IL-1 Family Blockade in Cytokine Storm Syndromes

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Interleukin-1 (IL-1)

Cytokines are substances, such as growth factors, interferons, and interleukins, which are secreted by cells in the immune system to influence other cells. Interleukins, as the name implies, are glycoproteins that regulate immune response by communicating between white blood cells. Interleukin-1 (IL-1) was one of the first cytokines described in the immune system, over 40 years ago [1], as it plays a central host defense role against infection. IL-1, formerly known as endogenous pyrogen for its fever inducing effect, is a representative of the 11-member IL-1 family of cytokines [2]. In addition, there are ten unique IL-1 receptor (IL-1R) family members that can result in either pro- or anti-inflammatory functions upon binding IL-1 family members depending on the individual receptor and its co-receptor, making for a highly complex system of signaling. IL-1α and IL-1β are two distinct gene products located adjacent to one another on the long arm of chromosome 2. Their regulation differs, but both are able to bind IL-1R1 and the natural inhibitor of both, IL-1R antagonist (IL-1Ra) (Fig. 1) [2].

IL-1β has been termed a gatekeeper of inflammation and is involved in the pathophysiology of a variety of autoinflammatory diseases [3]. Monocytes/macrophages are a primary source of IL-1β, and IL-1β activity is tightly controlled and dependent on the conversion of an inactive precursor to an active cytokine by limited proteolysis. IL-1β can be processed intracellularly by caspase-1, which is activated by the inflammasome, a multiprotein complex that detects pathogenic organisms as well as sterile stressors to the cell [2]. The protein, NLRP3 (cryopyrin) is important for the assembly of this complex, and hyper-activating mutations in NLRP3 can lead to excess IL-1β activity, resulting in a family of autoinflammatory disorders ranging from familial cold urticaria to Muckle–Wells syndrome to the severest form,

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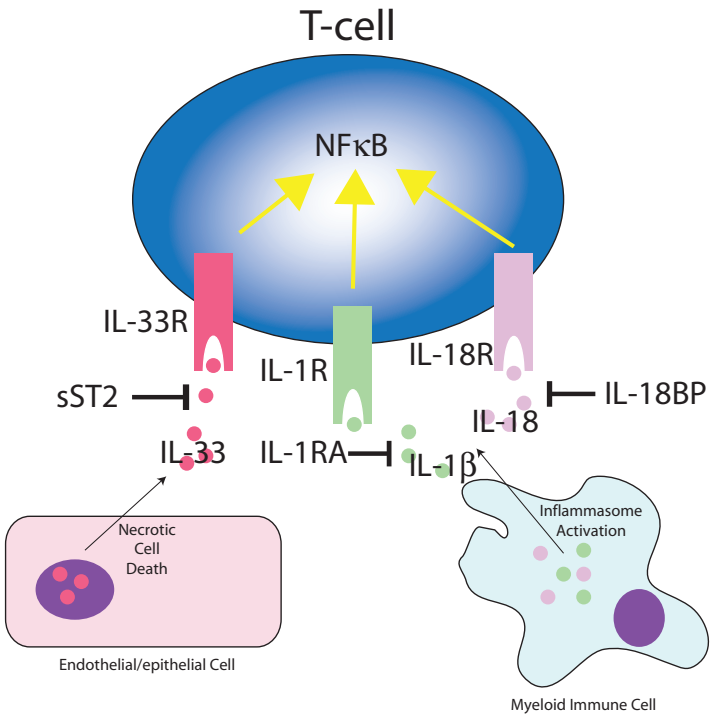

Fig. 1 IL-1 family member biology. The producers of and responders to IL-1 family members are numerous and complex; this figure illustrates some of the main actors in IL-1 family member biology. IL-1β and IL-18 are released from myeloid cells after activation of the inflammasome. IL-33, normally retained in the nucleus, is released by endothelial or epithelial cells after necrotic cell death. Each of the cytokines are then sensed by their respective receptors on CD4+ and CD8+ T-cells resulting in activation of the transcription factor NFκB. Additionally, soluble inhibitors of each of these cytokines are produced which displace binding of the cytokine to its receptor: IL-1 receptor antagonist (IL1-RA) for IL-1β, IL-18 binding protein (IL-18BP) for IL-18, and soluble ST2 receptor (sST2) for IL-33. Figure courtesy of Dr. Ed Behrens, University of Pennsylvania

neonatal onset multisystem inflammatory disease (NOMID) [4]. NOMID can be quite devastating to infants primarily affecting the central nervous system, the bones/joints, and the skin. Fortunately, IL-1β blockade by monoclonal antibody, IL-1R fusion protein, or recombinant human IL-1Ra (rhIL-1Ra) has revolutionized the care of individuals with cryopyrinopathies [4].

Another more common autoinflammatory disorder of childhood responsive to IL-1 blockade is systemic juvenile idiopathic arthritis (sJIA). sJIA affects approximately 1 in 10,000 children worldwide and is characterized clinically by high spiking fever, evanescent salmon-colored rash, arthritis, adenopathy, and occasionally serositis [5]. This used to be a quite devastating disease of childhood until it was found that large amounts of IL-1β were released by sJIA patient peripheral blood mononuclear cells, and IL-1Ra could dramatically treat children with refractory sJIA [6]. Initial treatment of sJIA patients with rIL-1Ra was also shown to improve

outcomes and reduce the requirement for corticosteroid use [7]. Eventually, randomized and blinded, placebo-controlled clinical trials with various IL-1 inhibitors bore out these initial anecdotal experiences [8–10]. IL-1 blockade, along with IL-6 blockade, have revolutionized the care of children with sJIA [11].

Children with sJIA are prone to develop a sometimes fatal cytokine storm syndrome (CSS) termed macrophage activation syndrome (MAS) or secondary hemophagocytic lymphohistiocytosis (sHLH) [12]. Seven to ten percent of sJIA patients will develop overt MAS, while another 30–40% will manifest with subclinical or occult MAS which can progress to multi-system organ failure [13, 14]. Those sJIA patients who are prone to MAS development frequently possess heterozygous mutations in known familial HLH genes involved in the perforin mediated cytolytic pathway (e.g., *PRF1, UNC13D*) employed by CD8 T cells and natural killer (NK) cells [15, 16]. This suggests some shared genetic risk factors for CSS/MAS in those with sJIA and other forms of sHLH/MAS [17]. Heterozygous defects in HLH genes have been shown to disrupt NK cell lytic activity by partial [17, 18] and complete dominant negative [19], and hypomorphic effects, including those with sJIA [20]. Defective cytotoxic killing of antigen presenting cells (APC) by lymphocytes has been shown to lead to prolonged interaction of the lytic lymphocyte and the APC resulting in a pro-inflammatory CSS [18, 21].

As CSS resembles MAS in sJIA patients, and sJIA patients were originally shown to be responsive to IL-1 blockade, rhIL-1Ra was employed as treatment for a severe CSS in a child with cytophagic histiocytic panniculitis [22]. This was the first explicit use of rhIL-1Ra reported to successfully treat CSS/MAS, and subsequently rhIL-1Ra was shown to effectively treat refractory MAS in another dozen patients with primarily rheumatic disorders, such as sJIA [23]. Since then, there have been numerous case reports and series of patients effectively treated with rhIL-1Ra for CSS/MAS/sHLH with etiologies ranging from sJIA to adult onset Still disease (Table 1), to systemic lupus erythematosus (Table 2), to autoinflammatory conditions (Table 3), to secondary infections in HIV/AIDS patients (Table 4). Moreover, a retrospective review of a large clinical trial in sepsis revealed that high dose rhIL-1Ra markedly improved survival in sepsis patients with features of MAS, namely hepatobiliary dysfunction and disseminated intravascular coagulopathy (Table 4) [24]. Thus, rhIL-1Ra therapy was anecdotally reported to effectively treat CSS in a variety of infectious and rheumatic disorders. Currently, a randomized, double-blind, placebo controlled clinical trial is underway to evaluate rhIL-1Ra treatment for children and adults with sHLH/CSS [ClinicalTrials.gov Identifier: NCT02780583].

Interleukin-18 (IL-18)

In 2014, activating mutations in the NLRC4 inflammasome component were demonstrated to lead to an autoinflammatory syndrome [25, 26], including an infant with recurrent MAS [27]. This child only partially responded to rhIL-1Ra treatment but was found to have very elevated serum IL-18 levels and was successfully treated with

Table 1 Effectiveness of anakinra in treating CSS as part of sJIA and AOSD

Ages (years)	Disease	Infectious trigger	Co-therapy	Outcome	References
13	sJIA	ND	CS, IVIG, CsA	Resolution	[39]
32	AOSD	ND	CS	Resolution	[40]
1–17	sJIA (8)	ND	CS, IVIG, CsA +/− VP16 or etanercept	Resolution	[23]
8–12	sJIA (2)	ND	CS	Resolution	[41]
20	AOSD	ND	CS	Resolution	[42]
11	sJIA	ND (MRSA later)	CS, IVIG, CsA	Resolution with high dose anakinra	[43]
1–17	sJIA (10)	ND	CS (10), CsA (8), PP (2), canakinumab (4), anakinra (5)	Resolution (9) Survival (10)	[44]
30	AOSD/ PAH	ND	CS, CsA	Resolution	[45]
19–70	AOSD (7)	Histoplasmosis (1)	CS (7), CsA (3), MTX (2), anakinra (5)	Improved (7) Survival (7)	[46]
1–16	sJIA (11)	ND	CS, CsA	Resolution (11)	[47]
34	AOSD	ND	CS	Resolution	[48]
28	AOSD	*Mycoplasma pneumonia*	AZ, CS	Improved and home	[49]
25	AOSD	EBV	CS, CsA, RTX	Resolution after CsA/RTX	[50]
42	AOSD	ND	CS, CsA	Resolution with high dose anakinra	[51]
0.5–16	sJIA (13)	ND	CS (13), PP (6), IVIG (2), CsA (11), anakinra (13)	Resolution (13), 2 flared with anakinra tapering	[52]

Abbreviations: *AOSD* adult-onset Still disease, *AZ* azithromycin, *CS* corticosteroids, *CsA* cyclosporine A, *CSS* cytokine storm syndrome, *IVIG* intravenous immunoglobulin, *MRSA* methicillin resistant *Staphylococcus aureus*, *MTX* methotrexate, *ND* none detected, *PAH* pulmonary artery hypertension, *PP* plasmapheresis, *RTX* rituximab, *sJIA* systemic juvenile idiopathic arthritis, *VP16* etoposide

addition of recombinant human IL-18 binding protein (IL-18BP) [28]. rhIL-18BP is naturally occurring and analogous to rhIL-1Ra in blocking IL-18 and IL-1 function, respectively (Fig. 1). IL-18 is a member of the IL-1 superfamily and analogous to IL-1β is first synthesized as an inactive precursor and is activated following cleavage by caspase-1 [2]. Unlike, IL-1, however, IL-18 does not trigger fever [29]. Thus, despite overlapping features and functions, IL-18 has unique features from IL-1.

In the presence of IL-12 or IL-15, IL-18 induces interferon-gamma (IFNγ) in NK cells, CD4 T cells, and CD8 T cells [29]. IFNγ is believed to a major driver of CSS/HLH in animal models and in humans, and a recent case report depicted the benefit of anti-IFNγ (emapalumab) in treating refractory HLH [30]. A recent clinical trial of emapalumab in treating HLH has resulted in FDA approval for this indication [31].

Table 2 Effectiveness of anakinra in treating CSS associated with autoimmune conditions

Age (years)	Disease	Infectious trigger	Co-therapy	Outcome	References
14	CHP	ND	CS, CsA, VP16 (one dose)	Resolution	[22]
13 5 0.5 6	ARF (1) KD (1) ANCA vasculitis (1) Churg–Strauss vasculitis (1)	ND (4)	CS, CsA, IVIG Cs, CsA, VP16 CS, IVIG CS, IVIG	Resolution (4)	[23]
12	JDMS	ND	CS, CsA, IVIG, VP16, MTX	Improvement with anakinra	[53]
0.25	KD	ND	CS, IVIG, infliximab (one dose)	Resolution with high dose anakinra	[54]
18	SpA, uveitis	ND	CS, CsA	Resolution	[18]
1.5	SpA, uveitis	ND	CS, CsA	Resolution	[55]
37	SLE	ND	CS, CsA	Resolution	[56]
5–15	SLE (6)	ND	CS (6), CsA (4), IVIG (2), VP16 (3), PP (2)	Resolution (2/2 on anakinra)	[47]

Abbreviations: *ANCA* anti-neutrophil cytoplasmic antibody, *ARF* acute rheumatic fever, *CHP* cytophagic histiocytic panniculitis, *CS* corticosteroids, *CsA* cyclosporine A, *IVIG* intravenous immunoglobulin, *KD* Kawasaki disease, *MTX* methotrexate, *ND* none detected, *PP* plasmapheresis, *SLE* systemic lupus erythematosus, *SpA* spondyloarthritis, *VP16* etoposide

Table 3 Effectiveness of anakinra in treating CSS secondary to genetic autoinflammatory conditions

Ages (years)	Disease	Infectious trigger	Co-therapy	Outcome	References
12	CAPS	ND	CS	Resolution	[57]
1	HIDS	ND	none	Resolution	[58]
0.1	NLRC4 mutation	Parainfluenza	CS, CsA, infliximab, vedolizumab, rhIL-18BP	Resolution on combined anakinra and rhIL-18BP	[28]
0.1	NLRC4	ND	CS, CsA, rapamycin	Resolution	[59]
?	CAPS (1) HIDS (1)	ND	CS	Resolution	[52]

Abbreviations: *CAPS* cryopyrin-associated periodic fever syndrome, *CS* corticosteroids, *CsA* corticosteroids, *HIDS* hyper-IgD syndrome, *ND* none detected, *NLRC4* Nod-like receptor family CARD domain containing 4, *rhIL-18BP* recombinant human interleukin-18 binding protein

IL-18 has also been shown to promote murine and human MAS demonstrating the pathogenicity of free (unbound) IL-18 [32, 33]. In addition, free IL-18 concentrations correlated with clinical status in sHLH/MAS patients [34], and IL-18 levels were predictive of MAS in children with sJIA [35]. Therefore, blockade of IL-18 may take on a more prominent role in treating a range of CSS.

Table 4 Effectiveness of anakinra in treating CSS secondary to infections or other conditions

Ages (years)	Disease	Infectious trigger	Co-therapy	Outcome	References
6	None	Parvovirus B19	CS, CsA, IVIG	Resolution	[60]
15 20 13 15 None 21 11 8 9	XHIM None None None Renal transplant/SLE None Liver transplant None	*Histoplasma capsulatum* *Mycobacterium avium* None None *Varicella zoster* *Candida sphaerica* EBV None	CS (6), IVIG (5), anakinra (8)	Resolution (7) One last onset death awaiting bone marrow transplantation (patient with Candida)	[61]
63	Renal transplant	Erlichiosis	Doxycycline, CS	Resolution	[62]
44	None	CMV	Ganciclovir, CS	Resolution	[63]
18–75	HBD/DIC (43) in sepsis clinical trial	Various forms of sepsis	Anakinra (26) versus placebo (17)	Survival: 65% anakinra 35% placebo	[24]
20–58	8 patients in ICU with HLH, HSCT/GVHD (1), lung transplant (1), ALL (1), AID (1)	EBV (1)	CS (5), IVIG (7), anakinra (8)	50% survival	[64]
18–71	AOSD (3) SLE (2) lymphoma (2) CVID (1) RA (1) CLL (1) UC (1) none (1) ANCA vasculitis (1)	HSV1, CMV URI (1) Rotavirus (1) cholangitis Histoplasmosis none EBV Legionella CMV	Anakinra (13), CS (12), CsA (11), IVIG (12), tocilizumab (2)	Survival: 69%	[65]
46	HIV/AIDS	Histoplasmosis	IVIG	Resolution	[66]
51	Renal transplant recipient	None	CS, CsA, PP	Resolution	[67]

Abbreviations: *ALL* acute lymphoblastic leukemia, *ANCA* anti-neutrophil cytoplasmic antibody, *CLL* chronic lymphocytic leukemia, *AOSD* adult onset Still disease, *CMV* cytomegalovirus, *CS* corticosteroids, *CsA* cyclosporine A, *CVID* common variable immunodeficiency, *DIC* disseminated intravascular coagulation, *EBV* Epstein–Barr virus, *GVHD* graft versus host disease, *HBD* hepatobiliary dysfunction, *HLH* hemophagocytic lymphohistiocytosis, *HSCT* hematopoietic stem cell transplant, *HSV1* herpes simplex virus 1, *HIV/AIDS* human immunodeficiency virus/acquired immune deficiency syndrome, *ICU* intensive care unit, *IVIG* intravenous immunoglobulin, *PP* plasmapheresis, *RA* rheumatoid arthritis, *SLE* systemic lupus erythematosus, *UC* ulcerative colitis, *URI* upper respiratory infection, *XHIM* X-linked immunodeficiency with hyper-IgM

Interleukin-33 (IL-33)

IL-33 is another IL-1 family member with close homology to IL-1, and it is considered an alarmin that is released as an active precursor upon cell damage [2]. IL-33 differs from IL-1 as it can act, depending on context, as either anti- or pro-inflammatory in nature [2]. In a pro-inflammatory setting, IL-33 binds the ST2 receptor which signals via MyD88, IL-1 receptor activated kinases (IRAKs), and the inflammatory transcription factor, NFκB (Fig. 1) [2]. A murine model of HLH showed a role for MyD88-dependent ST2 in disease, and demonstrated that blocking IL-33 signaling via monoclonal antibody directed against ST2 improved survival and the severity of multiple disease manifestations [36]. Moreover, in the long term ST2 blockage results in CD8 T cell exhaustion that does not alter mortality in the HLH murine model arguing for early use on ST2 blockade in CSS [37]. Thus, disruption of signaling of another IL-1 family member, IL-33, may be an option in treating CSS. Overall, these targeted (anti-cytokine) approaches to treating CSS are likely to be far less toxic then current chemotherapeutic approaches [38]. Identifying the correct target for individual patients remains the next challenge.

Summary Although CSSs are frequently fatal, in part from the disease process but also secondary to broad immunosuppression used during treatment, novel approaches of targeting pro-inflammatory cytokines are being explored. Members of the IL-1 superfamily, including IL-1, IL-18, and IL-33 are being explored clinically and/or in murine models of CSS. IL-1 blockade seems like promising therapy for CSS, particularly in the setting of children with sJIA. Similarly, targeting IL-18 may be an important therapeutic option for certain genetic inflammasomopathies, such as activating NLRC4 mutations. Finally, murine models of CSS suggest disrupting IL-33 signaling dampens disease parameters and increases survival. Knowing which cytokine, or combinations of cytokines, to target for individual patients will keep physician-scientists busy for some time to come, yet cytokine blockade for frequently fatal CSS has shown some early promising results.

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