Immunosuppressive Effects of Carbon Monoxide, a Gaseous Product of Heme Oxygenase-1

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Heme oxygenase-1 (HO-1) catabolizes heme into CO, biliverdin, and free iron and serves as a protective enzyme by virtue of its anti-inflammatory, antiapoptotic, and antiproliferative actions. Previously, we have demonstrated that human CD4(+) T cells express HO-1 and that HO-1-overexpressing Jurkat T cells tend to display lower proliferative response. The aim of this study is to elucidate the mechanism(s) by which HO-1 can mediate its antiproliferative effect on CD4(+) T cells Among the three HO-1 byproducts, only CO showed suppressive effect on T cell proliferation in response to anti-CD3 plus anti-CD28 Abs, mimicking the antiproliferative action of HO-1. CO blocked the cell cycle entry of T cells, which was independent of the guanylate cyclase/cGMP pathway. CO also suppressed the secretion of IL-2, and this suppressive effect of CO on IL-2 secretion mediated the antiproliferative action of CO. CO selectively inhibited the extracellular signal-regulated kinase pathway, which could explain the suppressive effects of CO on T cell proliferation and IL-2 secretion. Based on these findings, we suggest that HO-1/CO suppresses T cell proliferation and IL-2 secretion, possibly via its inhibition of extracellular signal-regulated kinase activation.