Kingfisher Biotech Circular

IFN-γ: "macrophage-activating factor" is just the tip of the iceberg

The role of IFN-γ as a pro-inflammatory cytokine that protects against intracellular pathogens has been well understood for decades. Originally called "macrophage-activating factor", IFN-γ stimulates macrophages to upregulate antigen presentation and pathogen recognition pathways, as well as inducing numerous directly anti-microbial functions. However, IFN-γ has critical roles in many other processes and cell types, including leukocyte migration, Th1 development, antibody production and class switching, and cell growth inhibition, with both anti-proliferative and pro-apoptotic effects. While loss of IFN-γ signaling results in severe susceptibility to intracellular pathogens, some viral infections, and impaired tumor surveillance, IFN-γ has also been associated with immunopathology in autoimmune diseases like lupus, multiple sclerosis, and diabetes. Administration of IFN-γ as a treatment is currently only approved by the FDA for chronic granulomatous disease and osteopetrosis, but many trials are under way for everything from infection, to cancer, to fibrosis.

The *other* interferon

The interferons were originally identified as factors that "interfered" with viral replication, and have since been divided into three structurally and functionally separate categories based upon homology: the Type I, Type II, and Type III interferons. While Type I has expanded over time to include many α interferons, as well as interferons β, κ, ω , and τ, among others, interferon-γ is still the only Type II interferon. [1] Type III was identified much later, and includes the interferon-λs, also called IL-28A, IL-28B and IL-29. [2] Type I interferons are classically induced during viral infections and are secreted primarily by hematopoietic cells, or fibroblasts and macrophages in the case of IFN- β. [3] IFN-γ is secreted by various cell types, including Th1 CD4 T cells, CD8 T cells, NK cells, NKT cells, and antigen-presenting cells (APCs), and plays a critical role during intracellular bacterial infections, due in large part to its functions as a macrophage activation factor.

How to train your macrophage

IFN-γ is a highly pleiotropic cytokine, inducing the production of an array of molecules involved in various aspects of inflammation. [3] As such, its effects on macrophages are generally simply referred to as activation. Macrophage activation by IFN-γ actually entails many pathways, however. Among these, up-regulation of the various components required for Class I and Class II antigen processing and presentation is crucial for adaptive immunity. Similarly, up-regulation of pathogen recognition pathways, including the LPS response pathway, is crucial to innate immunity. IFN-γ activation also induces many direct anti-microbial effects, including increased pinocytosis and phagocytosis, microbicidal products such as the NADPH oxidase

system, NO priming, tryptophan depletion, lysosomal enzymes, and antiviral enzymes. All of these functions are critical components of the activated state of macrophages, which in turn is critical to the clearance of intracellular pathogens, but it is important to note that these effects are not limited to macrophages.

Beyond the macrophage

The effects of IFN-γ stimulation extend far beyond the macrophage. For instance, the induction of microbicidal molecules also occurs in neutrophils, and the upregulation of antigen presentation pathways occurs in many cells. [3] Additionally, IFN-γ plays an important role in coordinating the immune response. It affects leukocyte trafficking by upregulating adhesion molecules and chemoattractants, promotes Th1 development, and induces both antibody production and isotype switching in B cells. Further, IFN-γ is known to regulate many genes involved with proliferation, cell cycle, and apoptosis, including many genes implicated as tumor suppressor or proto-oncogenes. Although there is some debate about its exact role in these pathways, both anti-proliferative and pro-apoptotic genes are upregulated by IFN-γ, while the cell cycle transition molecule c-myc is notably down-regulated. Together, all of these functions serve to highlight the vast impact of IFN-γ in inflammation, immunity, and cancer beyond the macrophage.

Living with or without IFN-γ

Given the widespread effects of IFN-γ, one might anticipate that loss of IFN-γ or IFN-γR signaling would be severely detrimental to the host. However, in both mice and humans with IFN-γ deficiencies there are no observed developmental defects or impairments in development of a normal immune system. [3] What is severely impacted is the immune response to intracellular bacterial infections, as well as some viral infections. For example, in children with deficient IFN-γ responses the highly attenuated vaccine strain of tuberculosis (bacillus Calmette-Guerin) can be lethal. Further, IFN-γ is critical for tumor surveillance. Administration of IFN-γ as a treatment is available, called Actimmune, but is only approved for use in chronic granulomatous diseases and severe osteopetrosis. Clinical trials in various stages are in progress for the treatment of many diseases, including numerous forms of cancer, several viral infections as well as drug resistant and granulomatous mycobacterial infections, and both pulmonary fibroses (cystic fibrosis and ideopathic pulmonary fibrosis). [4] While loss of IFN-γ increases susceptibility to intracellular pathogens and tumor progression, IFN-γ can also lead to unnecessary inflammation, and has been associated with numerous human autoimmune conditions, including systemic lupus erythematosus (SLE), multiple sclerosis, and insulin-dependent diabetes mellitus.

Across the species

While interferons were originally identified during work in chicken eggs, most of the succeeding work has focused in mammals. [1] Evidence of an IFN system has been found in most vertebrates, but the limited sequence homology to mammalian IFNs has made identifying and comparing these genes difficult. However, putative orthologs of IFN-γ have been identified in many mammals, birds, and fish, as well as within the frog genome. [5] Despite this wide distribution, IFN-γ has low cross-reactivity between

species. An interesting exception can be seen between chicken and turkey IFN-γs, which share 96% sequence homology. [1] All together, the data suggest that the IFN system plays a key role in immunity throughout the vertebrate species.

Conclusion

IFN-γ is a critical component of both innate and adaptive immunity within vertebrates. While it may be best known as a macrophage activating factor, it has many additional pro-inflammatory and anti-microbial functions. Loss of IFN-γ signaling leads to severe susceptibility to intracellular pathogens, and IFN-γ administration in humans can be used to treat chronic granulomatous diseases and osteopetrosis, but IFN-γ is also associated with immunopathology. Learning to walk the fine line between too much and too little IFN-γ will be a critical task in the efforts to tune the inflammatory rheostat.

References:

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