Interfering with a double-edged sword: Novel anti-inflammatory functions for interferons

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One of the body's first protective reactions to infection is inflammation, typically stimulated by the factor IL-1beta. Unfortunately, inflammation frequently occurs when it is not desired and so must be treated, e.g. by blocking IL-1beta production or activity. The picture is complicated by the fact that many other factors are involved in the process. A precise understanding of the regulatory networks is important for the development of anti-inflammatory treatments.

Animals react to infections in a number of ways. Among the first is the production of cell factors such as interferons and IL-1beta. Interferons have several functions, including activating a series of intracellular signals such as Tyk2 (Tyrosine kinase 2), while IL-1beta is important for the induction of inflammation, which helps directly to protect the body against attack.

However, inflammation must be kept tightly in check as it may also harm the body. Cells control IL-1beta activity in a number of ways, regulating not only the amount of messenger RNA (mRNA) that encodes the IL-1beta protein but also the processing and release of "mature" IL-1beta protein. Surprisingly, interferons may also inhibit the production of IL-1b protein and thus suppress inflammation. This conclusion comes from Marta Radwan and Rita Stiefvater in Birgit Strobl's group at the University of Veterinary Medicine, Vienna and is published in the current issue of the Journal of Immunology.

Radwan and Stiefvater have shown that cells control the way in which

the IL-1beta mRNA is used to make IL-1beta protein. They measured the levels of IL-1beta protein in cells that lack Tyk2, one of the key components of the interferon signalling pathway. Although the amount of IL-1beta protein in these cells was increased, the amount of IL-1beta mRNA was not affected by the absence of Tyk2 and there was no apparent change to the stability of the mRNA. Instead the mRNA was more actively translated (copied) to protein and Radwan and Stiefvater were able to prove that the effect stemmed from a heightened association with polysomes, the complexes that actively synthesize proteins.

Interferons have long been known to inhibit translation of mRNAs in general but there have been recent indications that they may also stimulate the translation of particular mRNAs. IL-1beta is known to be involved in a wide range of autoimmune and inflammatory diseases, conditions in which the immune system either overreacts or reacts against itself. IL-1beta thus represents an attractive target for treatment of such diseases. As Birgit Strobl says, "The novel mode of IL-1beta regulation and the finding that interferon can inhibit IL-1beta production could turn out to be very important." Indeed, the finding that Tyk2 may inhibit the production of IL-1beta protein might have consequences for the development of strategies for the treatment of these widespread and serious conditions.

More information: The paper Tyrosine kinase 2 controls interleukin-1beta production at the translational level by Marta Radwan, Rita Stiefvater, Tom Grunert, Omar Sharif, Ingrid Miller, Martina Marchetti-Deschmann, Günter Allmaier, Manfred Gemeiner, Sylvia Knapp, Pavel Kovarikl, Mathias Müller and Birgit Strobl is published in the 185(6)/2010 issue of the *Journal of Immunology*.