Natural and therapy-induced antibodies to cytokines

Cytokines constitute a large group of intercellular signal peptides that act at extremely low concentrations as regulators of cell growth and essential mediators of inflammation and immune reactions. The production and functions of cytokines are tightly regulated by the cytokines themselves and by several other factors. The potential for anti-cytokine antibody immune therapy has been highlighted and reviewed recently by Zagury and Gallo in *Drug Discovery Today* [1].

It is well known that blood from patients suffering from various immunoinflammatory diseases contains antibodies to certain cytokines and that antibodies might be induced in patients treated with recombinant human cytokines [2,3]. However, surprisingly little interest has been devoted to the fact that high-avidity IgG antibodies (*K*d 10^{-10} to 10^{-12} M) to some but not other even closely related cytokines are present in healthy individuals as well [4–6]. Thus, (auto)antibodies have been found to several cytokines, including interleukin (IL)-1α, IL-6, IL-10, interferon (IFN)-α and granulocyte-macrophage colony-stimulating factor (GM-CSF) but not to, for example, IL-1β, IL-1Ra, IL-4, IFNγ and granulocyte colony-stimulating factor (G-CSF) (4,5).

Although these antibodies neutralize their respective cytokines *in vitro*, it is generally obscure whether they always neutralize *in vivo*, or whether they might exhibit carrier functions or cytokine-protective or -stabilizing functions [4]. Even so, antibodies to cytokines are of great clinical interest, for several reasons:

(1) Naturally occurring, specific and high-avidity antibodies to cytokines interfere with biological and immunometric assays for these cytokines *in vitro* ([5], see also BioMonitor ApS; http://www.biomon.dk).

(2) Inappropriate production and/or function of antibodies to cytokines could be pathogenetically involved in infectious and other immunoinflammatory diseases, and circulating levels of certain anti-cytokine antibodies might help predict the outcome of certain diseases, for example, in chronic arthritis ([5,6], BioMonitor ApS).

(3) Anti-cytokine antibodies might contribute to the antiinflammatory and immunosuppressive effects of human high-dose IgG therapy and human IgG enriched or purified for specific anti-cytokine activities could prove particularly useful and economical in patients with cytokine-mediated diseases ([2,5,6], BioMonitor ApS).

(4) Although therapy with human high-dose IgG might be useful because of the content of anti-cytokine antibodies, IgG therapy of patients with viral diseases or at risk of contracting infectious diseases might benefit from the use of IgG pools selectively depleted of neutralizing anti-cytokine antibodies, for example to IFN.

(5) Anti-cytokine antibodies induced during therapy with human recombinant cytokines are already of major concern because their presence could result in loss of response to therapy and perhaps to chronic alterations in immune or other vital functions, including host responses to infectious agents and malignant tumors ([2,5], BioMonitor ApS). Therapy-induced antibodies that cross-react with native cytokines can cause serious side-effects, as demostrated in the case of anti-erythropoietin antibodies [2].

It should be emphasized that the detection of cytokine antibodies is fraught with difficulties; in fact, this could be a major reason why some investigators still doubt the significance or, indeed, the existence of these major cytokine-modulating molecules. For example, false-positive results could be obtained from the nonspecific and low-affinity binding that often occurs between IgG and recombinant human cytokines attached to plastic or nitrocellulose membranes, a procedure that is often used in immunometric or immunoblotting assays for cytokines (see BioMonitor ApS).

References

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