INTERFERON-β INHIBITS IN VITRO HUMAN CD4+CD25+ REGULATORY T LYMPHOCYTE FUNCTION: INVOLVEMENT OF AUTOCRINE/PARACRINE DOPAMINERGIC PATHWAYS

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CD4+CD25+ regulatory T lymphocytes (Treg) are specialized T cells which play crucial roles in the control of immune homeostasis. Active suppression by Treg plays a key role in the control of self-antigen–reactive T cells and the induction of peripheral tolerance in vivo. Recent evidence indicates that impairment of Treg function might contribute to the breakdown of immune tolerance in patients with multiple sclerosis (MS). Previous results from our group showed that endogenous catecholamines in human lymphocytes are extensively affected by interferons (IFNs) (1) and that Treg constitutively express dopaminergic receptors, α- and β-adrenoceptors (ARs), and contain high amounts of catecholamines stored in reserpine-sensitive compartments (2). We therefore decided to investigate *in vitro* the ability of interferon β (IFN-β) to affect human Treg function. Treg were isolated from healthy donors' blood by immunomagnetic sorting and cultured. IL-10 and TGF-β mRNAs and proteins were measured by RT-PCR and ELISA respectively. The ability of Treg to inhibit mitogen-induced proliferation of effector T lymphocytes (Teff) was assessed in co-cultures by standard ELISA measurement of cell proliferation. Incubation with IFN-β 1000 IU/ml significantly reduced IL-10 and TGF-β in Treg at both mRNA and protein levels (IL-10: mRNA = -51.8±12.0%, protein = -35.3±10.3%; TGF-β: mRNA = -42.7±16.7%, protein = -46.9±17.6%; $P<0.001$ vs control in all cases). In co-culture experiments, incubation with IFN-β 1000 IU/ml completely reversed Treg-induced inhibition of Teff proliferation. The D1-like receptor antagonist SCH23390 completely reversed all the effects of IFN-β. This is the first report showing a direct effect of IFN-β on human Treg function. The effect involves the activation of D1-like receptor pathways, likely through the autocrine/paracrine action of endogenous dopamine released from Treg by IFN-β itself. In view of the role or Treg in the regulation of the immune response in health and disease, further studies are needed to assess the clinical significance of these findings.