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Cloning IL-1 and the Birth of a New Era in Cytokine Biology

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In December of 1984, the sequence of the cDNA encoding for the human precursor of IL-1 was reported in a seminal paper by Charles Dinarello’s group (1). This work is the subject of this month’s selected paper for Pillars of Immunology based on its significant impact on the field of cytokine biology. Compared with today, cloning cDNAs in 1984 was still in its infancy. In November of the same year, another cDNA encoding for mouse IL-1 was reported (2). The two cDNAs were not similar, and this difference was unlikely due to genetic diversity between humans and mice. The conclusion was that there were two IL-1s. In fact, Dinarello’s laboratory had reported in 1974 that there were two “leukocytic pyrogens” with isoelectric points (pI) of 5.1 and 6.9 as well as molecular differences of 35,000 and 15,000, respectively. It subsequently became clear that the mouse cDNA coded for the pI 5.1 molecule (later to be termed IL-1α) and the human cDNA coded for the pI 6.9 IL-1 (later to be termed IL-1β). Another important question also arose from the two cDNAs: both coded for larger proteins lacking a signal peptide, but it was well known that natural IL-1 was purified from macrophage supernatants. So how did secretion and cleavage of IL-1 take place? Soon after the publication of the IL-1β cDNA, the N terminus of natural human IL-1β was reported by the group of Fons Billiau (3), and it was established that an unknown cleavage and secretion process was required. This process turned out to involve the IL-1β-converting enzyme, now known as caspase-1 (4, 5).

Taken together, these findings represented a major discovery since, for more than 50 years, investigators had attempted to prove the existence of a substance secreted by leukocytes that was able to induce fever (“leukocytic pyrogen”) and the synthesis of hepatic acute phase proteins, alter lymphocyte function (6), and exert other biological activities, including production of prostaglandin E2, collagenases (7), platelet-activating factor, (6), and exert other biological activities, including production of prostaglandin E2, collagenases (7), platelet-activating factor, and NO (8). In fact, multiple biologic properties were attributed to IL-1, but with no known amino acid sequence reported for this cytokine, it was unclear whether IL-1 represented a single substance or several different molecules. After the cloning of IL-1, experiments using rIL-1α and rIL-1β confirmed that these multiple functions were indeed due to a single cytokine, namely IL-1, and a new era in cytokine biology began.

The cloning of IL-1 has stimulated over 20 years of research and unique discoveries, with more than 40,000 reports published on IL-1 during this period. Of the multiple and diverse biological activities of IL-1, some have had a major impact on disease pathogenesis. For example, the discovery of IL-1β was injurious to the insulin-producing pancreatic β cell (9) has resulted in therapeutic advances in diabetes. In fact, a growing number of systemic inflammatory diseases characterized by fever, anemia, leukocytosis, and elevated acute phase proteins have been linked to increased IL-1 production and bioactivity as they dramatically respond to specific blockade of IL-1R type 1, the signaling receptor for IL-1. These include a group of inherited chronic auto-inflammatory syndromes (reviewed in Ref. 10) in which increased secretion of IL-1 is due to a single amino acid mutation in the NALP3 gene that is involved in the activation of caspase-1 in the IL-1β inflammasome (11).

The natural inhibitor of IL-1 (12–14), cloned in 1990 (15) and renamed the IL-1 receptor antagonist (IL-1ra), stimulated a great deal of interest since it was now possible to specifically block the biological activity of IL-1. Testing the efficacy of IL-1ra was to become a novel therapeutic approach, particularly in human conditions in which IL-1 was postulated to play a key pathogenic role (16). At the same time, skeptics who believed in the redundancy of the cytokine network criticized the concept that blockade of a single cytokine could have a significant impact on complex chronic inflammatory disorders, particularly since cytokines such as TNF and IL-6 had several overlapping activities. An important finding that took advantage of the availability of rIL-1ra clearly demonstrated that specific blockade of a single cytokine, in this case IL-1, markedly suppressed the severity of colitis in an animal model of inflammatory disease (17), thus resolving the question as to whether redundancy of the cytokine network was a key factor. This concept was endorsed rapidly by the biotechnology industry, and mAbs against a variety of cytokines, the prototypical of which are TNF and IL-1, have been developed for therapeutic use in a variety of human diseases. There are now many examples that represent the efficacy of single cytokine blockade in the treatment of human disease using neutralizing mAbs and soluble receptors, several of which are now approved worldwide for the treatment of a variety of conditions, including rheumatoid arthritis, inflammatory bowel disease, psoriasis (18, 19), as well as refractory adult and juvenile Still’s disease (also known as systemic onset juvenile idiopathic arthritis), which appears to be less responsive to anti-TNF treatment (20, 21). The original cloning of IL-1 by Charles Dinarello’s group made all these discoveries possible.

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3 Abbreviations used in this paper: pl, isoelectric point; IL-1ra, IL-1 receptor antagonist.
It is recognized now that there is a family of IL-1 ligands and IL-1Rs (Table I). IL-18 is another ligand belonging to the IL-1 family and was characterized initially in 1995 as a novel IFN-γ-inducing factor (22). IL-18 and IL-1 share many of the same biological activities, including modulating the increase of adhesion molecule expression and promoting angiogenesis and metastasis. Both also have soluble receptors that function to neutralize their respective activities. The IL-18-binding protein neutralizes IL-18 (23), and the type II IL-1R, also known as the IL-1 decoy receptor, neutralizes IL-1 (24). In addition to IL-1α, IL-1β, IL-1ra, and IL-18, six additional members of the IL-1 ligand family have been reported based on amino acid sequence conservation as well as identity of either gene or three-dimensional structure. The biological activities for the new IL-1 ligands have not been elucidated fully yet, and it is unclear at this point whether they serve as agonists or antagonists. Interestingly, as of March 2007, the latest IL to be described, IL-33, is yet another member of the IL-1 ligand family, which is related structurally to IL-18 more than to IL-1β (25). Similar to IL-1β and IL-18, IL-33 is synthesized as a precursor molecule and processed into bioactive cytokine by caspase-1. Among its biological activities, IL-33 induces splenomegaly, eosinophilia, TH type 2 responses, and significant mucus accumulation and leukocyte infiltration in the lungs and digestive tract of mice injected with rIL-33 (26). Further investigation, however, is warranted to determine whether these novel IL-1 ligands possess any of the characteristic biological activities of IL-1 and to investigate the ligands’ importance in human inflammatory disease states.

As we approach more than 20 years of research and discovery since the cloning of IL-1, much progress has been made in understanding the basic mechanism(s) of disease in which IL-1 and other cytokines play a key role. As a result, novel cytokine and anticytokine therapies have been developed that have markedly improved the quality of life of patients with a variety of diseases. We anticipate that this area of investigation will continue to move forward at a rapid pace and that the next generation of cytokine-based therapies will further improve the treatment of these chronic debilitating diseases.

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