Anti-proliferative effects of interferon beta associated with increased expression of p21 -
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Background: Recombinant interferon (IFN)-beta is an established therapy for multiple sclerosis (MS). The exact mechanism of action is not fully known, but may involve anti-proliferative effects, apoptosis-promoting effects and changes in cytokine secretion patterns. We studied the ex vivo effects of IFN-beta on mononuclear cells in order to address in more detail how these processes are influenced. Methods: Mononuclear cells and CD3+ T cells from 14 healthy volunteers were isolated by immunomagnetic beads and treated for 24 hours with recombinant IFN-beta1a (Avonex), 1ng/ml. Subsequently, gene expression in mononuclear cells was measured by real-time RT-PCR analysis, and the surface phenotype of CD4+ and CD8+ T cells was studied by flow cytometry. Then the cells were stimulated by anti-CD3 antibody ± anti-CD28 antibody. Supernatants were removed after two days for cytokine analysis by Luminex immunassays (IL-2, IL-4, IL-5, IL-7, IL-10, IL-15, IL-17, TNF, IFN-gamma). Cells were pulsed with tritiated thymidine, and thymidine incorporation was measured after 3 days of stimulation. Results: Treatment with IFN-beta resulted in T cell activation as assessed by increased expression of CD25, CD69 and CD71. However, treatment with IFN-beta also resulted in increased expression of the anti-proliferative p21 molecule. Treatment with IFN-beta did not result in T cell apoptosis as assessed by annexin-V binding. Pre-treatment with IFN-beta did not inhibit T cell proliferation in subsequent T cell activation studies, but an anti-proliferative effect of IFN-beta was readily observed when the cytokine was present throughout the ex vivo stimulation. No major effects of IFN-beta were observed on cytokine production in activated cells, and IFN-beta treatment did not influence expression of the T-bet and GATA3 transcription factors, which control Th1 and Th2 cytokine production. Conclusions: In the present study we found that treatment with IFN-beta resulted both in stimulatory and anti-proliferative effects on blood mononuclear cells and purified T cells from healthy volunteers. In contrast, we observed no clear effects on cytokine secretion patterns. We are currently studying T cell activation and cellular expression of the p21 molecule in MS patients treated with IFN-beta. Taken together these studies may provide a better understanding of the immunomodulatory effects of treatment with IFN-beta. FS and PSS have received unrestricted research grants from Biogen-Idec, Schering and Serono.

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