division, differentiation and morphogenesis to become spermatozoa [94]. These events take place continuously throughout the seminiferous epithelial cycle, which is divided into a defined number of stages. In the rat for instance, the seminiferous epithelial cycle consists of 14 stages, and each stage is characterized by a unique arrangement of specific germ cell types (i.e., spermatogonia, spermatocytes and spermatids) in the epithelium. (Please refer to recent reviews [95, 96] for detailed morphological characteristics and important cellular events that occur during the rat seminiferous epithelial cycle). Throughout germ cell development, these cells are structurally and nutritionally supported by somatic epithelial cells known as Sertoli cells, which span the entire height of the seminiferous epithelium [97]. One of the most important roles ascribed to Sertoli cells is the formation of the BTB, which is constituted by coexisting TJs, ectoplasmic specializations (ESs, a testis-specific actin-based anchoring junction), desmosomes and gap junctions that are found basolaterally and near the basement membrane [95, 98, 99].

The integrity of the BTB is critical for sequestering post-meiotic germ cells from the systemic circulation, and any compromise in its function may trigger an autoimmune response (and possibly subfertility or infertility) because antigens residing on the surfaces of meiotic germ cells would be seen as foreign by the host's immune system (i.e., immune tolerance develops well before mature spermatozoa). Still, the BTB must transiently restructure to allow the entry of spermatocytes into the adluminal compartment of the seminiferous epithelium for further development, and this event takes place during stages VIII to XI of the seminiferous epithelial cycle in the rat [100, 101]. Morphological observations from the late Lonnie Russell proposed that a "new" BTB assembles beneath spermatocytes while they migrate upwards and break through the gates, so to speak, of the "old" BTB that is situated above them [100]. In this way, the spermatogenic process and fertility can be maintained. Moreover, the movement of spermatocytes across the BTB also coincides with the release of spermatozoa (i.e., spermiation) at late stage VIII [102, 103]. These elaborate yet highly synchronized restructuring events, which also involve the cytoskeleton, are believed to be coordinated in large part by factors secreted by testicular cells (e.g., cytokines, androgens and estrogens) [104, 106]. In this regard, IL-1 α is emerging as an important regulator of cell junctions and the cytoskeleton in the seminiferous epithelium.

The IL-1 system in the testis

Cells of the adult mammalian testis constitutively express IL-1 α [38, 107–109] and its antagonist IL-1Ra [110, 111], as well as IL-1RI and IL-1RII [112] (Table 1). The identity of the protein exhibiting IL-1 bioactivity in the testis was confirmed to be the α subtype because its ability in promoting thymocyte proliferation was obliterated by IL-1 α [38, 108] but not by IL-1 β [108] antiserum. Furthermore, several immunoreactive IL-1 α isoforms are known to exist in the testis with apparent molecular weights ranging from 17–45 kDa [38, 113]. Besides the 17-kDa mature and 31-kDa proIL-1 α forms that were previously discussed, another variant of 24 kDa is known to be produced from an alternatively spliced transcript. While the function of this variant in the testis has yet to be determined, the 24-kDa form is also capable of promoting thymocyte proliferation, but unlike the other isoforms, it fails to inhibit human chorionic gonadotropin-driven steroidogenesis in Leydig cells (interstitial cells that produce testosterone when stimulated by luteinizing hormone)

[113]. In contrast, IL-1 β is absent and its transcripts are barely detectable in the testis under normal physiological conditions [38, 107, 114].

Interestingly, these IL-1 α isoforms are not only detected in testis extracts, but also in seminiferous tubule and interstitial fluids [38]. These findings are intriguing because IL-1 α is rarely secreted [1], and its occasional presence in bodily fluids is most likely due to dying cells releasing their cytoplasmic contents [36]. Moreover, when cultured in vitro, bioactive IL-1 α is secreted by seminiferous tubules [115] and Sertoli cells [108], but other testicular cell types (e.g., germ cells and interstitial cells) do not secrete it into the culture medium [108] even when immunoreactive IL-1 α is detected in their lysates [109] (Table 1). Even though Sertoli cells appear to be the major source of secreted IL-1 α in the testis, germ cells play an equally important role because their loss from the seminiferous epithelium halted IL-1 α production by Sertoli cells [107], illustrating that germ cells regulate Sertoli cell production of IL-1 α . To further support the role of IL-1 α as a paracrine regulator, IL-1 α showed a stage specific expression pattern in the seminiferous epithelium [107, 115, 116]. As detected by both ELISA and a bioactivity assay, IL-1 α is highly expressed throughout the entire seminiferous epithelial cycle except at stage VII when its level is the lowest [107, 115, 116]. This is followed by an increase of more than threefold beginning at stage VIII, which may be the result of Sertoli cells phagocytosing residual bodies emanating from elongated spermatids [115, 117].

Since this increase in IL-1 α temporally coincides with both BTB restructuring and spermiation, which take place at stage VIII of the seminiferous epithelial cycle, the possible role of IL-1 α in coordinating these events was explored in two recent studies [12, 13]. Results from these studies have illustrated IL-1 α to regulate the remodeling of the cytoskeleton and cell junctions during spermatogenesis, which we will discuss in the following sections. Furthermore, numerous studies have demonstrated IL-1 α to be a multi-functional regulator of spermatogenesis. First, IL-1 α is a growth factor used by testicular cells, including immature Sertoli cells [118, 119] and spermatogonia [120]. For example, the lowest level of IL-1 α expression during stage VII of the seminiferous epithelial cycle in the adult rat testis coincides with the lack of germ cell proliferation at this stage [107]. Second, IL-1 α regulates the production of other cytokines and paracrine factors, as well as other cellular processes, in the testis. These include the production of IL-6 [115] and activin A (a member of the transforming growth factor [TGF]- β family) [121] in Sertoli cells, and the regulation of steroidogenesis in Leydig cells [122–124].

Effects of IL-1 α on cell adhesion in the seminiferous epithelium

Two critical cellular events take place simultaneously at stage VIII of the seminiferous epithelial cycle, namely the restructuring of the BTB and the release of spermatozoa [103–105]. Thus, the increase in IL-1 α at stage VIII is likely to facilitate these two events (Fig. 2). The earliest findings to support this concept emerged from an in vivo study where intratesticular injection of recombinant IL-1 α was shown to perturb both Sertoli–germ cell adhesion and BTB integrity [12]. Owing to the fact that IL-1 α is normally present in the adult rat testis at the physiological level of ~200 pM [116], this study sought to unmask the phenotype of IL-1 α signaling by treating testes with an acute dose of recombinant IL-1 α (three doses each at ~50 times the physiological level) [12]. This IL-1 α treatment regimen resulted in severe germ cell loss from the seminiferous epithelium, and elongated spermatids from stage VII and VIII tubules were depleted before other germ cell types [12], in a way resembling aberrant “spermiation”. This indicates that a precise and tightly controlled level of IL-1 α in the seminiferous tubule microenvironment is essential for maintaining Sertoli–germ cell adhesion. Equally important, the adverse effects of IL-1 α on BTB restructuring were also investigated by an in vivo BTB integrity assay. In brief, a small fluorescent probe (i.e., inulin–FITC) was injected into the jugular vein of rats. Thereafter, the integrity of the

BTB was assessed by its ability to block the diffusion of inulin-FITC from the systemic circulation, across the BTB and into the adluminal compartment of the seminiferous epithelium. In this case, inulin-FITC was able to penetrate the compromised BTB in IL-1 α -treated testes [12]. Likewise, the organization of filamentous (F-) actin at the BTB and at sites of Sertoli-germ cell adhesion was adversely affected after IL-1 α treatment. Specifically, there was a loss of actin filament bundles that constitute the ES when examined by electron microscopy [12]. While the increase in TJ permeability is reminiscent of the effects of IL-1 in other tissues [62, 74], no obvious signs of stress fiber formation were noted in our study. Nevertheless, actin remodeling is likely to be a key factor in IL-1 α -induced BTB disruption because no changes in the levels of BTB constituent proteins were noted, and this is in contrast to the effects of other cytokines in the testis such as TGF- β 3 [125] and TNF- α [126].

Mechanisms of IL-1 α -induced remodeling of the Sertoli cell cytoskeleton and BTB

Additional data to support the role of IL-1 α in actin remodeling at the BTB were provided by a subsequent in vitro study that used polarized Sertoli cells having a functional TJ permeability barrier [13]. In line with the in vivo results just described, treatment of Sertoli cells with IL-1 α led to F-actin disorganization and barrier disruption when assessed by fluorescence microscopy and transepithelial electrical resistance measurements, respectively [13]. Instead of uniformly distributed actin bundles, IL-1 α -treated cells showed haphazard clusters of F-actin and overgrown filaments, which appeared to stretch over to neighboring Sertoli cells [13]. These effects were mediated in part by two actin regulatory proteins previously shown to regulate the BTB and Sertoli-germ cell adhesion, namely epidermal growth factor receptor pathway substrate 8 (Eps8) [127] and actin-related protein (Arp) 3 [128] (Fig. 2). Arp3 is a member of the Arp2/3 complex which is known to function as the major actin nucleation machinery during the formation of the branched actin network [129], whereas Eps8 is a multi-functional actin regulator with barbed-end capping activity [130]. Eps8 also participates in actin bundling mediated by insulin receptor substrate p53 [131], as well as in the activation of Rac, which is mediated by the GTP exchange factor Sos (son of sevenless)-1. Therefore, by associating with different protein complexes, Eps8 not only plays a role in the formation of actin bundles, but also in the branching of actin by virtue of its actin barbed-end capping activity and Rac activation.

The mislocalization of Eps8 in Sertoli cells following IL-1 α treatment may very well explain the overgrowth of actin filaments and the loss of their bundle-like appearance [13], observations which are comparable to those observed after Eps8 knockdown by RNAi [127]. Likewise, an increase in the Arp3 protein level may facilitate the formation of an actin network, as opposed to unbranched actin bundles [13]. The differential activity of these two actin regulators is also reflected by their contrasting expression patterns at the BTB in vivo prior to the onset of BTB restructuring at stage VIII. The highest level of Eps8 is detected at the BTB in earlier stages (i.e., V–VI), followed by a decrease until it is no longer detectable at stage VIII [127]. On the contrary, Arp3 peaks at the BTB precisely at stage VIII during BTB restructuring, which allows the transit of preleptotene spermatocytes [128]. Thus, considering the stage specific expression pattern of these two actin regulators, IL-1 α may be coordinating the down-regulation of Eps8 and the recruitment of Arp3 to the site of the BTB during stage VIII. In this way, the actin cyto-skeleton can be remodeled from rigid bundles into more flexible branches to facilitate the restructuring of the BTB and the movement of preleptotene spermatocytes (Fig. 2). Given these interesting results, additional studies are needed to confirm whether Eps8 and the Arp2/3 complex indeed mediate restructuring of the actin cytoskeleton in response to IL-1 α . For example, can Eps8 overexpression rescue the defects in actin capping following IL-1 α treatment? Furthermore, the participation of other

actin-regulating proteins such as Rho, which is known to mediate IL-1-induced actin remodeling, should also be investigated in the future.

In the context of the seminiferous epithelium in vivo, IL-1 α -mediated regulation of Eps8 and Arp2/3 activity likely represents an important mechanism for ES disassembly. As described previously, the ES is a unique actin-based anchoring junction type found in Sertoli cells. By electron microscopy, the ES is typified by the presence of unipolar actin bundles sandwiched in between cisternae of the endoplasmic reticulum and the plasma membrane at the cell–cell interface [98, 99, 132, 133]. ESs found at the BTB (defined as basal ES) coexist with other junction types, and they mediate strong intercellular adhesion in the Sertoli cell epithelium. Likewise, analogous structures (i.e., apical ES) are found within Sertoli cells at the sites where elongating spermatids attach, serving as the sole anchoring device for post-step 8 spermatids until their release [134]. Removal of these strong adhesions is thus necessary for the impending restructuring of the BTB and release of spermatozoa during stage VIII. The gradual process of ES degeneration is associated with the remodeling of the characteristic actin bundles at the ES into a highly branched network [132, 133]. As such, this process likely involves the participation of Eps8 and the Arp2/3 complex. Furthermore, the removal of adhesion protein complexes at the ES is mediated, at least in part, by their internalization via endocytic pathways [103, 135, 136]. At the Sertoli cell–elongated spermatid interface, sites of apical ES disassembly just prior to spermiation are occupied by unique structures known as apical tubulobulbar complexes (TBCs), which are tubular invaginations in Sertoli cells arising from protrusions of plasma membrane at the site. Analogous structures defined as basal TBCs also exist at the BTB [132, 133]. Accumulating knowledge supports the hypothesis that TBCs are sites where ES constituent proteins undergo endocytosis [137, 138]. For instance, apical TBCs not only contain components of the endocytic machinery (e.g., dynamin III [139] and clathrin [140]); they are also enriched by important actin regulators with known functions in branch formation or actin turnover. These include the Arp2/3 complex and its activators, neuronal-WASP (N-WASP) [128, 140] and cortactin [140], Rac-1 [141], as well as cofilin [142]. These proteins serve to regulate actin dynamics at TBCs, thereby generating force required for the invagination, scission and release of newly formed endocytic vesicles [143], which in turn facilitate ES protein internalization. At the BTB, an analogous mechanism is believed to be at play. Taken together, these findings support the emerging view that IL-1 α serves as a master regulator of basal ES disassembly by inducing actin remodeling from rigid bundles to a branched network, thereby facilitating protein endocytosis in concert with other cytokines (e.g., TGF- β 2, TGF- β 3 and TNF- α [135, 144]) at the BTB. This hypothesis is also consistent with the observation that IL-1 α accelerates the kinetics of occludin endocytosis from the cell surface [13]. Whether IL-1 α affects the apical ES in a similar manner remains to be investigated in future.

IL-1 α also affects junction dynamics by regulating the levels of BTB-constituent proteins. In contrast to TGF- β 3 and TNF- α [126, 145–147], treatment of Sertoli cells with IL-1 α in vitro increased the levels of several BTB constituent proteins, including integral membrane proteins occludin and N-cadherin, and their adaptors ZO-1 and β -catenin [13]. In another study using a Sertoli cell line, IL-1 α increased the mRNA level of JAM-B by promoting its transcriptional activation [148]. While it is not known if IL-1 α also affects the transcription of occludin and N-cadherin, the increased levels of these proteins were due in part to their accumulation in the cytoplasm after being endocytosed [13]. At this point, we believe that IL-1 α initiates BTB disassembly by remodeling the Sertoli cell actin cytoskeleton and that it also encourages BTB assembly by slowing down the degradation of endocytosed structural proteins, which may be needed to assemble the “new” BTB below migrating spermatocytes (Fig. 2). It is worth noting that IL-1 α alone cannot initiate BTB assembly because TJs were unable to recover after prolonged IL-1 α treatment both in vivo and in vitro [13]. Additional

factors are clearly at play. For instance, recycling of endocytosed integral membrane proteins, which may have accumulated in the cytoplasm, back to the cell surface may require the action of testosterone [135]. Therefore, the delicate balance between IL-1 α and other paracrine factors and hormones (e.g., testosterone, estrogen) throughout stages VIII to XI is likely to be critical for inducing the disassembly of the “old” BTB above spermatocytes in transit concurrent to the assembly of the “new” BTB underneath.

Concluding remarks

While IL-1 α is an autocrine and/or paracrine factor involved in normal tissue homeostasis, knockout animals displayed normal development and fertility [149]. In addition, our knowledge of IL-1 remains incomplete as most studies were performed on cells treated with recombinant mature proteins. As such, the contribution of proIL-1 α signaling in mediating cytoskeletal and cell junctional remodeling remains virtually unexplored. For this reason, future studies are warranted to better understand the regulatory pathway of IL-1 α maturation, the differential fate and activity of precursor and mature IL-1 α , as well as the identities of proteins mediating alternative IL-1 signaling.

Acknowledgments

Research in the authors' laboratory is supported by NICHD, NIH (R03 HD061401 to D.D.M.; R01 HD056034, R01 HD056034-02S1 and U54 HD029990 Project 5 to C.Y.C.).

References

1. Dinarello CA. Immunological and inflammatory functions of the interleukin-1 family. *Annu Rev Immunol.* 2009; 27:519–550. [PubMed: 19302047]
2. Dinarello CA. Interleukin 1 and interleukin 18 as mediators of inflammation and the aging process. *Am J Clin Nutr.* 2006; 83:447S–455S. [PubMed: 16470011]
3. Lomedico PT, Gubler U, Hellmann CP, Dukovich M, Giri JG, Pan YE, Collier K, Semionow R, Chua AO, Mizel SB. Cloning and expression of murine interleukin-1 cDNA in *Escherichia coli*. *Nature.* 1984; 312:458–462. [PubMed: 6209582]
4. Auron PE, Webb AC, Rosenwasser LJ, Mucci SF, Rich A, Wolff SM, Dinarello CA. Nucleotide sequence of human monocyte interleukin 1 precursor cDNA. *Proc Natl Acad Sci USA.* 1984; 81:7907–7911. [PubMed: 6083565]
5. Schmitz J, Owyang A, Oldham E, Song Y, Murphy E, McClanahan TK, Zurawski G, Moshrefi M, Qin J, Li X, Gorman DM, Bazan JF, Kastelein RA. IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. *Immunity.* 2005; 23:479–490. [PubMed: 16286016]
6. Dinarello CA. Blocking IL-1 in systemic inflammation. *J Exp Med.* 2005; 201:1355–1359. [PubMed: 15867089]
7. Hoffman HM, Rosengren S, Boyle DL, Cho JY, Nayar J, Mueller JL, Anderson JP, Wanderer AA, Firestein GS. Prevention of cold-associated acute inflammation in familial cold autoinflammatory syndrome by interleukin-1 receptor antagonist. *Lancet.* 2004; 364:1779–1785. [PubMed: 15541451]
8. Maier JA, Voulalas P, Roeder D, Maciag T. Extension of the life-span of human endothelial cells by an interleukin-1 α antisense oligomer. *Science.* 1990; 249:1570–1574. [PubMed: 2218499]
9. Corradi A, Franzi AT, Rubartelli A. Synthesis and secretion of interleukin-1 α and interleukin-1 receptor antagonist during differentiation of cultured keratinocytes. *Exp Cell Res.* 1995; 217:355–362. [PubMed: 7698236]
10. Walsh SV, Hopkins AM, Nusrat A. Modulation of tight junction structure and function by cytokines. *Adv Drug Deliv Rev.* 2000; 41:303–313. [PubMed: 10854688]
11. Harhaj NS, Antonetti DA. Regulation of tight junctions and loss of barrier function in pathophysiology. *Int J Biochem Cell Biol.* 2004; 36:1206–1237. [PubMed: 15109567]

12. Sarkar O, Mathur PP, Cheng CY, Mruk DD. Interleukin 1 α (IL1A) is a novel regulator of the blood–testis barrier in the rat. *Biol Reprod*. 2008; 78:445–454. [PubMed: 18057314]
13. Lie PPY, Cheng CY, Mruk DD. Interleukin-1 α is a regulator of the blood–testis barrier. *FASEB J*. 2011; 25:1244–1253. [PubMed: 21191089]
14. March CJ, Mosley B, Larsen A, Cerretti DP, Braedt G, Price V, Gillis S, Henney CS, Kronheim SR, Grabstein K, Conlon PJ, Hopp TP, Cosman D. Cloning, sequence and expression of two distinct human interleukin-1 complementary DNAs. *Nature*. 1985; 315:641–647. [PubMed: 2989698]
15. Dinarello CA. Interleukin-1. *Cytokine Growth Factor Rev*. 1997; 8:253–265. [PubMed: 9620641]
16. Dinarello CA. Biologic basis for interleukin-1 in disease. *Blood*. 1996; 87:2095–2147. [PubMed: 8630372]
17. Mosley B, Urdal DL, Prickett KS, Larsen A, Cosman D, Conlon PJ, Gillis S, Dower SK. The interleukin-1 receptor binds the human interleukin-1 α precursor but not the interleukin-1 β precursor. *J Biol Chem*. 1987; 262:2941–2944. [PubMed: 2950091]
18. Kobayashi Y, Yamamoto K, Saido T, Kawasaki H, Oppenheim JJ, Matsushima K. Identification of calcium-activated neutral protease as a processing enzyme of human interleukin 1 α . *Proc Natl Acad Sci USA*. 1990; 87:5548–5552. [PubMed: 2115174]
19. Thornberry NA, Bull HG, Calaycay JR, Chapman KT, Howard AD, Kostura MJ, Miller DK, Molineaux SM, Weidner JR, Aunins J, et al. A novel heterodimeric cysteine protease is required for interleukin-1 β processing in monocytes. *Nature*. 1992; 356:768–774. [PubMed: 1574116]
20. Kuida K, Lippke JA, Ku G, Harding MW, Livingston DJ, Su MS, Flavell RA. Altered cytokine export and apoptosis in mice deficient in interleukin-1 β converting enzyme. *Science*. 1995; 267:2000–2003. [PubMed: 7535475]
21. Li P, Allen H, Banerjee S, Franklin S, Herzog L, Johnston C, McDowell J, Paskind M, Rodman L, Salfeld J, Towne E, Tracey D, Wardwell S, Wei FY, Wong W, Kamen R, Seshadri T. Mice deficient in IL-1 β -converting enzyme are defective in production of mature IL-1 β and resistant to endotoxic shock. *Cell*. 1995; 80:401–411. [PubMed: 7859282]
22. Rubartelli A, Cozzolino F, Talio M, Sitia R. A novel secretory pathway for interleukin-1 β , a protein lacking a signal sequence. *EMBO J*. 1990; 9:1503–1510. [PubMed: 2328723]
23. Martinon F, Burns K, Tschopp J. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL- β . *Mol Cell*. 2002; 10:417–426. [PubMed: 12191486]
24. Martinon F, Mayor A, Tschopp J. The inflammasomes: guardians of the body. *Annu Rev Immunol*. 2009; 27:229–265. [PubMed: 19302040]
25. Ferrari D, Pizzirani C, Adinolfi E, Lemoli RM, Curti A, Idzko M, Panther E, Di Virgilio F. The P2X₇ receptor: a key player in IL-1 processing and release. *J Immunol*. 2006; 176:3877–3883. [PubMed: 16547218]
26. Mariathasan S, Monack DM. Inflammasome adaptors and sensors: intracellular regulators of infection and inflammation. *Nat Rev Immunol*. 2007; 7:31–40. [PubMed: 17186029]
27. Martinon F, Tschopp J. Inflammatory caspases and inflammasomes: master switches of inflammation. *Cell Death Differ*. 2007; 14:10–22. [PubMed: 16977329]
28. Skaper SD, Debetto P, Giusti P. The P2X₇ purinergic receptor: from physiology to neurological disorders. *FASEB J*. 2010; 24:337–345. [PubMed: 19812374]
29. Khakh BS, North RA. P2X receptors as cell-surface ATP sensors in health and disease. *Nature*. 2006; 442:527–532. [PubMed: 16885977]
30. Solle M, Labasi J, Perregaux DG, Stam E, Petrushova N, Koller BH, Griffiths RJ, Gabel CA. Altered cytokine production in mice lacking P2X₇ receptors. *J Biol Chem*. 2001; 276:125–132. [PubMed: 11016935]
31. Humphreys BD, Rice J, Kertesz SB, Dubyak GR. Stress-activated protein kinase/JNK activation and apoptotic induction by the macrophage P2X₇ nucleotide receptor. *J Biol Chem*. 2000; 275:26792–26798. [PubMed: 10854431]
32. Aga M, Johnson CJ, Hart AP, Guadarrama AG, Suresh M, Svaren J, Bertics PJ, Darien BJ. Modulation of monocyte signaling and pore formation in response to agonists of the nucleotide receptor P2X₇. *J Leukoc Biol*. 2002; 72:222–232. [PubMed: 12101284]

33. Potucek YD, Crain JM, Watters JJ. Purinergic receptors modulate MAP kinases and transcription factors that control microglial inflammatory gene expression. *Neurochem Int.* 2006; 49:204–214. [PubMed: 16735081]
34. Andrei C, Margiocco P, Poggi A, Lotti LV, Torrisi MR, Rubartelli A. Phospholipases C and A2 control lysosome-mediated IL-1 β secretion: implications for inflammatory processes. *Proc Natl Acad Sci USA.* 2004; 101:9745–9750. [PubMed: 15192144]
35. MacKenzie A, Wilson HL, Kiss-Toth E, Dower SK, North RA, Surprenant A. Rapid secretion of interleukin-1 β by microvesicle shedding. *Immunity.* 2001; 8:825–835. [PubMed: 11728343]
36. Chen C, Kono H, Golenbock D, Reed G, Akira S, Rock KL. Identification of a key pathway required for the sterile inflammatory response triggered by dying cells. *Nat Med.* 2007; 13:851–856. [PubMed: 17572686]
37. Dinarello CA. The interleukin-1 family: 10 years of discovery. *FASEB J.* 1994; 8:1314–1325. [PubMed: 8001745]
38. Gustafsson K, Sultana T, Zetterstrom CK, Setchell BP, Siddiqui A, Weber G, Soder O. Production and secretion of interleukin-1 α proteins by rat testis. *Biochem Biophys Res Commun.* 2002; 297:492–497. [PubMed: 12270120]
39. O'Neill LAJ. The interleukin-1 receptor/Toll-like receptor superfamily: 10 years of progress. *Immunol Rev.* 2008; 226:10–18. [PubMed: 19161412]
40. Colotta F, Re F, Muzio M, Bertini R, Polentarutti N, Sironi M, Giri JG, Dower SK, Sims JE, Mantovani A. Interleukin-1 type II receptor: a decoy target for IL-1 that is regulated by IL-4. *Science.* 1993; 261:472–475. [PubMed: 8332913]
41. Mantovani A, Locati M, Polentarutti N, Vecchi A, Garlanda C. Extracellular and intracellular decoys in the tuning of inflammatory cytokines and Toll-like receptors: the new entry TIR8/SIGIRR. *J Leukoc Biol.* 2004; 75:738–742. [PubMed: 14673019]
42. Greenfeder SA, Nunes P, Kwee L, Labow M, Chizzonite RA, Ju G. Molecular cloning and characterization of a second subunit of the interleukin 1 receptor complex. *J Biol Chem.* 1995; 270:13757–13765. [PubMed: 7775431]
43. Lang D, Knop J, Wesche H, Raffetseder U, Kurrle R, Boraschi D, Martin MU. The type II IL-1 receptor interacts with the IL-1 receptor accessory protein: a novel mechanism of regulation of IL-1 responsiveness. *J Immunol.* 1998; 161:6871–6877. [PubMed: 9862719]
44. Dunne A, O'Neill LAJ. The interleukin-1 receptor/Toll-like receptor superfamily: signal transduction during inflammation and host defense. *Sci STKE.* 2003; 171:re3–re17. [PubMed: 12606705]
45. Burns K, Martinon F, Esslinger C, Pahl H, Schneider P, Bodmer JL, Di Marco F, French L, Tschopp J. MyD88, an adaptor protein involved in interleukin-1 signaling. *J Biol Chem.* 1998; 273:12203–12209. [PubMed: 9575168]
46. Wesche H, Henzel WJ, Shillinglaw W, Li S, Cao Z. MyD88: an adaptor that recruits IRAK to the IL-1 receptor complex. *Immunity.* 1997; 7:837–847. [PubMed: 9430229]
47. Wang Z, Wesche H, Stevens T, Walker N, Yeh WC. IRAK-4 inhibitors for inflammation. *Curr Top Med Chem.* 2009; 9:724–737. [PubMed: 19689377]
48. Gottipati S, Rao NL, Fung-Leung WP. IRAK1: a critical signaling mediator of innate immunity. *Cell Signal.* 2008; 20:269–276. [PubMed: 17890055]
49. Janssens S, Beyaert R. Functional diversity and regulation of different interleukin-1 receptor-associated kinase (IRAK) family members. *Mol Cell.* 2003; 11:293–302. [PubMed: 12620219]
50. Suzuki N, Suzuki S, Yeh WC. IRAK-4 as the central TIR signaling mediator in innate immunity. *Trends Immunol.* 2002; 23:503–506. [PubMed: 12297423]
51. Barton GM, Medzhitov R. Toll-like receptor signaling pathways. *Science.* 2003; 300:1524–2525. [PubMed: 12791976]
52. Kawaguchi Y, Nishimagi E, Tochimoto A, Kawamoto M, Katsumata Y, Soejima M, Kanno T, Kamatani N, Hara M. Intracellular IL-1 α -binding proteins contribute to biological functions of endogenous IL-1 α in system sclerosis fibroblasts. *Proc Natl Acad Sci USA.* 2006; 103:14501–14506. [PubMed: 16971486]

53. Maier JAM, Statuto M, Ragnotti G. Endogenous interleukin 1 α must be transported to the nucleus to exert its activity in human endothelial cells. *Mol Cell Biol*. 1994; 14:1845–1851. [PubMed: 8114717]
54. Wessendorf JHM, Garfinkel S, Zhan X, Brown S, Maciag T. Identification of a nuclear localization sequence within the structure of the human interleukin-1 α precursor. *J Biol Chem*. 1993; 268:22100–22104. [PubMed: 8408068]
55. Hu B, Wang S, Zhang Y, Feghali CA, Dingman JR, Wright TM. A nuclear target for interleukin-1 α : interaction with the growth suppressor necdin modulates proliferation and collagen expression. *Proc Natl Acad Sci USA*. 2003; 100:10008–10013. [PubMed: 12913118]
56. Luheshi NM, Rothwell NJ, Brough D. The dynamics and mechanisms of interleukin-1 α and β nuclear import. *Traffic*. 2009; 10:16–25. [PubMed: 18939951]
57. Fadeel B, Grzybowska E. HAX-1: a multifunctional protein with emerging roles in human disease. *Biochim Biophys Acta*. 2009; 1790:1139–1148. [PubMed: 19524642]
58. Yin HL, Morioka H, Towle CA, Vidal M, Watanabe T, Weissbach L. Evidence that HAX-1 is an interleukin-1 α N-terminal binding protein. *Cytokine*. 2001; 15:122–137. [PubMed: 11554782]
59. Kawaguchi Y, McCarthy SA, Watkins SC, Wright TM. Autocrine activation by interleukin 1 α induces the fibrogenic phenotype of systemic sclerosis fibroblasts. *J Rheumatol*. 2004; 31:1946–1954. [PubMed: 15468358]
60. Campos SB, Ashworth SL, Wean S, Hosford M, Sandoval RM, Hallett MA, Atkinson SJ, Molitoris BA. Cytokine-induced F-actin reorganization in endothelial cells involves RhoA activation. *Am J Physiol Renal Physiol*. 2009; 296:F487–F495. [PubMed: 19144696]
61. Nilsson M, Husmark J, Bjorkman U, Ericson LE. Cytokines and thyroid epithelial integrity: interleukin-1 α induces dissociation of the junctional complex and paracellular leakage in filter-cultured human thyrocytes. *J Clin Endocrinol Metab*. 1998; 83:945–952. [PubMed: 9506754]
62. Al-Sadi RM, Ma TY. IL-1 β causes an increase in intestinal epithelial tight junction permeability. *J Immunol*. 2007; 178:4641–4649. [PubMed: 17372023]
63. Quagliarello VJ, Wispelwey B, Long WJ, Scheld WM. Recombinant human interleukin-1 induces meningitis and blood–brain barrier injury in the rat. *J Clin Invest*. 1991; 87:1360–1366. [PubMed: 2010549]
64. Singh R, Wang B, Shirvaikar A, Khan S, Kamat S, Schelling JR, Konieczkowski M, Sedor JR. The IL-1 receptor and Rho directly associate to drive cell activation and inflammation. *J Clin Invest*. 1999; 103:1561–1570. [PubMed: 10359565]
65. Ridley AJ. Rho GTPases and actin dynamics in membrane protrusions and vesicle trafficking. *Trends Cell Biol*. 2006; 16:522–529. [PubMed: 16949823]
66. Heasman SJ, Ridley AJ. Mammalian Rho GTPases: new insights into their functions from in vivo studies. *Nat Rev Mol Cell Biol*. 2008; 9:690–701. [PubMed: 18719708]
67. Burridge K, Wennerberg K. Rho and Rac take center stage. *Cell*. 2004; 116:167–179. [PubMed: 14744429]
68. Jaffe AB, Hall A. Rho GTPases: biochemistry and biology. *Annu Rev Cell Dev Biol*. 2005; 21:247–269. [PubMed: 16212495]
69. Bishop AL, Hall A. Rho GTPases and their effector proteins. *Biochem J*. 2000; 348:241–255. [PubMed: 10816416]
70. Barth BM, Stewart-Smeets S, Kuhn TB. Proinflammatory cytokines provoke oxidative damage to actin in neuronal cells mediated by Rac1 and NADPH oxidase. *Mol Cell Neurosci*. 2009; 41:274–285. [PubMed: 19344766]
71. Ridley AJ, Hall A. The small GTP-binding protein rho regulates the assembly of focal adhesions and actin stress fibers in response to growth factors. *Cell*. 1992; 70:389–399. [PubMed: 1643657]
72. Quarnstrom EE, Page RC, Gillis S, Dower SK. Binding, internalization, and intracellular localization of interleukin-1 β in human diploid fibroblasts. *J Biol Chem*. 1988; 263:8261–8269. [PubMed: 2967293]
73. Wang Q, Downey GP, Herrera-Abreu MT, Kapus A, McCulloch CA. SHP-2 modulates interleukin-1-induced Ca²⁺ flux and ERK activation via phosphorylation of phospholipase C γ 1. *J Biol Chem*. 2005; 280:8397–8406. [PubMed: 15563458]

74. Ganter MT, Roux J, Miyazawa B, Howard M, Frank JA, Su G, Sheppard D, Violette SM, Weinreb PH, Horan GS, Matthay MA, Pittet J. Interleukin-1 β causes acute lung injury via $\alpha v\beta 5$ and $\alpha v\beta 6$ integrin-dependent mechanisms. *Circ Res.* 2008; 102:804–812. [PubMed: 18276918]
75. Summers L, Kangwantas K, Nguyen L, Kiely C, Pinteaux E. Adhesion to the extracellular matrix is required for interleukin-1 β actions leading to reactive phenotype in rat astrocytes. *Mol Cell Neurosci.* 2010; 44:272–281. [PubMed: 20380881]
76. Novakofski K, Boehm A, Fortier L. The small GTPase Rho mediates articular chondrocyte phenotype and morphology in response to interleukin-1 α and insulin-like growth factor-I. *J Orth Res.* 2009; 27:58–64.
77. Chrzanowska-Wodnicka M, BurrIDGE K. Rho-stimulated contractility drives the formation of stress fibers and focal adhesions. *J Cell Biol.* 1996; 133:1403–1415. [PubMed: 8682874]
78. Pittet J, Griffiths MJD, Geiser T, Kaminski N, Dalton SL, Huang X, Brown LAS, Gotwals PJ, Kotliansky VE, Matthay MA, Sheppard D. TGF- β is a critical mediator of acute lung injury. *J Clin Invest.* 2001; 107:1537–1544. [PubMed: 11413161]
79. Lui WY, Lee WM, Cheng CY. Transforming growth factor- $\beta 3$ regulates the dynamics of Sertoli cell tight junctions via the p38 mitogen-activated protein kinase pathway. *Biol Reprod.* 2003; 68:1597–1612. [PubMed: 12606350]
80. Baker RG, Hayden MS, Ghosh S. NF- κ B, inflammation and metabolic disease. *Cell Metab.* 2011; 13:11–22. [PubMed: 21195345]
81. Schneider G, Kramer OH. NF- κ B/p53 crosstalk—a promising new therapeutic target. *Biochim Biophys Acta.* 2011; 1815:90–103. [PubMed: 20951769]
82. Tak PP, Firestein GS. NF- κ B: a key role in inflammatory diseases. *J Clin Invest.* 2001; 107:7–11. [PubMed: 11134171]
83. Aggarwai BB. Nuclear factor- κ B: the enemy within. *Cancer Cell.* 2004; 6:203–208. [PubMed: 15380510]
84. Al-Sadi R, Ye D, Said HM, Ma TY. IL-1 β -induced increase in intestinal epithelial tight junction permeability is mediated by MEKK-1 activation of canonical NF- κ B pathway. *Am J Pathol.* 2010; 177:2310–2322. [PubMed: 21048223]
85. Al-Sadi R, Ye D, Dokladny K, Ma TY. Mechanism of IL-1 β -induced increase in intestinal epithelial tight junction permeability. *J Immunol.* 2008; 180:5653–5661. [PubMed: 18390750]
86. Kamm KE, Stull JT. Dedicated myosin light chain kinases with diverse cellular functions. *J Biol Chem.* 2001; 276:4527–4530. [PubMed: 11096123]
87. Shen Q, Rigor RR, Pivetti CD, Wu MH, Yuan SY. Myosin light chain kinase in microvascular endothelial barrier function. *Cardiovasc Res.* 2010; 87:272–280. [PubMed: 20479130]
88. Ivanov AI, Parkos CA, Nusrat A. Cytoskeletal regulation of epithelial barrier function during inflammation. *Am J Pathol.* 2010; 177:512–524. [PubMed: 20581053]
89. Kumar S, Millis JT, Baglioni C. Expression of interleukin 1-inducible genes and production of interleukin 1 by aging human fibroblasts. *Proc Natl Acad Sci USA.* 1992; 89:4683–4687. [PubMed: 1584804]
90. Dewberry RM, Crossman DC, Francis SE. Interleukin-1 receptor antagonist (IL-1RN) genotype modulates the replicative capacity of human endothelial cells. *Circ Res.* 2003; 92:1285–1287. [PubMed: 12764021]
91. Maas-Szabowski N, Fusenig NE. Interleukin-1-induced growth factor expression in postmitotic and resting fibroblasts. *J Invest Dermatol.* 1996; 107:849–855. [PubMed: 8941673]
92. Barland CO, Zettersten E, Brown BS, Ye J, Elias PM, Ghadially R. Imiquimod-induced interleukin-1 α stimulation improves barrier homeostasis in aged murine epidermis. *J Invest Dermatol.* 2004; 122:330–336. [PubMed: 15009713]
93. Ye J, Garg A, Calhoun C, Feingold KR, Elias PM, Ghadially R. Alterations in cytokine regulation in aged epidermis: implications for permeability barrier homeostasis and inflammation. I. IL-1 gene family. *Exp Dermatol.* 2002; 11:209–216. [PubMed: 12102659]
94. Clermont Y. Kinetics of spermatogenesis in mammals: seminiferous epithelium cycle and spermatogonial renewal. *Physiol Rev.* 1972; 52:198–235. [PubMed: 4621362]

95. Lie PPY, Cheng CY, Mruk DD. The biology of the desmosome-like junction: a versatile anchoring junction and signal transducer in the seminiferous epithelium. *Int Rev Cell Mol Biol.* 2011; 286:223–269. [PubMed: 21199783]
96. Wong EWP, Cheng CY. Polarity proteins and cell–cell interactions in the testis. *Int Rev Cell Mol Biol.* 2009; 278:309–353. [PubMed: 19815182]
97. Bardin, CW.; Cheng, CY.; Musto, NA.; Gunsalus, GL. The Sertoli cell. In: Knobil, E.; Neill, JD.; Ewing, LL.; Greenwald, GS.; Markert, CL.; Pfaff, DW., editors. *The physiology of reproduction.* Vol. 1. Raven Press; New York: 1988. p. 933-974.
98. Mruk DD, Cheng CY. Sertoli–Sertoli and Sertoli–germ cell interactions and their significance in germ cell movement in the seminiferous epithelium during spermatogenesis. *Endocr Rev.* 2004; 25:747–806. [PubMed: 15466940]
99. Cheng CY, Mruk DD. Cell junction dynamics in the testis: Sertoli–germ cell interactions and male contraceptive development. *Physiol Rev.* 2002; 82:825–874. [PubMed: 12270945]
100. Russell LD. Movement of spermatocytes from the basal to the adluminal compartment of the rat testis. *Am J Anat.* 1977; 148:313–328. [PubMed: 857632]
101. Parvinen M. Regulation of the seminiferous epithelium. *Endocr Rev.* 1982; 3:404–417. [PubMed: 6295753]
102. Cheng CY, Mruk DD. An intracellular trafficking pathway in the seminiferous epithelium regulating spermatogenesis: a biochemical and molecular perspective. *Crit Rev Biochem Mol Biol.* 2009; 44:245–263. [PubMed: 19622063]
103. Lie PPY, Cheng CY, Mruk DD. Coordinating cellular events during spermatogenesis: a biochemical model. *Trends Biochem Sci.* 2009; 34:366–373. [PubMed: 19535250]
104. Cheng CY, Mruk DD. A local autocrine axis in the testes that regulates spermatogenesis. *Nat Rev Endocrinol.* 2010; 6:380–395. [PubMed: 20571538]
105. O'Donnell L, Nicholls OK, O'Bryan MK, McLachlan RI, Stanton PG. Spermiation: the process of sperm release. *Spermatogenesis.* 2011; 1:14–35. [PubMed: 21866274]
106. Li MWM, Mruk DD, Lee WM, Cheng CY. Cytokines and junction restructuring events during spermatogenesis in the testis: an emerging concept of regulation. *Cytokine Growth Factor Rev.* 2009; 20:329–338. [PubMed: 19651533]
107. Jonsson CK, Zetterstrom RH, Holst M, Parvinen M, Soder O. Constitutive expression of interleukin-1 α messenger ribonucleic acid in rat Sertoli cells is dependent upon interaction with germ cells. *Endocrinology.* 1999; 140:3755–3761. [PubMed: 10433236]
108. Gerard N, Syed V, Bardin W, Genetet N, Jegou B. Sertoli cells are the site of interleukin-1 α synthesis in rat testis. *Mol Cell Endocrinol.* 1991; 82:R13–R16. [PubMed: 1761160]
109. Haugen TB, Landmark BF, Josefsen GM, Hansson V, Hogset A. The mature form of interleukin-1 α is constitutively expressed in immature male germ cells from rat. *Mol Cell Endocrinol.* 1994; 105:R19–R23. [PubMed: 7859917]
110. Zeyse D, Lunenfeld E, Beck M, Prinsloo I, Huleihel M. Interleukin-1 receptor antagonist is produced by Sertoli cells in vitro. *Endocrinology.* 2000; 141:1521–1527. [PubMed: 10746659]
111. Rozwadowska N, Fiszer D, Jedrzejczak P, Kosicki W, Kurpisz M. Interleukin-1 superfamily genes expression in normal or impaired human spermatogenesis. *Genes Immun.* 2007; 8:100–107. [PubMed: 17215863]
112. Gomez E, Morel G, Cavalier A, Lienard M, Haour F, Courtens J, Jegou B. Type I and type II interleukin-1 receptor expression in rat, mouse and human testes. *Biol Reprod.* 1997; 56:1513–1526. [PubMed: 9166705]
113. Sultana T, Svechnikov K, Weber G, Soder O. Molecular cloning and expression of a functionally different alternative splice variant of pro-interleukin-1 α from the rat testis. *Endocrinology.* 2000; 141:4413–4418. [PubMed: 11108249]
114. Janitz M, Fiszer D, Lukaszyn A, Skorupski W, Kurpisz M. Analysis of mRNA expression for interleukin-1 genes on human testicular cells. *Immunol Lett.* 1995; 48:139–143. [PubMed: 8719113]
115. Syed V, Stephan J, Gerard N, Legrand A, Parvinen M, Bardin CW, Jegou B. Residual bodies activate Sertoli cell interleukin-1 α (IL-1 α) release, which triggers IL-6 production by an

- autocrine mechanism, through the lipoxygenase pathway. *Endocrinology*. 1995; 136:3070–3078. [PubMed: 7789334]
116. Wahab-Wahlgren A, Holst M, Ayele D, Sultana T, Parvinen M, Gustafsson K, Granholm T, Soder O. Constitutive production of interleukin-1 α mRNA and protein in the developing rat testis. *Int J Androl*. 2000; 23:360–365. [PubMed: 11114982]
 117. Gerard N, Syed V, Jegou B. Lipopolysaccharide, latex beads and residual bodies are potent activators of Sertoli cell interleukin-1 α production. *Biochem Biophys Res Commun*. 1992; 185:154–161. [PubMed: 1599451]
 118. Petersen C, Boitani C, Froya B, Soder O. Interleukin-1 is a potent growth factor for immature rat Sertoli cells. *Mol Cell Endocrinol*. 2002; 186:37–47. [PubMed: 11850120]
 119. Petersen C, Svechnikov K, Froya B, Soder O. The p38 MAPK pathway mediates interleukin-1-induced Sertoli cell proliferation. *Cytokine*. 2005; 32:51–59. [PubMed: 16181786]
 120. Pollanen P, Soder O, Parvinen M. Interleukin-1 α stimulation of spermatogonial proliferation in vivo. *Reprod Fertil Dev*. 1989; 1:85–87. [PubMed: 2496437]
 121. Okuma Y, Saito K, O'Connor AE, Phillips DJ, de Kretser DM, Hedger MP. Reciprocal regulation of activin A and inhibin B by interleukin-1 (IL-1) and follicle-stimulating hormone (FSH) in rat Sertoli cells in vitro. *J Endocrinol*. 2005; 185:99–110. [PubMed: 15817831]
 122. Colon E, Svechnikov KV, Carlsson-Skewir C, Bang P, Soder O. Stimulation of steroidogenesis in immature rat Leydig cells evoked by interleukin-1 α is potentiated by growth hormone and insulin-like growth factors. *Endocrinology*. 2005; 146:221–230. [PubMed: 15486223]
 123. Bornstein SR, Rutkowski H, Vrezas I. Cytokines and steroidogenesis. *Mol Cell Endocrinol*. 2004; 215:135–141. [PubMed: 15026186]
 124. Calkins JH, Sigel MM, Nankin HR, Lin T. Interleukin-1 inhibits Leydig cell steroidogenesis in primary culture. *Endocrinology*. 1988; 123:1605–1610. [PubMed: 3261237]
 125. Lui WY, Lee WM, Cheng CY. Transforming growth factor- β 3 perturbs the inter-Sertoli tight junction permeability barrier in vitro possibly mediated via its effects on occludin, zonula occludens-1, and claudin-11. *Endocrinology*. 2001; 142:1865–1877. [PubMed: 11316752]
 126. Li MWM, Xia W, Mruk DD, Wang CQF, Yan HHN, Siu MKY, Lui WY, Lee WM, Cheng CY. Tumor necrosis factor α reversibly disrupts the blood–testis barrier and impairs Sertoli–germ cell adhesion in the seminiferous epithelium of adult rat testes. *J Endocrinol*. 2006; 190:313–329. [PubMed: 16899565]
 127. Lie PPY, Mruk DD, Lee WM, Cheng CY. Epidermal growth factor receptor pathway substrate 8 (Eps8) is a novel regulator of cell adhesion and the blood–testis barrier integrity in the seminiferous epithelium. *FASEB J*. 2009; 23:2555–2567. [PubMed: 19293393]
 128. Lie PPY, Chan AYN, Mruk DD, Lee WM, Cheng CY. Restricted Arp3 expression in the testis prevents blood–testis barrier disruption during junction restructuring at spermatogenesis. *Proc Natl Acad Sci USA*. 2010; 107:11411–11416. [PubMed: 20534520]
 129. Goley ED, Welch MD. The ARP2/3 complex: an actin nucleator comes of age. *Nat Rev Mol Cell Biol*. 2006; 7:713–726. [PubMed: 16990851]
 130. Disanza A, Carlier MF, Stradal TEB, Didry D, Frittoli E, Confalonieri S, Croce A, Wehland J, Di Fiore PP, Scita G. Eps8 controls actin-based motility by capping the barbed ends of actin filaments. *Nat Cell Biol*. 2004; 6:1180–1188. [PubMed: 15558031]
 131. Disanza A, Mantoani S, Hertzog M, Gerboth S, Frittoli E, Steffen A, Berhoerster K, Kreienkamp H, Milanesi F, Di Fiore PP, Ciliberto A, Stradal TEB, Scita G. Regulation of cell shape by Cdc42 is mediated by the synergic actin-bundling activity of the Eps8-IRSp53 complex. *Nat Cell Biol*. 2006; 8:1337–1347. [PubMed: 17115031]
 132. Lie PPY, Mruk DD, Lee WM, Cheng CY. Cytoskeletal dynamics and spermatogenesis. *Philos Trans R Soc Lond B Biol Sci*. 2010; 365:1581–1592. [PubMed: 20403871]
 133. Vogl, AW.; Vaid, KS.; Guttman, J. The Sertoli cell cytoskeleton. In: Cheng, CY., editor. *Molecular mechanisms in spermatogenesis*. Landes Bioscience/Springer Science + Business Media LLC; Austin: 2008. p. 186–221.
 134. Mruk DD, Silvestrini B, Cheng CY. Anchoring junctions as drug targets: role in contraceptive development. *Pharmacol Rev*. 2008; 60:146–180. [PubMed: 18483144]

135. Yan HHN, Mruk DD, Lee WM, Cheng CY. Blood–testis barrier dynamics are regulated by testosterone and cytokines via their differential effects on the kinetics of protein endocytosis and recycling in Sertoli cells. *FASEB J.* 2008; 22:1945–1959. [PubMed: 18192323]
136. Su L, Mruk DD, Lee WM, Cheng CY. Differential effects of testosterone and TGF- β 3 on endocytic vesicle-mediated protein trafficking events at the blood–testis barrier. *Exp Cell Res.* 2010; 316:2945–2960. [PubMed: 20682309]
137. Russell LD. Further observations on tubulobulbar complexes formed by late spermatids and Sertoli cells in rat testis. *Anat Rec.* 1979; 194:213–232. [PubMed: 464323]
138. Guttman J, Takai Y, Vogl AW. Evidence that tubulobulbar complexes in the seminiferous epithelium are involved with internalization of adhesion junctions. *Biol Reprod.* 2004; 71:548–559. [PubMed: 15084482]
139. Vaid KS, Guttman JA, Babyak N, Deng W, McNiven MA, Mochizuki N, Finlay BB, Vogl AW. The role of dynamin 3 in the testis. *J Cell Physiol.* 2007; 210:644–654. [PubMed: 17133358]
140. Young JS, Guttman JA, Vaid KS, Vogl AW. Cortactin (CTTN), N-WASP (WASL), and clathrin (CLTC) are present at podosome-like tubulobulbar complexes in the rat testis. *Biol Reprod.* 2009; 80:153–161. [PubMed: 18799755]
141. Chapin RE, Wine RN, Harris MW, Borchers CH, Haseman JK. Structure and control of a cell–cell adhesion complex associated with spermiation in rat seminiferous epithelium. *J Androl.* 2001; 22:1030–1052. [PubMed: 11700851]
142. Guttman JA, Obinata T, Shima J, Griswold M, Vogl AW. Non-muscle cofilin is a component of tubulobulbar complexes in the testis. *Biol Reprod.* 2004; 70:805–812. [PubMed: 14627549]
143. Kaksonen M, Toret CP, Drubin DG. Harnessing actin dynamics for clathrin-mediated endocytosis. *Nat Rev Mol Cell Biol.* 2006; 7:404–414. [PubMed: 16723976]
144. Xia W, Wong EWP, Mruk DD, Cheng CY. TGF- β 3 and TNF α perturb blood–testis barrier (BTB) dynamics by accelerating the clathrin-mediated endocytosis of integral membrane proteins: a new concept of BTB regulation during spermatogenesis. *Dev Biol.* 2009; 327:48–61. [PubMed: 19103189]
145. Siu MKY, Lee WM, Cheng CY. The interplay of collagen IV, tumor necrosis factor- α , gelatinase B (matrix metalloprotease-9), and tissue inhibitor of metalloproteases-1 in the basal lamina regulates Sertoli cell-tight junction dynamics in the rat testis. *Endocrinology.* 2003; 144:371–387. [PubMed: 12488366]
146. Xia W, Cheng CY. TGF- β 3 regulates anchoring junction dynamics in the seminiferous epithelium of the rat testis via the Ras/ERK signaling pathway: an in vivo study. *Dev Biol.* 2005; 280:321–343. [PubMed: 15882576]
147. Xia W, Mruk DD, Lee WM, Cheng CY. Differential interactions between transforming growth factor- β 3/T β R1, TAB 1, and CD2AP disrupt blood–testis barrier and Sertoli–germ cell adhesion. *J Biol Chem.* 2006; 281:16799–16813. [PubMed: 16617054]
148. Wang Y, Lui WY. Opposite effects of interleukin-1 α and transforming growth factor- β 2 induce stage-specific regulation of junctional adhesion molecule-B gene in Sertoli cells. *Endocrinology.* 2009; 150:2404–2412. [PubMed: 19164472]
149. Horai R, Asano M, Sudo K, Kanuka H, Suzuki M, Nishihara M, Takahashi M, Iwakura Y. Production of mice deficient in genes for interleukin (IL)-1 α , IL-1 β , IL-1 α/β and IL-1 receptor antagonist shows that IL-1 β is crucial in turpentine-induced fever development and glucocorticoid secretion. *J Exp Med.* 1998; 187:1463–1475. [PubMed: 9565638]

Fig. 1.

IL-1 signaling leads to actin stress fiber formation. The IL-1 signaling complex (green symbols) is assembled when IL-1 binds to its receptor IL-1RI. The heterodimeric receptor complex consisting of IL-1RI and IL-1RAcP leads to the recruitment of MyD88 and IRAKs (see text). Subsequently, IRAK4 phosphorylates IRAK1, which in turn phosphorylates Pellino-1, an E3-ligase that causes poly-ubiquitination (Uq, yellow symbols) of IRAK1. Traf6 is also polyubiquitinated as a result of IRAK2 activity. These events lead to the activation of the NF- κ B pathway (purple symbols) by providing a platform for the recruitment of TGF- β activated kinase 1 (TAK1, a MAPK kinase kinase) and the IKK complex. TAK1 activates IKK2, which in turn phosphorylates I κ B α , thereby freeing NF- κ B. The nuclear translocation of NF- κ B leads to the transcriptional regulation of multiple genes (e.g., increased MLCK expression, see text). MLCK phosphorylates myosin light chain (MLC), thereby promoting actomyosin contraction (pink symbols). Other than the NF- κ B pathway, IL-1 signaling also activates the Rho-ROCK pathway (blue symbols, see text). Phosphorylation of ROCK and LIM kinase (LIMK) leads to the phosphorylation and inactivation of cofilin, thereby promoting actin stabilization. Additionally, ROCK inhibits MLC phosphatase and thus promotes actomyosin contraction. As such, IL-1 signaling leads to the remodeling of actin filaments associated with intercellular junctions (dark purple symbols) or focal adhesion complexes (orange symbols)

Fig. 2.

BTB restructuring and spermiogenesis are coordinated by IL-1 α during spermatogenesis. In stages VI and VII of the seminiferous epithelial cycle (*left panel*), an intact BTB and apical ES are associated with hexagonally packed actin bundles. A surge in IL-1 α at stage VIII (*right panel*) is believed to play a role in BTB restructuring and apical ES disassembly. IL-1 signaling (*green arrows*) may contribute to the (i) remodeling of actin bundles into a branched network by mislocalizing Eps8 and increasing Arp2/3 activity; (ii) disassembly and/or endocytosis of BTB junctional complexes, which possibly involves the p38 MAP kinase pathway; (iii) inhibition of BTB protein degradation; and (iv) disassembly of Sertoli-germ cell adhesion, which possibly involves the ERK pathway. These effects, together with testosterone, which is known to promote the recycling of BTB proteins, result in the simultaneous disassembly of the "old" BTB and the assembly of a "new" BTB. Thus, BTB integrity is maintained while preleptotene spermatocytes enter the adluminal compartment with spermiogenesis occurring at the opposite end of the seminiferous epithelium

Table 1

Expression of IL-1 family members and their receptors in the adult mammalian testis

	Testis	Sertoli cells	Germ cells	Interstitial cells/fluid
IL-1 α	mRNA [107] and protein ^{a,b} [38]	mRNA [107]; protein ^b secreted into culture media [108]	mRNA and protein ^a in immature germ cells ^c [109]; absent in culture media [108]	protein ^a [38]; absent in culture media [108]
IL-1 β	low level of mRNA in intratubular cells; level undetectable in some cases [107, 114]			mRNA [114]
IL-1Ra		mRNA and protein ^a [110]	mRNA in round spermatids [111]	mRNA [111]
IL-1RI & IL-1RII	mRNA [112]	mRNA [112]	mRNA in immature germ cells ^c from rodents but not from humans [112]	mRNA [112]

^aImmunoreactive protein^bBioactive protein detected by thymocyte proliferation assay^cPachytene spermatocytes and round spermatids