# Kingfisher Biotech Circular

## *Context is critical for the pivotal functions of Interleukin-6*

*Interleukin-6 (IL-6), once known as interferon-beta 2, has long been studied for its role in pro-inflammatory responses, notably the acute phase response and B cell maturation. However, the vastly pleiotropic functions of IL-6 have begun to be appreciated, including an anti-inflammatory role for IL-6 as a myokine in response to physical stress. To achieve such different outcomes a complex interplay is required between various cytokines, receptors and signaling pathways, much of which still requires elaboration. For instance, IL-6 can be recognized by either a surface or soluble IL-6 receptor. Evolutionary conservation of distant piscine orthologs, associations with a wide assortment of autoimmune disorders and cancers, and the availability of monoclonal antibody therapies targeting both IL-6 and IL-6R further emphasize the importance of understanding this multifunctional cytokine.*

One only has to see the list of names that IL-6 has gone by to appreciate its varied roles: From interferon-beta 2, to B-cell stimulatory factor-2, T cell-replacing factor, hybridoma growth factor, hepatocyte-stimulating factor and thrombopoietein (among others), these disparate functions were unified under the name IL-6 when they were discovered to be, in fact, the same glycoprotein. (1, 2) The best-studied member of the gp130 receptor family of cytokines, IL-6 is now understood to be involved in a variety of distinct response pathways, but the mechanisms for how one cytokine can result in such differing effects is still under active investigation. Although the IL-6 gene shares only moderate sequence homology across species including dog, cow, mouse, chicken and fish, the protein structure is fairly well conserved and consistent with the tertiary structure seen throughout the gp130 family. Further, it appears to maintain some functional similarity, as mononuclear phagocytes of rainbow trout were shown to produce IL-6 in response to LPS. (1, 3)

As a pro-inflammatory cytokine, Il-6 plays a key role in induction of fever and the acute phase response, alongside IL-1 and TNF-alpha. In response to injury or inflammation, local cells secrete these cytokines into the bloodstream to trigger a host of responses, including inflammatory cell recruitment, leukocyte activation, and the complement pathway. The interplay between these cytokines is critical, but complicated by the fact that IL-6 can also up-regulate antagonists of both IL-1 and TNF-alpha. It has been proposed that this acts as a mechanism to control inflammation and prevent chronic inflammatory states. Thus, IL-6 regulation may act as a pivotal point in the progression of inflammation, and may actually be required to resolve inflammatory states such as sepsis. (4) A better understanding of IL-6 regulation is therefore imperative, particularly in light of the success of monoclonal IL-6R antibody (tocilizumab) therapy against several inflammatory states, including rheumatoid arthritis, Crohn's and the rare Castleman's disease. (5)

One proposed mechanism for the differential regulation of IL-6 is the ability of the IL-6R alpha chain to function as either a cell surface or secreted receptor. The IL-6 receptor is composed of the common signal-transducing chain gp130 (CD130) and the IL-6-binding chain, called IL-6Ra or CD126. While gp130 is almost ubiquitously expressed, IL-6Ra is much more tissue-restricted. However, a secreted, soluble form of the receptor chain (sIL-6R) is able to bind IL-6, and this complex can then signal through gp130, known as trans-signaling. Trans-signaling has been shown to play a separate and important role in T cells, where the surface IL-6R is downregulated upon activation. (4, 6) It is likely that these different routes of IL-6 recognition result in subtle differences in downstream signaling pathways, which might explain in part the ability of IL-6 to mediate such different outcomes, but more elaboration of these mechanisms is needed.

In addition to its roles as a cytokine in the inflammatory response, IL-6 is highly upregulated during exercise and secreted by muscles, thus it is also considered a myokine. While this IL-6 production was originally attributed to inflammation resulting from muscle injury, it is now understood that this IL-6 production not only occurs in the absence of inflammation, but is anti-inflammatory. During exercise IL-6 is produced at high levels very early, and induces the anti-inflammatory cytokine IL-10 and the receptor antagonists for IL-1R and TNF-R. It has been suggested that the anti-inflammatory effects of exercise-induced IL-6 may be one of the factors that contributes to the health benefits of regular exercise, since exercise protects against many inflammatory conditions, such as atherosclerosis. At the same time, high levels of IL-6 are correlated with the inflammation seen in diabetes and arthritis, and anti-IL-6R treatments have effectively improved outcomes in these diseases. This juxtaposition of IL-6 as both pro-inflammatory and anti-inflammatory, beneficial and harmful, demonstrates the complexity of the role of IL-6 in inflammation, immunity, and chronic disease states. (2, 7)

Together, these studies show that we have just scratched the surface in our understanding of IL-6 function. IL-6 is an early mediator of inflammation and a key component of the acute phase response. It regulates activation and trafficking of leukocytes, but also metabolism in adipocytes. At the same time, it moderates inflammation by dampening the responses of TNF-alpha and IL-1. Understanding these differences is critical to interpreting the role of IL-6 in a given system, and to determining the impact and best use of IL-6-targeting therapies. Whether in blood, fat or muscle, cis or trans, cytokine or myokine, and in collaboration with TNF or orchestrating an anti-inflammatory milieu, Il-6 is truly a context-dependent chameleon!

## References


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