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Interleukin-1 and Related Cytokines in the Regulation of Inflammation and Immunity

Alberto Mantovani,[1,2,3,*] Charles A. Dinarello,[4,5] Martina Molgora,[1] and Cecilia Garlanda[1,2,*]
[1]IRCCS Humanitas Clinical and Research Center, via Manzoni 56, 20089 Rozzano Milan, Italy
[2]Humanitas University, via Rita Levi Montalcini, 20090 Pieve Emanuele Milan, Italy
[3]William Harvey Research Institute, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ, UK
[4]Department of Medicine, University of Colorado Denver, Aurora, CO 80045, USA
[5]Department of Medicine, Radboud University Medical Center, Nijmegen, the Netherlands
*Correspondence: alberto.mantovani@humanitasresearch.it (A.M.), cecilia.garlanda@humanitasresearch.it (C.G.)
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Forty years after its naming, interleukin-1 (IL-1) is experiencing a renaissance brought on by the growing understanding of its context-dependent roles and advances in the clinic. Recent studies have identified important roles for members of the IL-1 family—IL-18, IL-33, IL-36, IL-37, and IL-38—in inflammation and immunity. Here, we review the complex functions of IL-1 family members in the orchestration of innate and adaptive immune responses and their diversity and plasticity. We discuss the varied roles of IL-1 family members in immune homeostasis and their contribution to pathologies, including autoimmunity and autoinflammation, dysmetabolism, cardiovascular disorders, and cancer. The trans-disease therapeutic activity of anti-IL-1 strategies argues for immunity and inflammation as a metanarrative of modern medicine.

Introduction

Interleukin-1 (IL-1) was born as a term in 1979 (Aarden et al., 1979) in a pre-gene-cloning era, at the intersection between fever, lymphocyte activation, hematopoiesis, and more. Although the term IL-1 hinted to a single molecule, previous work on endogenous pyrogens had already shown the existence of two cytokines with different isoelectric points (pIs) 5 and 7 (Dinarello et al., 1974). Therefore, early on it was apparent that IL-1 was more than a single molecule, a view vindicated by gene cloning and molecular identification of a complex and diverse family of mediators that now include IL-1α, IL-1β, IL-18, IL-33, IL-36α, IL-36β, IL-36γ, IL-37, and IL-38.

The discovery of IL-1 has had far reaching implications beyond its own properties and activities. The concept of pleiotropic action of cytokines was born from the observation that IL-1 at vanishingly low concentrations affected tissues and cells as diverse as T cells and hypothalamus. Moreover, as discussed elsewhere (Garlanda et al., 2013), IL-1 and its receptors are upstream of ground-breaking discoveries ranging from Toll-like receptors (TLRs), to inflammasomes, to decoy receptors.

The IL-1 family is complex with ligands endowed with agonist (6), antagonist (3), or anti-inflammatory (1) activity and 9 receptor chains. IL-1 has long been associated with inflammation and innate immunity. It is now apparent that this complex family has a broader role extending beyond classically defined generic inflammation. IL-1 itself and the related family members IL-33 and IL-18 play differential roles in shaping and orienting innate immunity and inflammation in response to different microbial or environmental challenges. Differentiation and polarization of myeloid cells and innate or adaptive lymphoid cells is driven by IL-1, IL-33, and IL-18. Moreover, specialized circuits of homeostasis and defense at mucosal surfaces require IL-1 family members.

Here, we review the complexity of IL-1 family members and their receptors and discuss their involvement in the activation and orientation of innate and adaptive immunity and immunopathology. Previous reviews provide a framework for the present essay (Dinarello, 2009b; Gabay et al., 2010; Garlanda et al., 2013). Building on these works, we will focus on recent developments and discoveries pertaining to the IL-1 family, including the regulatory pathways such as IL-37 and IL-1R8. In this context, we will discuss the implications of new vistas on the complexity and pathophysiological role of "IL-1 and Friends" for human disease and therapeutics.

Complexity and Diversity of Receptors, Ligands, and Negative Regulators

The IL-1 family is composed of 11 soluble molecules and 10 receptors (Figure 1). IL-1 family cytokines are divided into three subgroups, on the basis of the IL-1 consensus sequence and the signaling receptor chain and include secreted molecules with agonistic activity (IL-1α, IL-1β, IL-18, IL-33, IL-36α, IL-36β, and IL-36γ), receptor antagonists (IL-1Ra, IL-36Ra, and IL-38), and an anti-inflammatory cytokine (IL-37) (Dinarello, 2018). IL-1-related cytokines are not translated and secreted as bioactive molecules, but they are found in the cytoplasm as precursors. With the exception of IL-1Ra, IL-1 cytokines carry a consensus sequence (AXD), located 9 amino acids after the cleavage site to reach the optimal bioactivity for the molecule (Afonina et al., 2015). In the case of IL-1β, this is a cleavage site for caspase-1 (Figure 1A). Genomic organization and evolution analysis showed that agonists co-evolved with receptor antagonists and anti-inflammatory molecules, given that most of them (IL-1β, IL-1Ra, the IL-36 subgroup, IL-38, IL-37, and IL-18) are present in all vertebrates from cartilaginous fish to mammals and appeared about 420 million years ago (Rivers-Auty et al., 2018). This suggests the evolutive relevance of balanced responses in the IL-1 system.

Interleukin-1 receptor family members (ILRs) are present in all vertebrates and originated through ancestral gene duplication

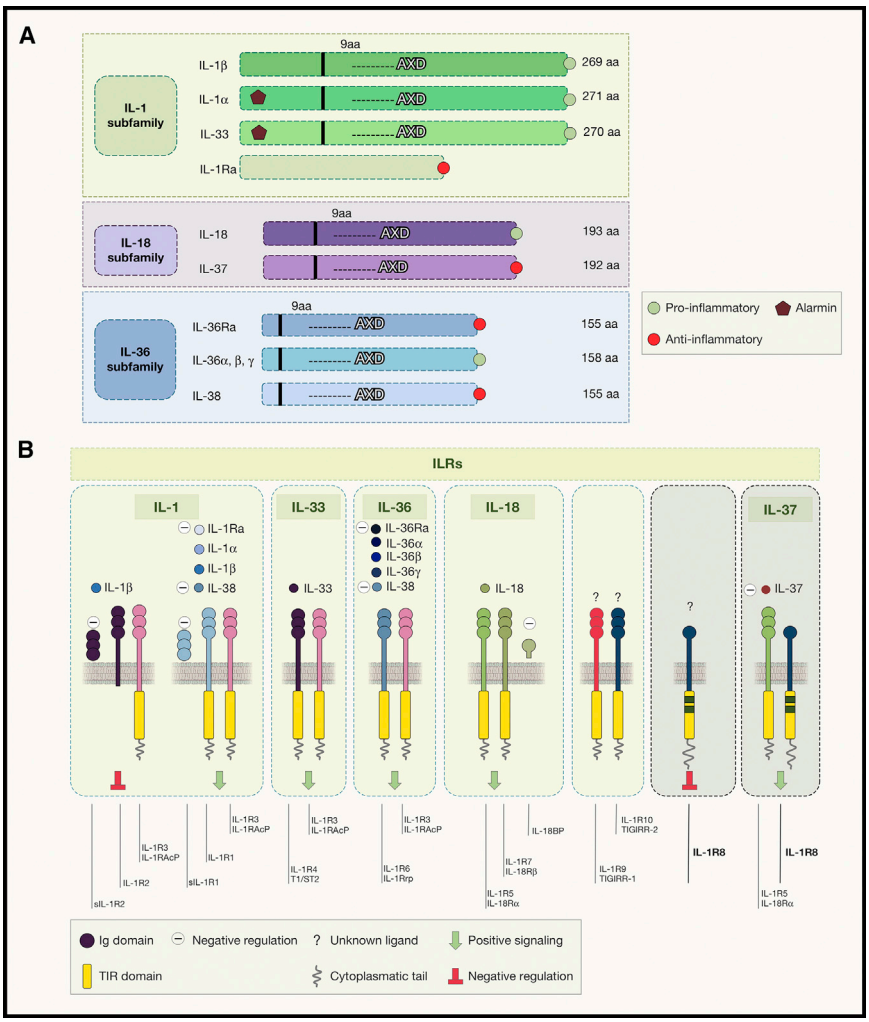

Figure 1. Structural Organization of IL-1 Family Members and Their Receptors

(A) Subfamilies of IL-1 ligands, grouped by structural similarity. The consensus sequence (AXD), which located 9 amino-acids after the cleavage site, is shown.

(B) IL-1 receptors and their cognate agonists and antagonists. The ILR subfamily is composed by receptors and accessory proteins (AcPs) for the cytokines of the IL-1 family. A novel nomenclature of ILRs has been recently proposed and it is as follows: IL-1R1 (IL-1RI), IL-1R2 (IL-1RII), IL-1R3 (IL-1RAcP), IL-1R4 (ST2), IL-1R5 (IL-18Rα), IL-1R6 (IL-1Rrp2 and IL-36R), IL-1R7 (IL-18Rβ), IL-1R8 (TIR8 or SIGIRR), IL-1R9 (TIGIRR- 2), and IL-1R10 (TIGIRR-1).

events, with some exceptions, including IL-1R8, which did not evolve from a common IL-1R ancestral gene (Rivers-Auty et al., 2018). Interestingly, the IL-33 receptor (IL-1RL1) probably originally acted as an orphan receptor or by interacting with other ligands, as suggested by its role in rainbow trout, given that IL-33 appeared only in mammals between 320 and 160 million years ago (Rivers-Auty et al., 2018). ILRs share a common intracellular signaling domain with TLRs, named Toll-IL-1 resistance (TIR) domain, and are characterized by extracellular immunoglobulin (Ig)-like domains (Figure 1B). Upon ligand binding, ILRs dimerize through their TIR domains, inducing the recruitment of the TIR domain-containing adaptor protein MyD88, which couples to downstream protein kinases (e.g., IL-1R-associated kinases [IRAKs], and tumor necrosis factor receptor-associated factor 6 [TRAF6]). The signal leads to the activation of key transcription factors associated with inflammatory and immune responses, such as nuclear factor-κB (NF-κB), activator protein-1 (AP-1), c-Jun N-terminal kinase (JNK), p38 and other mitogen-associated protein kinases (MAPKs), extracellular signal-regulated kinases (ERKs), and members of the interferon-regulatory factor (IRF) (Dinarello, 2009a).

The shared usage of MyD88 by IL-1R family members raises the issue of the mechanism(s) responsible for generation of response specificity. The IL-1R receptor repertoire is a major determinant of specificity. For instance, the IL-18 receptor is highly expressed in natural killer (NK) cells, as is IL-1R8, and IL-18 is a driver of the differentiation and activation of NK cells. Moreover, negative regulators are also differentially expressed and regulated, thus resulting in differential tuning of the response. For instance, IL-4 and IL-13 dampen the response of myelomonocytic cells to IL-1 by upregulating the decoy IL-1R2 (Colotta et al., 1993), but it leaves the responsiveness to IL-33 and expression of type 2 immunity unaffected. Thus, differential expression of receptors and regulatory molecules underlies specificity of action of different members of the IL-1 family.

The strict regulation of this system is essential under physiological and pathological conditions and is controlled by decoys, antagonists, and anti-inflammatory cytokines. IL-1R2 exerts regulatory functions acting in membrane-bound or released form as a decoy receptor for IL-1, as a dominant negative, and as a scavenger (Colotta et al., 1993). In addition, IL-1R2 is also present in the cytoplasm where it binds pro-IL-1α, preventing its cleavage and activation (Zheng et al., 2013). IL-1R8, also known as TIR8 or SIGIRR, lacks conventional signaling capacities and acts as a negative regulator of the family, acting intracellularly. Available information suggests that IL-1R8 interferes with the association of TIR-containing adaptor molecules to the receptor complex, thus dampening the signaling pathway leading to signal transduction (Molgora et al., 2018). In addition, IL-1R8 is a component of the receptor recognizing the anti-inflammatory cytokine IL-37 (Nold-Petry et al., 2015). IL-37 is an anti-inflammatory cytokine that acts as a natural brake of inflammation and immunity, signaling through IL-1R5 (also known as IL-18Rα) and IL-1R8 (Nold-Petry et al., 2015). IL-18BP is an extracellular protein that binds IL-18, preventing its interaction with the receptor

IL-1R5 (IL-18Rα), and thus neutralizing its activity (Novick et al., 1999). IL-1Ra and IL-36Ra are highly conserved receptor antagonists that bind IL-1R1 and IL-1R6, respectively, and evolved under strong evolutionary pressure due to specificity of function (Rivers-Auty et al., 2018).

Similarities and Differences between IL-1α and IL-1β

The usage of the same receptor by IL-1α and IL-1β raises the general question as to why there are two IL-1s; perhaps the redundancy adds robustness, or maybe each has a specialized function (Mantovani, 2018). Phylogenetic analysis indicates that IL-1α likely arose through a duplication event of the ancestral IL-1β gene, between 320 and 160 million years ago, and then IL-1α underwent a divergent evolutionary pressure associated with distinct functions of the pro-domain of the precursor (Rivers-Auty et al., 2018). In contrast to IL-1β, which is not constitutively expressed and is produced only by myeloid cells, the IL-1α precursor is present in mesenchymal cells of healthy humans, including keratinocytes, the type 2 epithelial cells of the lung, the entire gastrointestinal tract and in brain astrocytes. IL-1α is also produced by all myeloid cells but is not constitutive as in mesenchymal cells. Unlike IL-1β and IL-18, there is no requirement for caspase-1 cleavage of the IL-1α precursor to process and release the active cytokine. In contrast, the IL-1α is active as a precursor whereas the IL-1β precursor is not (Kim et al., 2013). The 31-kDa IL-1α precursor can be cleaved *in vitro*, particularly in murine cell lines, to a 17-kDa cytokine by unknown proteases. Calcium-activated membrane calpains also process the IL-1α precursor, although it is unlikely that this takes place under physiological conditions. In fact, the consistent failure to detect IL-1α in the circulation under severe inflammatory conditions supports the notion that this member of the family is primarily a local mediator in tissues. Recently, pro-IL-1α was shown to be activated by thrombin cleavage at a conserved consensus site, indicating a novel link between coagulation and inflammation (Burzinsky et al., 2019).

The most distinctive characteristic of IL-1α is that it acts as an integral membrane protein, particularly on macrophages. Membrane IL-1α activates the IL-1R1 on adjacent cells through a mechanism termed "juxtacrine" (Kurt-Jones et al., 1985). The IL-1α precursor is also constitutively present in endothelial cells and during inflammation, and it is released in membrane-bound "apoptotic bodies," which are biologically active (Berda-Haddad et al., 2011).

Similar to IL-33 and IL-37, IL-1α is a dual function cytokine in the IL-1 family. Extracellularly, IL-1α binds to the IL-1R1 on the surface of the cell, recruits its co-receptor IL-1R3 and initiates a pro-inflammatory signal, identical to that of IL-1β. With its nuclear localization sequence at the N terminus, the IL-1α precursor functions in the nucleus as a transcription factor (Dinarello, 2009a; Wessendorf et al., 1993). Inside the cell, IL-1α shuttles between the cytosol and the nucleus with amazing rapidity. During natural apoptosis, for example such that takes place in the lining epithelium of the gut or in keratinocytes of the skin, IL-1α leaves the cytosol and binds tightly to chromatin. When that cell dies, there is no inflammation from the cell contents, because IL-1α bound to chromatin does not bind to its cell surface receptor. In contrast, when the cell becomes necrotic, the IL-1α leaves the nucleus and is found in the cytosol. The IL-1α precursor is released with cell contents, where it binds to IL-1R1 on adjacent live cells. Sterile inflammation due to necrotic tissue appears to be IL-1α-mediated and independent of TLR4 (Chen et al., 2007). IL-1α released in this manner has earned the IL-1α precursor term "alarmin" (Figure 2).

Because IL-1α and IL-1β trigger the same IL-1R1 and signal transduction is the same for both cytokines, defining a disease due to IL-1α is, in the strict sense, not possible. However, in mice, the specific deficiency of IL-1α compared with IL-1β can be used as pre-clinical data for neutralizing IL-1α in human diseases. The skin remains an IL-1α "organ." Anakinra was used to treat hidradenitis suppurativa (Tzanetakou et al., 2016), but a second study in this disease specifically targeting IL-1α revealed a more robust response (Kanni et al., 2018). Other inflammatory neutrophil dermatoses such as pyoderma granulosum appear to be primarily IL-1α-driven and in a mouse model, caspase recruitment domain family member 9 (CARD9) signaling was identified as increasing IL-1α (Tartey et al., 2018). In murine neonatal sepsis, IL-1α and not IL-1β drives mortality (Benjamin et al., 2018). IL-1α deficiency after spinal cord injury in the mouse is protective (Bastien et al., 2015).

Although there is no clinical trial specifically targeting IL-1α in inflammatory bowel disease, studies in mice with dextran sulfate sodium (DSS) colitis clearly implicate IL-1α from the intestinal epithelium as driving the inflammation, whereas IL-1β acts to heal the intestinal barrier (Bersudsky et al., 2014). A similar study also in mice showed that intestinal inflammation from infection with *Yersinia enterocolitica* is IL-1α– and not IL-1β-mediated (Dube et al., 2001). As clinical studies using antibodies that specifically neutralize IL-1α increase, it is likely that IL-1α will be identified as a target.

IL-1 is a Driver of Emergency Hemopoiesis and Trained Innate Immunity

Under homeostatic conditions, hematopoietic stem cells (HSCs) are capable of constantly replenishing the differentiated cells, undergoing a physiological turnover. In case of infection or any kind of damage associated with the need of an increased number of hematopoietic cells, such as sterile, acute, and chronic inflammation; aging; and blood regeneration after chemotherapy, radiotherapy, or bleeding, the system rapidly responds with a specific program generally named "emergency hematopoiesis" (Boettcher and Manz, 2017; Manz and Boettcher, 2014; Takizawa et al., 2012) (Figure 3A). IL-1 was originally discovered as hemopoietin-1. Steady-state levels of IL-1 are dispensable for homeostatic hemopoiesis, whereas acute and chronic IL-1 exposure drives the "emergency" response, leading to a sustained myeloid skewing and a consequent loss and damage of HSCs (Pietras et al., 2016). The transcriptional regulator PU.1, downstream of IL-1R1, was shown to be the key molecule governing IL-1 response in HSCs (Pietras et al., 2016) (Figure 3A). Although IL-1β has been mostly investigated as a systemic stimulus for the emergency response, both IL-1α and IL-1β were locally induced in the bone marrow niche in response to damage (Mitroulis et al., 2018; Pietras et al., 2016), thus suggesting that both contribute to emergency myelopoiesis. HSCs respond to inflammatory mediators and microbial compounds, allowing a rapid immune response but having short- and long-term effects on the stem cell niche preservation (Baldridge

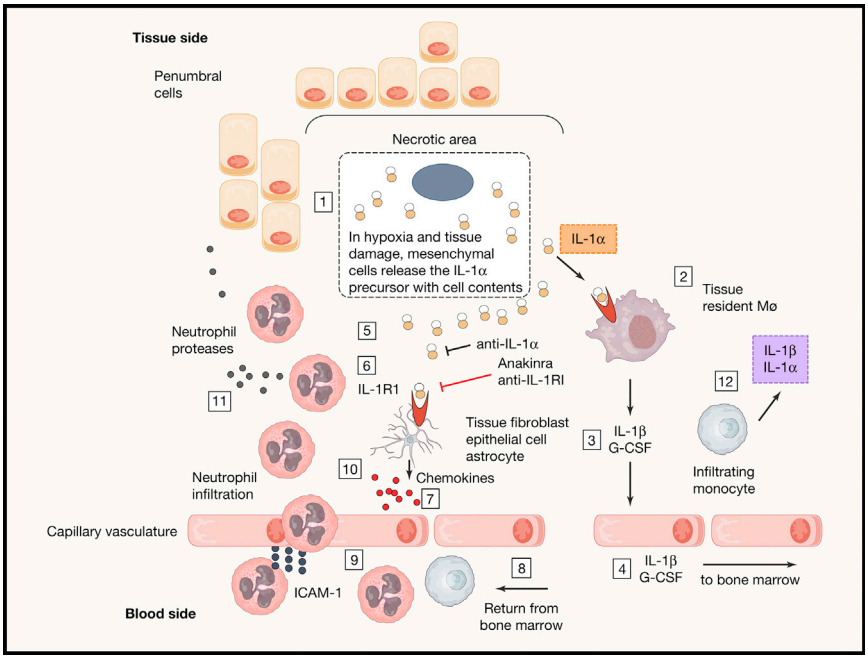

Figure 2. IL-1α as an Alarmin in Tissue Damage

Ischemia is shown as a prototypic cause of tissue damage. (1) Subjected to low oxygen and increased acidity, cells in the ischemic or damaged tissues lose membrane integrity and the constitutively present IL-1α precursor leaves the cell. (2) IL-1α binds to the IL-1R1 on resident macrophages. (3) IL-1β is released via NLRP3 inflammasome activation with ATP derived from hypoxic cell. Also released is granulocyte-colony stimulating factor (G-CSF). At this point, anakinra, anti-IL-1α, and anti-IL-1R1 reduce inflammation. (4) IL-1β and G-CSF enter the venous circulation and into the right ventricle. From the heart, arterial blood reaches the bone marrow and IL-1β and G-CSF induce the release of neutrophils and monocytes into the venous drainage. (5) The IL-1α precursor accumulates in the extracellular space of the ischemic tissue. (6) IL-1α binds to IL-1R1 on tissue fibroblasts, epithelial cells, and astrocytes in the respective tissue type. Anti-IL-1α, anakinra, or anti-IL-1R1 reduce the inflammatory process at this point. (7) Production of chemokines such as CCL1 follows binding. (8) Arterial circulation reaches the ischemic tissue with neutrophils and monocytes from the bone marrow. (9) Neutrophils bind to ICAM-1 and cross the endothelial barrier with the assistance of chemokines. (10) Neutrophils accumulate in the tissue. (11) Neutrophils mediate damage to the penumbral cells. (12) In addition to IL-1α, infiltrating monocytes produce IL-1β, and the ischemic site becomes dominated by IL-1β, which contributes to steps 6–11, sustaining the inflammatory cascade.

et al., 2010; Essers et al., 2009; Liu et al., 2015; Maeda et al., 2009; Sato et al., 2009).

In line with this, IL-1 was suggested to be involved in HSC aging, which is associated with immune senescence, a functional defect in both the innate and adaptive immune response, and a consequent increased susceptibility to infections, autoimmune diseases, hematological malignancies, and impaired response to vaccines (Bottazzi et al., 2018; Ciabattini et al., 2018; Kovtonyuk et al., 2016). An increased frequency of somatic mutations and the unbalanced expansion of a somatic clone in the hematopoietic lineage, defined as "clonal hematopoiesis of indeterminate potential" (CHIP), often occur in elderly individuals, even in the absence any other hematological disorder (Steensma et al., 2015). Recent studies revealed that CHIP was associated with the risk of coronary heart disease in humans and atherosclerosis in a murine model (Fuster et al., 2017; Jaiswal et al., 2017). In particular, the expansion of ten-eleven-translocation-2 (TET2) mutant hematopoietic clones, which represents a common condition in CHIP, augmented the pathology and was suggested to be the major driver of atherosclerosis. IL-1β was shown to be responsible for atherosclerosis promotion in mice with bone marrow TET2-deficiency (Fuster et al., 2017). Indeed, IL-1β production was increased in macrophages in the atherosclerotic plaque upon transplant with 10% TET2 mutant bone marrow and the inhibition of NACHT, LRR, and PYD domains-containing protein 3 (NLRP3) abolished the greater disease severity observed (Fuster et al., 2017).

CHIP, sustained by IL-1, is a feature of aging. Inflammation is a key feature of senescence at a cellular and organism level. At the cellular level, senescence results in production of a set of cytokines in the so-called senescence-associated secretory phenotype (SASP) (Coppé et al., 2010). SASP includes IL-1α and IL-1β, which are major drivers of senescence at a cellular level. As for CHIP, IL-1 has emerged as a key component of inflammation associated with aging and associated disease manifestations (inflammaging), as also discussed below (Bottazzi et al., 2018; Ciabattini et al., 2018).

Immunological memory has long been considered as a property unique to adaptive immunity. Microbial recognition triggers short- (in the form of priming and tolerance) and long-term reshaping of the response of myeloid cells to pathogens, a property referred to as memory, adaptive, or trained innate immunity (Arts et al., 2016; Bowdish et al., 2007). IL-1β was shown to drive an epigenetic reprogramming in monocytes, similar to that acquired by monocytes trained by β-glucan, bacillus Calmette-Guerin (BCG), and oxidized low-density lipoprotein oxLDL (Mitroulis et al., 2018; Moorlag et al., 2018). Moreover, metabolic changes associated with trained immunity were mimicked in monocytes upon treatment with IL-1β, suggesting a key role for IL-1β in trained immunity (Arts et al., 2018; Cheng et al., 2014) (Figure 3A). Importantly, pharmacologic inhibition of IL-1 by Anakinra abolished the effect of β-glucan on HSCs, in terms of cell-cycle modulation, myeloid skewing, and metabolic switch (Mitroulis et al., 2018).

The original description of trained immunity was centered on long term education of macrophages in lower organisms and mammals (Kurtz and Franz, 2003; Locati et al., 2013; Netea et al., 2016). More recent results point to a key role of neutrophils and on the effect of IL-1 on hematopoietic precursors (Mitroulis et al., 2018; Moorlag et al., 2018). IL-1 has long been known to

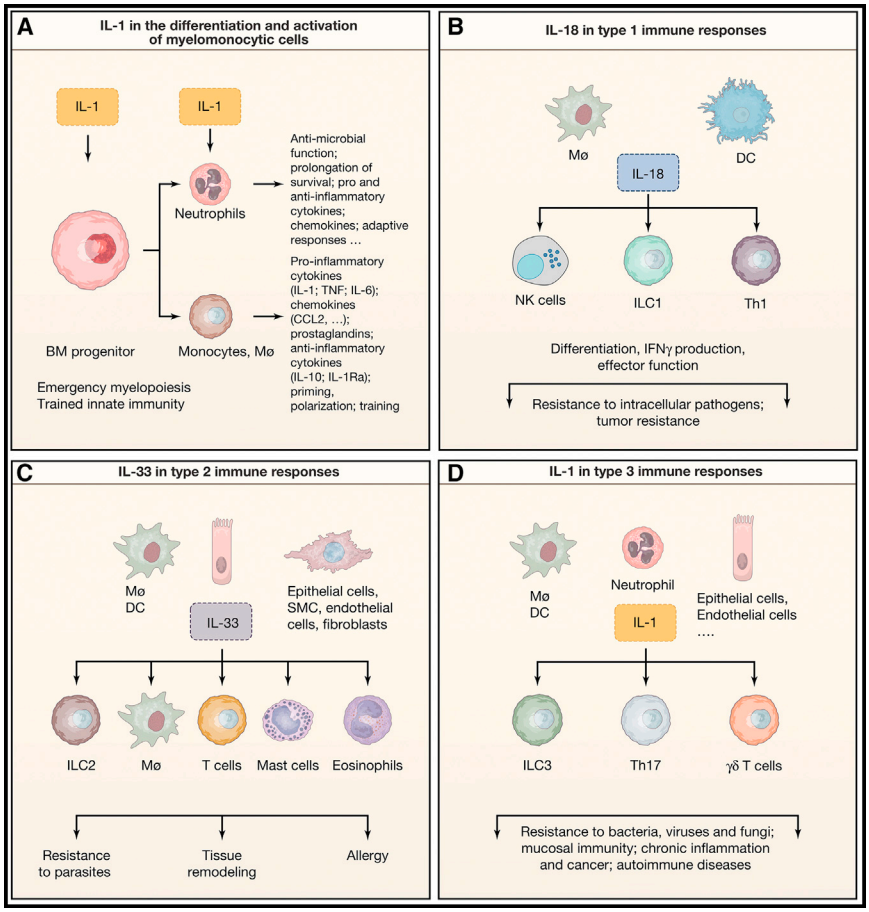

Figure 3. Role of IL-1 Family Members in the Differentiation and Function of Myelomonocytic Cells and in the Orchestration of Innate and Adaptive Immune Responses

(A) IL-1β regulates emergency hematopoiesis, trained innate immunity acting on bone marrow hematopoietic progenitors, and mature myeloid cell functional activity and survival.

(B–D) Schematic representation of type 1 (B), type 2 (C), and type 3 immunity (D) activated by IL-18, IL-33, and IL-1, respectively.

promote survival of neutrophils (Colotta et al., 1992). One could speculate that IL-1-mediated prolongation of survival of neutrophils and monocytes and macrophages plays a permissive role in their training.

IL-18 and IL-1 as Drivers of Type 1 Immunity

IL-18 is a powerful inducer of type-1 responses in innate and adaptive lymphocytes (Figure 3B). IL-18 was first described as an interferon-γ (IFN-γ)-inducing factor, and it is indeed involved in the activation of NK and Th helper 1 (Th1) cells (Okamura et al., 1995). Similar to IL-1, it is synthetized as an inactive precursor and processed by caspase-1 upon inflammasome activation. It binds its specific receptor IL-18Rα (IL-1R5), leading to the recruitment of the accessory chain IL-18Rβ (IL-1R7), myddosome activation, and signaling via NF-κB.

Because group 1 innate lymphoid cells (ILC1s) and NK cells share several functional similarities as well as overlapping identification markers, they were both originally considered as part of the ILC1 group. Recently, a distinct precursor that drives the development of ILC1, but not NK cells, has been characterized. Moreover, phenotypic analysis in different tissues have revealed distinct markers to distinguish NK cells and ILC1s (Colonna, 2018). Both ILC1 and NK cells have emerged as prime targets for IL-18. IL-18, including a membrane-bound form expressed on monocytes-macrophages, cooperates with signal transducers and activators of transcription (STAT)-inducing cytokines (i.e., IL-12 and/or IL-15) to trigger NK cell effector functions, in terms of IFN-γ production, cytotoxicity, and Fas ligand (FasL) expression (Bellora et al., 2014; Bellora et al., 2012; Chaix et al., 2008; Madera and Sun, 2015; Tsutsui et al., 1996) (Figure 3B).

IL-18R-deficient NK cells exhibited an impaired anti-viral response in a cytomegalovirus (CMV) infection model and IL-18-MyD88 signaling was necessary for optimal NK cell activation and differentiation during the infection (Madera and Sun, 2015). Human and murine NK cells treated with IL-18, together with IL-12 and IL-15, acquired a memory-like phenotype and after adoptive transfer were able to persist long term and exhibited increased activation, even though IL-18 signaling was demonstrated to be dispensable for Ly49H-mediated recall response in the mouse model (Cerwenka and Lanier, 2016; Madera and Sun, 2015; Romee et al., 2012).

In a colorectal-cancer-derived liver metastasis model (MC38), mice deficient in NLRP3 inflammasome components showed augmented liver disease, which was dependent on a defective IL-18-mediated regulation of NK cells (Dupaul-Chicoine et al., 2015). In particular, in the absence of mature IL-18, NK cell differentiation and FasL-mediated killing was impaired in the liver, causing exacerbated metastasis growth (Dupaul-Chicoine et al., 2015). In a lung metastasis model, the treatment with IL-18 alone and in combination with IL-2 led to NK-cell-mediated tumor control, in a FasL- and perforin-dependent manner, but independently of natural killer group 2D (NKG2D) (Smyth et al., 2004).

Recently, the inhibitory receptor IL-1R8 was shown to be highly expressed in human and murine NK cells and plays a key role in the modulation of NK cell differentiation and effector functions (Molgora et al., 2017). In particular, IL-1R8-deficient NK cells showed unleashed IL-18-driven activation and displayed enhanced maturation, IFN-γ production, cytotoxicity, and FasL expression. IL-1R8-mediated regulation in NK cells was dependent on the IL-18-MyD88 pathway, whereas no involvement of IL-1 signaling was observed. Importantly, *Il1r8*$^{-/-}$ NK cells were protective in mouse models of hepatocellular carcinoma, sarcoma-derived lung metastasis, colorectal-cancer-derived liver

metastasis, and murine cytomegalovirus (MCMV) infection (Molgora et al., 2017), as discussed below. In parallel, it was found that T regulatory cell (Treg)-derived IL-37 suppressed activation of $CD3^{-}CD56^{dim}CD57^{+}Fc\varepsilon R\gamma^{+}NKG2C^{-}$ NK cells, but not adaptive ($CD3^{-}CD56^{dim}CD57^{+}Fc\varepsilon R\gamma^{-}NKG2C^{+}$) NK cells, which are expanded in CMV seropositive donors. Treg-mediated suppression in canonical NK cells was associated with TIM-3 downregulation and programmed cell death protein 1 (PD-1) and IL-1R8 upregulation, and the blockade of IL-37, PD-1, or IL-1R8 rescued the suppression (Sarhan et al., 2018). IL-1R8, therefore, emerges as a novel regulator of NK cell anti-tumor and anti-viral potential, inhibiting the IL-18 pathway and promoting IL-37-mediated NK cell suppression.

In group 1 ILCs, IL-18, together with IL-12, IL-21, and IL-15, induces IFN-γ production (Bernink et al., 2015; Cortez et al., 2015; Vivier et al., 2018). IFN-γ was not induced in $CD127^{+}$ and $CD103^{+}$ ILC1 upon stimulation with IL-15 alone, in contrast to conventional NK cells, whereas IL-12 plus IL-18 activated in all populations an equivalent IFN-γ response, which was even greater than that with the treatment with IL-12 plus IL-15 (Bernink et al., 2015). RNA sequencing (RNA-seq) analysis revealed that IL-1R8 is expressed in ILC1 cells (Shih et al., 2016). IL-1R8-deficient liver resident ILC1 cells were shown to produce higher levels of IFN-γ upon CMV infection *in vivo* (Molgora et al., 2017).

Finally, IL-18 sustains Th1 and cytotoxic T cell activation (Nakanishi, 2018). IL-18 synergizes with IL-12 and TCR triggering to induce IFN-γ and consequent defense against microbes and tumors, being on the other hand involved in autoimmune reactions and tissue damage (Nakanishi et al., 2001). Recently, it was reported that the colonization with the commensal protozoan *Tritrichomonas musculis* led to a substantial IL-18 release in the colon, favoring the expansion of both $CD4^{+}$IFN-γ^{+} and $CD4^{+}$IL-17^{+} T cells and being protective against mucosal bacterial infections. On the other hand, it promoted pathogenic intestinal inflammation and colorectal tumors (Chudnovskiy et al., 2016).

IL-1 enhances antigen-driven response in both CD4 and CD8 T cells, supporting the expansion and activation of specific Th1, Th2, Th17, and Granzyme B^{+} CD8 T cells *in vivo* (Ben-Sasson et al., 2009). IL-1 was necessary for naive $CD4^{+}$ T cells to overcome Treg-mediated inhibition and memory $CD4^{+}$ T cells to acquire a fully functional memory phenotype (Schenten et al., 2014). In addition, IL-1β in combination with IL-23 promoted the plasticity of Th17 cells toward a Th1 phenotype, and the generation of $CD161^{+}$ Th1 subsets, named as "non-classic" Th1 cells (Santarlasci et al., 2013).

Finally, IL-1β was shown to enhance Th9 cell function through the IRF1-dependent increase in the production of IL-21, which promoted IFN-γ production and antitumor activity of $CD8^{+}$ and NK cells (Végran et al., 2014).

Thus, IL-18 produced by macrophages and DCs is a driver of Type 1 immunity by activating NK cells, ILC1, and Th1 cells. Moreover, although IL-1 is an important component of Th17 cell differentiation, it can promote a broad spectrum of T cell responses, including $CD8^{+}$ cells.

IL-33 as a Driver of Type 2 Immunity

IL-33 is a central cytokine involved in type 2 innate and adaptive immunity and inflammation, modulating ILC2, Th2, and M2 macrophage response, responsible for the control of type 2 infections and tissue repair, as well as harmful allergic responses (Figure 3C). IL-33 is mainly secreted by unconventional mechanisms or upon cell necrosis, by hematopoietic, stromal, and parenchymal cells, and by signals via the suppression of tumorgenicity 2 (ST2) (IL-1R4) receptor coupled with the accessory protein IL-1RAcP (IL-1R3), inducing MyD88 activation.

IL-33 plays a protective role in the elimination of parasites through the induction of IL-13 in ILCs, which is beneficial for nematode expulsion and control of *Toxoplasma gondii* encephalitis (Moro et al., 2010; Neill et al., 2010). In helminthic infections, IL-1β inhibits IL-33 and IL-25 production, suppressing the clearance of the pathogen and contributing to infection chronicity (Zaiss et al., 2013).

IL-33 drives the amplification of neutrophil maturation and eosinophilia *in vivo*, inducing IL-5 in ILC2s (Bouffi et al., 2013; Ikutani et al., 2012; Molofsky et al., 2013; Pecaric-Petkovic et al., 2009). Indeed, in ILC2-deficient mice IL-33-mediated eosinophilic lung inflammation was abolished (Halim et al., 2014). Intranasal injection of IL-33 directly induced ILC proliferation and IL-13 and IL-5 secretion and favored basophil production of IL-4, which in turn activated ILC2s (Halim et al., 2014; Motomura et al., 2014). The release of uric acid by allergen-stimulated or damaged epithelial cells was shown to induce IL-33 release *in vivo* (Enoksson et al., 2011; Shi et al., 2003). IL-33-deficient mice showed defective response to papain intranasal injection, which resembles allergen response, stimulating ILC2s and causing mucus hyperproduction and eosinophilia (Halim et al., 2014). IL-33 was also demonstrated to induce amphiregulin secretion by ILC2s, which promotes tissue healing, suggesting a role of IL-33 in ILC2-mediated tissue repair (Monticelli et al., 2011).

Moreover, dendritic cells activated by IL-33 promoted Th2 response (Besnard et al., 2011). Mouse models of allergic lung inflammation, *A. fumigatus* airway hyperreactivity, and influenza virus revealed a key role of IL-33 as a driver of type 2 responses, in terms of Th2 cell polarization, mucus secretion, eosinophil recruitment, and goblet cell hyperplasia (Albacker et al., 2013; Tjota et al., 2013). In humans, single nucleotide polymorphisms (SNPs) have been identified in IL-33 and ST2 genes and are associated with asthma development (Moffatt et al., 2010). In line with this, IL-33 upregulation occurs in the bronchial mucosa of asthmatic patients and positively correlates with disease severity (Bianchetti et al., 2012; Li et al., 2018).

IL-1β was recently shown to be involved in the regulation of ILC2 function and plasticity, inducing proliferation, cytokine production, and promoting the responsiveness to IL-25 and IL-33. Interestingly, IL-1β also induced the expression of T-cell-specific T-box transcription factor (T-bet)- and Th1-associated genes (e.g., *IL12RB1*, *IL12RB2*, *STAT1*, *EOMES*, and *NFIL3*) in ILC2s and affected the ILC2 epigenetic landscape, driving the generation of a hybrid ILC2-ILC1 population and enabling the conversion into ILC1-like cells in response to IL-12 (Ohne et al., 2016). Therefore, IL-1 contributes to the plasticity of ILCs.

IL-1 as a Driver of Type 3 Immunity

IL-17 responses are powerful tools in protective immunity against infections with bacteria, fungi, and some viruses, especially at mucosal tissues (Korn et al., 2009; Zhou et al., 2009). On the other hand, IL-17 has a major pathogenic role in several

chronic inflammatory and autoimmune diseases. IL-23 was characterized as the fundamental cytokine driving IL-17 production in T cells and both IL-1α and IL-1β synergize with IL-23 to promote IL-17A production by human and murine T cells, either in the presence or the absence of TCR engagement (Langrish et al., 2005; Mills et al., 2013) (Figure 3D). Indeed, IL-1R1-deficient mice lack IL-17A secretion upon IL-23 stimulation and are protected in experimental autoimmune encephalomyelitis (EAE) models, similarly to IL-23-deficient mice (Cua et al., 2003; Sutton et al., 2006).

In line with this, IL-1R8-deficient mice showed an augmented susceptibility to Th17-dependent EAE as a result of an uncontrolled IL-1 signaling in Th17 cells, leading to increased Th17 proliferation and function (Gulen et al., 2010). Moreover, IL-1 induces IL-6 production in innate immune cells, indirectly supporting T cell differentiation toward IL-17-producing T cells (Acosta-Rodriguez et al., 2007). The IL-23/IL-17 axis is also sustained by both IL-1α and IL-1β in γδ T cells, which express IL-1R1 and, similarly to Th17, are pathogenic in several inflammatory diseases (Sutton et al., 2009). Furthermore, γδ T cells express very high levels of IL-18R, and IL-18 together with IL-23 promotes IL-17 production (Lalor et al., 2011). IL-1R8 is highly expressed in γδ T cells and suppresses IL-17A production in γδ T cells. In psoriasis models, IL-1R8-deficient mice showed enhanced γδ T cell infiltration and activation and developed more severe disease, reverted by IL-17A neutralization (Russell et al., 2013). These data highlight the importance of IL-1 and IL-1 regulation in Th17 immunity as well as the IL-17 pathogenic effects.

ILC3s are enriched at mucosal sites, where they control homeostasis and are important components of the early immune response (Vivier et al., 2018). IL-1β supports IL-17A and IL-22 production in ILC3s (Bernink et al., 2015; Cella et al., 2010; Longman et al., 2014). *In vitro* cultures of sorted ILC3s demonstrated that IL-2, IL-23, and IL-1β preserved the ILC3 phenotype and favored the acquisition of NKp44. Moreover, IL-23 plus IL-1β were shown to be sufficient for the $CD127^+$ ILC1 switch toward ILC3, losing the capacity to produce IFN-γ and instead producing IL-22 *in vitro* and *in vivo*. In agreement, IL-1, together with IL-2 and IL-23, promoted retineic-acid-receptor-related orphan nuclear receptor gamma (RORγt) upregulation in $CD127^+$ ILC1s induced by retinoic acid (Bernink et al., 2015).

IL-1 Family Members Are Involved in Regulatory T Cell Function

Arpaia et al. (2015) showed that selective Treg cell deficiency in amphiregulin, which promotes tissue repair during organ damage and inflammatory conditions, caused severe lung injury in a model of influenza virus infection. In this context, IL-18 and IL-33 were responsible for amphiregulin secretion by Treg cells, which was independent of TCR triggering (Arpaia et al., 2015). In mice infected with CMV, Treg cells were enriched in the liver and played a key role in controlling liver damage. In this infection, ST2 expression was upregulated in liver Treg cells and IL-33 was fundamental for Treg cell enrichment and function. IL-33 production increased in CMV-infected livers and localized in close proximity with the foci of infection only in $F4/80^+$ cells. In agreement, ST2-deficient mice exhibited increased liver injury and mortality, whereas viral control was not affected. IL-33 administration favored Treg expansion in the liver, suggesting a promising therapeutic application in CMV-induced hepatitis (Popovic et al., 2017). In contrast, in models of airway inflammation, IL-33 caused a dysregulation of Treg suppression activity, promoting a pathogenic Th2 phenotype and impairing their ability to inhibit effector T cells (Chen et al., 2017).

Single-cell RNA-seq (scRNA-seq) analysis of T cells in colorectal cancer, non-small-cell lung cancer, and breast carcinoma patients revealed that tumor-infiltrating Treg cells had a marked suppressive phenotype and upregulated immune checkpoint molecules and distinct signature molecules including IL-1R2, which was also validated at the protein level (De Simone et al., 2016; Guo et al., 2018; Plitas et al., 2016). These data suggest that IL-1R2 might be a promising target to inhibit Treg-mediated suppression and pave the way for further studies to address the role of IL-1R2 in Treg in tumors.

IL-1 Family Members in the Pathophysiology of the Central Nervous System and Neurodegeneration

IL-1 has been shown to be involved in a wide range of human pathologies ranging from autoinflammatory diseases to rheumatoid arthritis, and IL-1-blocking agents (IL-1Ra, Anakinra; anti-IL-1β monoclonal antibody [mAb], Canakinumab; and anti-IL-1α, MABp1) have been approved for clinical use or are being evaluated in some of these disorders (Dinarello, 2009b; Gabay et al., 2010; Garlanda et al., 2013; Udalova et al., 2016). Here, we will focus on the role of IL-1 family members at selected anatomical sites and related pathologies with emphasis on recent developments.

IL-1 was originally identified as endogenous pyrogen and has long been known to regulate sleep, appetite, and the hypothalamus-pituitary-adrenal axis. IL-1 has functions in the brain unrelated to inflammatory conditions. IL-1 is physiologically expressed in the brain with a circadian rhythm, it activates neurons at much lower concentrations than those required for the activation of other cell types (Huang et al., 2011), and regulates several neurophysiological processes, such as sleep, adult neurogenesis, synaptic plasticity, and modulation of long-term potentiation (Liu and Quan, 2018). IL-1 modulates perception and learning in a time- and concentration-dependent manner: acute and low amounts of IL-1 facilitate memory and increase hippocampal-dependent learning and behavior, whereas chronic or high amounts of IL-1 reduce sensory function and memory, retard learning, and cause fatigue (del Rey et al., 2013; Liu and Quan, 2018).

IL-1 also has physiological neuroendocrine functions, via inducing adrenocorticotropic hormone (ACTH), corticotropin-releasing hormone (CRH), and glucocorticoids in response to psychological and metabolic stress, and stimulates brain metabolism (Liu and Quan, 2018).

In addition, depending on the concentration, IL-1 can facilitate neuronal survival by promoting the expression of nerve growth factors (NGFs) and other neurotrophic factors or impair neurogenesis, for instance by favoring the astrocyte rather than neuronal lineage (Garber et al., 2018; Liu and Quan, 2018).

In inflammatory or stress murine models IL-1β, produced by brain microglia in response to TLR activation, complement components, other cytokines (such as tumor necrosis factor-α [TNF-α]), and IL-1 itself (Dinarello, 2011), decreased neurogenesis, and

influenced synaptic plasticity, processes that are vital for the development and retention of spatial memory (Garber et al., 2018; Tong et al., 2012).

The involvement of IL-1 in distinct immunological, neural, and physiological activities in the brain was recently dissected *in vivo* and shown to depend on different cell-type-specific IL-1R1 signaling. In particular, endothelial IL-1R1 mediated sickness behavior, drove leukocyte recruitment to the central nervous system (CNS); and impaired neurogenesis; ventricular IL-1R1 regulated monocyte recruitment; and the non-inflammatory ventricular, astrocyte, and neuronal IL-1R1 mediated neuromodulatory activities (Liu et al., 2019).

Induction of brain pro-inflammatory cytokine synthesis has been described in different brain pathological conditions associated with neuroinflammation such as acute brain injury, Alzheimer's disease, Parkinson's disease, CNS autoimmunity, post-infectious neuropathology, temporal lobe epilepsy, schizophrenia, and febrile convulsions (Khazim et al., 2018; Liu and Quan, 2018). In these neuroinflammatory conditions, microglia inflammasome activation and IL-1 production have been shown to contribute to neuroinflammation and neurodegeneration. For instance, NLRP3 or caspase-1 deficiency protected mice from neuroinflammation and cognitive decline in models of Alzheimer's disease, or during aging (Heneka et al., 2013). The contribution of the IL-1 system in neuroinflammation has been demonstrated also through *in vitro* studies, showing that IL-1 (and TNF-α) induces neuronal death directly or indirectly by activating glial production of neurotoxic substances (Liu and Quan, 2018).

In agreement with studies in mice, in selected human ethnic groups, *IL1A* allelic polymorphisms that lead to increased expression of IL-1α have been associated with susceptibility to Alzheimer's disease because of IL-1α-dependent production of amyloid precursor protein and further IL-1α and IL-1β production by activated microglia. Similarly, IL1B and IL1RN polymorphisms leading to an imbalanced IL-1/IL-1Ra ratio have been proposed to contribute to susceptibility to Alzheimer's disease and dementia (Khazim et al., 2018).

In ischemic or hemorrhagic stroke, NLRP3 inhibition reduced stroke-induced neural damage and functional deficits (Liu and Quan, 2018). Increased inflammasome activation and IL-1 expression have also been described in anxiety disorder, major depression, and autism. NLRP3 pharmacological inhibition or deficiency was shown to reduce depressive behavior and anxiety in animal models of these disorders (Liu and Quan, 2018). Along the same line, treatment with IL-1Ra was effective in reducing infarct size in animal models of stroke, stress-induced depression and anxiety (Koo and Duman, 2009), and in improving clinical outcomes in experimental epilepsy (Vezzani et al., 2000).

These preclinical experiments paved the way for the use of IL-1Ra to treat cerebral stroke. A randomized, double-blind, placebo-controlled trial of Anakinra was carried out in patients with acute stroke. Anakinra-treated patients showed lower systemic inflammation (white blood cells, neutrophil counts, C-reactive protein [CRP], and IL-6 levels) and cognitive impairment than placebo-treated patients (Dinarello, 2011; Wong et al., 2019). In addition, Anakinra was used to treat autoinflammation-associated epilepsy syndrome (DeSena et al., 2018).

In line with findings showing that physiological levels of IL-1R activation are required for correct long-term potentiation, deficiency of IL-1R8 was associated with impaired novel object recognition, spatial reference memory, and long-term potentiation, even in the absence of any external inflammatory stimuli (Costello et al., 2011). In addition, it has recently been shown that hyperactivation of the IL-1 pathway due to IL-1R8-deficiency or IL-1 treatment leads to upregulation of the mechanistic target of rapamycin (mTOR) pathway and increased levels of the epigenetic regulator methyl-CpG-binding protein 2 (MeCP2), a synaptopathy protein involved in neurological diseases, causing disruption of dendritic spine morphology, synaptic plasticity, and plasticity-related gene expression. Anakinra restored MeCP2 levels and spine plasticity and ameliorated cognitive defects in IL-1R8-deficient mice (Tomasoni et al., 2017).

IL-1 has gained attention for its impact on cognitive function in the context of neuroinflammation during CNS viral infection (Vasek et al., 2016). In West Nile virus neuroinvasive disease (WNND), a condition associated with loss of hippocampal synapses and cognitive dysfunction, astrocytes were shown to be the predominant source of IL-1. In a mouse model of WNND, IL-1R1 deficiency was associated with normal neurogenesis, recovery of pre-synaptic termini, and resistance to spatial learning defects, indicating that pro-inflammatory astrocytes impair neuronal progenitor cell homeostasis via IL-1 overexpression (Garber et al., 2018).

In addition to IL-1, IL-18, and IL-33 play a role in inflammatory diseases of the CNS. Brain resident cells constitutively express IL-18, IL-33, and caspase-1, thus providing a local source of these cytokines. Experimental and clinical studies suggest a crucial role for IL-18-mediated neuroinflammation and neurodegeneration in different conditions, including multiple sclerosis, bacterial meningitis, ischemic stroke, and head injury. In contrast, in specific viral infections (e.g., Influenza A), IL-18 was shown to support IFN-γ-mediated viral clearance of infected neurons (Felderhoff-Mueser et al., 2005). In Alzheimer's disease, IL-18 overexpression has been detected in microglia, astrocytes, and neurons and has been found to be co-localized with both amyloid plaques and tau (Singhal et al., 2014).

Treatment with IL-33 exacerbated EAE, but also promoted the differentiation of M2-like microglia and Treg cells, limiting glial scarring in experimental stroke and spinal cord injury (Liew et al., 2016). Treatment with IL-33 reduced synaptic plasticity impairment and cognitive deficits in a mouse model of Alzheimer's disease and reduced amyloid plaque deposition by promoting the recruitment and polarization of microglia toward an anti-inflammatory phenotype (Fu et al., 2016). In agreement with results in mice, IL-33 expression was decreased in Alzheimer's disease patients' brains, and *IL33* and *ST2* SNPs have been associated with susceptibility to Alzheimer's disease (Liew et al., 2016).

The highly homologous orphan receptors IL-1R9 (TIGIRR-2) and IL-1R10 (TIGIRR-1) and a specific form of the IL-1RAcP, called IL- 1RAcPb, are expressed almost exclusively in the brain. IL-1R9 regulates glutamatergic synapse formation and stabilization, and IL-1R9 mutations are associated with cognitive impairment, such as intellectual disability, autism, and schizophrenia (Born et al., 2000).

Thus, members of the IL-1 family and their receptors are expressed in the CNS and serve physiological functions. Several lines of evidence, including genetic associations, suggest that IL-1 and related cytokines are key mediators of neurodegenerative diseases. These results pave the way to assessing their potential as therapeutic targets in vascular and degenerative diseases of the nervous system.

IL-1 Family Members in Maintenance of Homeostasis and Gastrointestinal Pathology

IL-1 cytokines contribute to maintain the equilibrium between immune tolerance to commensal microbiota and response to intestinal pathogens. The players involved in this process (inflammasomes, IL-1 cytokines, IL-1 receptors, and negative regulators) are expressed by epithelial cells or by leukocytes residing in the lamina propria. Several lines of evidence indicate that IL-1 family members, such as IL-1, IL-1Ra, IL-18, and IL-33, possess dual functions depending on the phase of intestinal disease, as well as on their role in initiating versus sustaining chronic gut inflammation, and finally on the cell type targeted by the cytokine.

Th17 responses have a pro-tumor role in colorectal cancer (Grivennikov et al., 2012). The role of IL-1 in colorectal cancer was recently dissected by using cell-type-specific IL-1R1-deficient mice. This study showed that IL-1 had pro-tumor effects by promoting Th17-mediated inflammation through IL-17 and IL-22, and epithelial-cell-autonomous mechanisms, whereas IL-1 had tumor-suppressive effects by promoting neutrophil-mediated control of bacterial invasion (Dmitrieva-Posocco et al., 2019).

Under homeostatic conditions, NLRP6 and NLRP3 inflammasome activation in epithelial cells drives IL-18 expression, which favors the production of antimicrobial peptides. These are essential for the maintenance of intestinal barrier integrity and normal commensal microbiota. IL-18 was also reported to promote Treg cell effector functions and decrease Th17 polarization (Harrison et al., 2015). In contrast, in inflammatory conditions associated with disruption of the epithelial barrier and dysbiosis, activation of inflammasomes in epithelial cells and myeloid cells leads to the release of huge amounts of IL-18, which promotes inflammation and blocks the development of goblet cells, leading to reduced mucus in the colon and presumably increased bacterial access to the intestine surface (Nowarski et al., 2015). The regulation of inflammasome activation and IL-18 secretion were shown to depend on the presence of the microbiota and in particular on specific metabolites such as taurine, histamine, and spermine (Levy et al., 2015).

Accordingly, inflammasome activation and high IL-18 and IL-18BP levels have been detected in the serum and intestinal tissue of Crohn's disease patients. In addition, an NLR family CARD domain-containing protein 4 (NLRC4) mutation that leads to high serum IL-18 concentrations is associated with severe intestinal inflammation, and IL-18 transgenic mice are more susceptible to colitis, whereas IL-18 inhibition plays a protective effect in experimental models of inflammatory bowel diseases (Kaplanski, 2018; Sivakumar et al., 2002).

IL-33 is constitutively expressed in epithelial cells of the intestine, where it functions as an endogenous alarmin in response to tissue damage. IL-33 is highly expressed in inflamed lesions of IBD patients, and it plays dual roles in animal models of intestinal inflammation, depending on the phase of the disease (early and inflammatory or repair and healing) and the inflammatory state (acute or chronic), given that IL-33 might influence Th2 responses, Th1 inflammation, mucosal regeneration and fibrosis (Lopetuso et al., 2013). Studies supporting a regulatory role for IL-33 in gut inflammation show that the IL-33 receptor ST2 promotes transforming growth factor-β1 (TGF-β1)-mediated differentiation of Treg cells, favoring Treg-cell accumulation and maintenance, and inducing a regulatory phenotype to Th17 cells recruited in inflammatory conditions (Schiering et al., 2014) or an epithelial-derived miR-320 that promotes epithelial repair and restitution and the resolution of inflammation (Lopetuso et al., 2018).

IL-36 cytokines contribute to intestinal inflammation. Indeed, IL-36R-deficiency was associated with reduced innate, inflammatory, and Th1 responses in different models of colitis. However, IL-36 signaling is also important for the resolution of mucosal inflammation and healing of mucosal wounds, by promoting IL-22 expression (Medina-Contreras et al., 2016).

Concerning negative regulatory receptors, IL-1R2 was shown to be highly upregulated in epithelial cells in ulcerative colitis remission compared with active disease, suggesting its involvement in dampening IL-1β pro-inflammatory activity and favoring the return to mucosal homeostasis (Mora-Buch et al., 2016). In addition, IL-1R8 was shown to be crucial in the modulation of intestinal epithelial cell metabolism, differentiation, cell cycle, and effector functions both in homeostatic conditions and in inflammation, through the regulation of NF-κB, JNK, and mTOR activation driven by IL-1 or TLR agonists derived from commensal flora in intestinal epithelial cells (Garlanda et al., 2004; Xiao et al., 2007). In experimental models of colitis, IL-1R8 deficiency caused exacerbated intestinal inflammation, in terms of weight loss, intestinal bleeding, local tissue damage, and reduced survival. This correlated with an increased leukocyte infiltration and higher level of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β, IL-12p40, and IL-17), chemokines (CXCL1 and CCL2), and prostaglandins. In agreement with the pro-tumoral role of chronic inflammation, in different murine models, IL-1R8 was shown to play a key protective role in the pathogenesis of intestinal cancer (Garlanda et al., 2007; Xiao et al., 2007; Zhao et al., 2015). The data suggest that IL-1R8 exerts a tumor suppressor activity by controlling IL-1- and TLR-induced cancer-related inflammation and mTOR-mediated cell cycle progression and consequent genetic instability.

IL-1 as a Driver of Atherosclerosis and Cardiovascular Pathology

IL-1 affects all components of the vessel wall and cardiomyocytes and, accordingly, it plays an important role in atherosclerosis and its complications including myocardial infarction (Abbate and Dinarello, 2015; Hansson, 2005; Libby, 2017). Early on it was shown that IL-1 activates endothelial cells in a prothrombotic/proinflammatory direction (Mantovani et al., 1992). The proinflammatory program of IL-1 included induction of monocyte-attracting chemokines such as CCL2, procoagulant activity, prostaglandins, platelet activating factor (PAF) and an inhibitor of thrombin dissolution (PAI). A similar set of responses was observed in smooth muscle cells (Libby, 2017), which also are induced to proliferate.

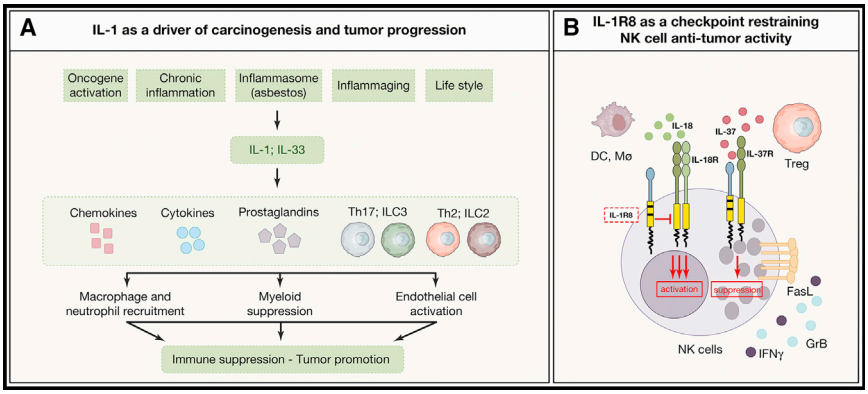

Figure 4. Mechanisms of Tumor Promotion and Control by IL-1 Family Members

(A) Upstream conditions and downstream cell types and mediators involved in the networks of IL-1- and IL-33-driven tumor promotion and immune suppression.

(B) Representation of IL-1R8-dependent modulation of IL-18 activity on NK cells and its role as co-receptor for IL-37.

Studies using IL-1R1 or IL-1Ra gene-targeted mice provided strong genetic evidence for IL-1 being a driver of atherosclerosis and its complications. Moreover, IL-1 directly affects the function of cardiomyocytes. The discovery of cholesterol crystal-mediated activation of the NLRP3 inflammasome provided a direct link between lipid metabolism and activation of IL-1β (Duewell et al., 2010). Moreover, IL-1β and IL-1α are stored in platelets which can represent an additional source of this cytokine (Semple et al., 2011). Interestingly platelets also express the negative regulator IL-1R8 and genetic evidence showed that this molecule limits their activation and thrombosis (Anselmo et al., 2016).

IL-1 is a potent inducer of IL-6 which in turn reshapes liver function in the acute phase response including production of C reactive protein (CRP). IL-6, CRP and a distant relative of CRP, PTX3, induced by IL-1 were found to serve as biomarkers of the severity and risk of cardiovascular pathology (Garlanda et al., 2018; Peri et al., 2000; Ridker et al., 2001).

These preclinical and clinical results set the stage for the CANTOS study aimed at assessing the potential of an anti-IL-1β mAb (Canakinumab) to protect against atherosclerotic disease. A total of 10,061 patients were treated with increasing doses of Canakinumab, and non-fatal myocardial infarction, non-fatal stroke or cardiovascular death were used as efficacy end-points (Ridker et al., 2017a). The results of this seminal study showed that anti-IL-1β therapy was effective in preventing recurrence of cardiovascular disease (Ridker et al., 2017a). Interestingly, treatment with Canakinumab also protected against arthritis, gout, osteoarthritis, and cancer, as discussed in the next section.

IL-1 Family Members in Cancer Progression

IL-1 family members have complex, divergent roles in the control of carcinogenesis and tumor progression. In general, stage of progression and the tissue contexture are important determinants of the impact of IL-1 family members on cancer. As discussed above, IL-18 is a potent inducer of IFN-γ in NK cells, ILC1s, and Th1 cells. In murine tumors, IFN-γ is associated with resistance to carcinogenesis, and in human cancers, IFN-γ and related signatures including IL-18 are generally associated with better prognosis (Fridman et al., 2017). In contrast, several lines of evidence link IL-33-driven type 2 immunity to promotion of tumor progression (Hong et al., 2019), although there is evidence, for instance in pre-clinical models of hepatocellular carcinoma, of a protective function of this cytokine (Jin et al., 2018). Evidence linking IL-33 to tumor promotion include pre-clinical models and human prognostic and genetic associations (Amôr et al., 2018; Ding et al., 2018; Wen et al., 2019). Interestingly IL-33 was associated with stromal-cell-driven Treg differentiation in oral squamous cell carcinoma (Wen et al., 2019) and promoted Treg-dependent metastatic mammary tumor growth in the lung (Halvorsen et al., 2018).

The prevailing function of IL-1α and IL-1β in cancer is tumor promotion, based on pre-clinical and clinical data, though early in malignant transformation, dendritic cell membrane IL-1α might play an anti-tumor role as an alarmin acting as an adjuvant for presentation of tumor neoantigens (Marhaba et al., 2008; Song et al., 2003). Early on, it was shown that IL-1β increased tumor progression in mouse tumors (Chirivi et al., 1993; Giavazzi et al., 1990; Vidal-Vanaclocha et al., 1994), a finding confirmed and extended by using IL-1β or IL-1R1 gene targeted mice (Voronov et al., 2003). IL-1α and IL-1β are downstream of the intrinsic, oncogene-driven and the extrinsic, inflammatory-disease-driven pathways linking inflammation and cancer (Mantovani et al., 2008). IL-1α and IL-1β were found to be downstream of the RAS and rearranged in transformation/papillary thyroid carcinoma (RET-PTC) oncogenes in the intrinsic pathway (Borrello et al., 2005; Cataisson et al., 2012). IL-1β was also found to be a mediator of chronic non-resolving inflammation, which increases the risk of developing tumors in the gastrointestinal tract (Mantovani et al., 2008). In a model of skin carcinogenesis, IL-1α was shown to have dual functions downstream of RAS, affecting both transformed cells and the tumor microenvironment (TME) (Cataisson et al., 2012). On tumor cells, it blocked the expression of differentiation markers. Via NF-κB, IL-1α orchestrated the construction of an inflammatory microenvironment via induction of cytokines and chemokines.

IL-1-mediated tumor promotion has been identified in different murine and human tumor types, including sarcomas, melanoma, pancreatic ductal adenocarcinoma (Ling et al., 2012; Melisi et al., 2009; Tjomsland et al., 2013; Zhuang et al., 2016), myelomas (Lust et al., 2016), and breast carcinomas (Wu et al., 2018) and involves different mechanisms (Figure 4A). IL-1 has been shown to sustain the expansion and immunosuppressive function of myeloid cells in tumor-bearing mice (Elkabets et al., 2010; Kaplanov et al., 2019; Pan et al., 2017).

In mouse and human melanoma, the IL-1R-MyD88 pathway was found to cause upregulation of TET2 in tumor-associated macrophages (TAMs). TET2 is a DNA methylcytosine dioxygenase, which skewed macrophage function in an

immunosuppression M2-like mode (Pan et al., 2017). TET2 gene targeting changed the polarization state of macrophages and reactivated T-cell-mediated anti-tumor resistance.

Vascular cells are a prime target of IL-1 (see above). In the context of neoplasia, IL-1 was shown to promote angiogenesis. Induction of endothelial cell adhesion molecules E-selectin and vascular cell adhesion molecule-1 (VCAM-1) was involved in augmentation of metastasis.

Recent studies have identified an IL-1β signature in the peripheral blood mononuclear cells from patients with metastatic, hormone-negative breast cancer. There is expression of several genes, but the most dominant are an IL-1β signature, which includes IL-1R1, MyD88, and IL-1β itself (Wu et al., 2018). When the primary tumor tissue from 145 patients with breast cancer was stimulated in culture, both IL-1β and IL-1α were found in the supernatants. When treated with daily Anakinra for two weeks, each of the IL-1β signature proteins decreased, and the reduction was sustained when Anakinra was added to a standard of care chemotherapeutic (Wu et al., 2018). The IL-1β signature includes IL-1 signaling kinases, which are common to both IL-1β and IL-1α. Thus, it is likely that treating patients with Anakinra includes blocking IL-1α. A key player in breast cancer is thymic stromal cell lymphopoietin (TSLP); increased production of TSLP is associated with poor prognosis not only in breast cancer but also in other epithelial cancers (Kuan and Ziegler, 2018). In breast cancer tissue from 145 patients, TSLP amounts correlated with IL-1β (Wu et al., 2018). In addition to IL-1β, there is a unique role for IL-1α with TSLP. Breast-cancer-tumor-derived IL-1α stimulates the production of TSLP from the infiltrating myeloid cells in the microenvironment of breast cancer. The increase in TSLP promotes the survival of the tumor cells via B-cell lymphoma 2 (Bcl-2) (Kuan and Ziegler, 2018).

IL-1R8 has recently been shown to serve as a checkpoint for IL-18-driven differentiation and activation of NK cells and ILC1 cells (Molgora et al., 2017). This observation was independently confirmed, and it was also found that IL-37, produced by Treg cells, suppressed NK function via IL-1R8 (Sarhan et al., 2018). Blocking IL-1R8 unleashed NK-cell-mediated resistance against primary carcinogenesis and metastasis in the liver and lung, two NK-cell-rich anatomical sites (Molgora et al., 2017). The checkpoint function of IL-1R8 was also observed in human NK cells. These results suggest that IL-1R8 can act as a double-edged sword in carcinogenesis. On the one hand, it tames tumor-promoting inflammation driven by IL-1 or TLRs; on the other hand, it serves as a checkpoint for NK cells which, if unleashed, can mediate anti-cancer resistance, at least at NK-cell-rich anatomical sites (Figure 4B). Consistent with these results, in breast cancer, IL-1R8 expression was found to be associated with an NK-cell-inflamed molecular signature (Campesato et al., 2017). These results raise the possibility to target the IL-1R8 checkpoint, in particular in the context of liver metastasis.

Human genetics is consistent with a role of IL-1 and related molecules in carcinogenesis. IL-1 polymorphisms setting the system in a pro-inflammatory mode were associated with risk of gastric cancer (El-Omar et al., 2000). Along the same line, IL-1α and IL-1β and IL-1Ra genetic polymorphisms were associated with risk of developing other tumors, including lung cancer (Bhat et al., 2014; Hu et al., 2006; Khazim et al., 2018; Lind et al., 2005; Zienolddiny et al., 2004). Thus, mouse and human genetics is consistent with IL-1 and its regulatory pathways being drivers of tumor promotion.

These results set the stage for therapeutic translation of IL-1 blocking strategies using Anakinra or anti-IL-1α or -IL-1β mAb. A 10-year trial of daily Anakinra with weekly low dose dexamethasone in 47 patients with smoldering myeloma resulted in significantly increased survival (Lust et al., 2009; Lust et al., 2016). Improved survival has been reported when Anakinra is added to the standard of therapy with fluorouracil in advanced metastatic colorectal cancer (Isambert et al., 2018), hormone negative breast cancer (Wu et al., 2018), and in advanced pancreatic cancer (Becerra et al., 2018; Whiteley et al., 2016). In pre-clinical studies, Anakinra also abated chimeric antigen receptor (CAR)-T-cell-induced cytokine release syndrome and neurotoxicity (Giavridis et al., 2018; Norelli et al., 2018). In a phase I study in patients with end-stage tumors of different types, blocking IL-1α reduced cancer cachexia (lean body mass, fatigue, and appetite loss) (Hong et al., 2014).

IL-1α had long been known to mediate muscle loss and cachexia. Three trials have administered anti-IL-1α to patients with advanced cancers of various origins (Hong et al., 2014; Hong et al., 2015) as well as patients with colorectal cancer (Hickish et al., 2017). In these trials, end-stage patients were losing lean body mass as a manifestation of cancer cachexia. The most recent trial was a randomized, placebo-controlled study in 333 patients with advanced, metastatic colorectal cancer who were treated with an 8-week monotherapy course of IL-1α-neutralizing human antibody (Hickish et al., 2017). The study met its primary and secondary end-points with an increase in lean body mass, improved parameters of quality of life, decreased pain, decreased constitutional symptoms, and significantly lower circulating IL-6 and platelet counts than in placebo-treated patients. Increased survival was observed in responders compared with non-responders. In this study, amounts of circulating IL-1Ra predicted responsiveness to treatment with the IL-1α-targeting antibody (Kurzrock et al., 2018).

There are several lessons derived from these studies besides reduction in cancer cachexia (McDonald et al., 2018). Reducing IL-1α might also reduce inflammation-mediated immunosuppression, both affecting increased survival and immune-mediated tumor regression (Mantovani et al., 2008).

The wealth of pre-clinical and clinical data accumulated since 1990 (Giavazzi et al., 1990) has set the stage for assessing the effect of blocking IL-1β in human cancer development. In the seminal CANTOS study discussed above, in 10,061 patients with atherosclerosis and high CRP levels, Canakinumab caused a dramatic (> 50%) reduction in the incidence and mortality from lung cancer (Ridker et al., 2017a). These impressive results raise questions as to immunological mechanisms and further therapeutic exploitation. The follow-up was relatively short (3.7 years) in relation to the natural history of cancer in humans. We speculate that blocking IL-1-driven recruitment and immunosuppressive function of myeloid cells and unleashing innate- and lymphoid-cell-mediated effector pathways is a determinant of this impressive result.

Concluding remarks

Starting in the early 1970s, over 40 years since its official consensus naming (Aarden et al., 1979), IL-1 has grown into

a complex, multifaceted family of cytokines with complex regulatory mechanisms, diverse functions, and a role in immunopathology. In more recent years, largely forgotten ligands (IL-36, IL-37, and IL-38) and receptor chains (IL-1R8) have joined the classic stars IL-1, IL-33, and IL-18 as important orchestrators of immunity in different contexts. However, a number of fundamental questions remain unanswered. For instance, the actual significance of IL-37 in immunoregulation remains an open question due to the lack of a murine counterpart, which has hampered the use of stringent genetic approaches to dissect its role in immunity and pathology. The occurrence of genetic variants of IL-37 and IL-1R8 in humans might shed new light on the actual importance of these molecules as fundamental mechanisms of immunoregulation. In the same line, the signaling pathways responsible for the immunosuppressive and anti-inflammatory activity of IL-37 remain only partially defined. These open questions bear not only on immunopathology but also on translation of IL-37 as a candidate for becoming a therapeutic agent. Even for classic members of the family, a number of important questions are still open. Among these, the discovery that IL-1R2 has been found to be elevated in several studies of tumor-infiltrating Treg cells raises the important question as to the cell-autonomous or non-cell-autonomous function of this decoy molecule and its cognate ligands in Treg pathophysiology.

The role of IL-1β and related cytokines has extended beyond classic immunopathology to include degenerative diseases of the CNS and of the cardiovascular system and cancer. The CANTOS study showed in over 10,000 patients that blocking IL-1β protected not only against atherosclerosis-driven cardiovascular mortality but also against a range of diseases including lung cancer, arthrosis, and gout (Ridker et al., 2017a; Ridker et al., 2017b). This finding, revealing of the diversity and yet commonality of disease mechanisms, suggests that IL-1 represents a paradigm for inflammation and immunity being a metanarrative of 21st century medicine. The CANTOS study also raises questions in terms of translation: can anti-IL-1 strategy actually prevent cancer in high-risk subjects? Can it be combined with checkpoint blockade strategies? What is the potential of other members of the IL-1 family, such as IL-37, as therapeutic tools or targets? Further dissection of the role of members of this complex family, their regulatory mechanisms and genetic determinants might pave the way to better exploitation of current therapeutic tools and development of novel intervention strategies.

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DECLARATION OF INTERESTS

A.M. and C.G. receive royalties from the sale of reagents related to molecules discussed here, are involved in related patents, and have served as Advisory Boards members and Consultants for companies in the field. C.D. declares no competing interests.

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