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Suppression of autoimmunity by TNF

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Keywords

Multiple sclerosis, T cells, TNF, TNF receptor p55

Context

In rheumatoid arthritis (RA), tumor necrosis factor (TNF) is a major pathogenetic cytokine; consequently, TNF-blocking agents have been established as a successful therapy for RA. TNF induces a variety of cellular effects through specific receptors (p55 and p75) that are coupled to complex signal transduction pathways involving NF-?B, JNK and intracellular proapoptotic proteins. In addition to its strong proinflammatory effects, TNF may also exert potent immunosuppressive effects on T cells. Treatment with TNF inhibitors has been associated with autoimmune phenomena such as the development of antinuclear antibodies or lupus-like syndromes, and with the onset or flares of demyelinating syndromes, including multiple sclerosis (MS). MS is a disabling inflammatory disease of the central nervous system, considered to result from self-reactivity to myelin antigens. TNF has been implicated in the pathogenesis of MS but, paradoxically, its blockade may have both immune system and disease activating effects.

Significant findings

In TNF-deficient mice, myelin basic protein (MBP)-specific T-cell reactivity fails to regress. This leads to susceptibility to EAE in otherwise resistant H-2b mice. In contrast to wild-type C57BL/6 mice, which develop rapid onset disease, immunization of $TNF^{-/-}$ or $p55p75^{-/-}$ mice with myelin oligodendrocyte glycoprotein (MOG) led to delayed onset of EAE, but abnormally prolonged disease which failed to remit. This phenotype correlated with persistent T-cell responses and expansion of activated/memory T cells specific for myelin antigens. Interestingly, the beneficial long-term immunosuppressive effects of TNF that protect against chronic EAE do not require the p55 TNF receptor, as demonstrated in $p55^{-/-}$ mice, whereas the same receptor is necessary for the detrimental effects of TNF during the acute phase of the disease.

Comments

The inhibition of the immunosuppressive effects of TNF by anti-TNF therapies may have clinical consequences. One of them is worsening or onset of central nervous system autoimmune demyelinating disease. The elucidation of the p55 receptor pathway as responsible for the proinflammatory effects of TNF but not the immunosuppressive effects in EAE autoimmunity provides the basis for more specific anti-TNF strategies to treat MS. Blocking the function of the p55 TNF receptor in autoimmune demyelination may inhibit the noxious proinflammatory activities of TNF without compromising its immunosuppressive properties. In RA, the relative pathogenetic contributions of p55 and p75 have not been fully elucidated. Clinically, withdrawal of anti-TNF therapy is rapidly followed by disease flares, suggesting that TNF antagonists may not modify the underlying autoimmune process. Therefore, a better elucidation of the contribution of p55 and p75 to the pathogenesis of RA might also improve the specificity of anti-TNF-based therapies.

Methods

$TNF^{-/-}$, $p55p75^{-/-}$, $p55^{-/-}$ and control mice; immunization with MBP or MOG; histopathological analysis; flow cytometry; analysis of T cell proliferative responses

Additional information

References

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