

Pentoxifylline functions as an adjuvant in vivo to enhance T cell immune responses by inhibiting activation-induced death

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Inducing long-lasting immune responses is an essential part of vaccine design. Most currently available immunological adjuvants empirically used for this purpose cause some inflammation, limiting clinical acceptability. We show that pentoxifylline (PF), a phosphodiesterase (PDE) inhibitor in common clinical use, if given to mice for a brief period during initial immunization, enhances long-term persistence of T cell responses. This includes protective responses to a bacterial immunogen, *Salmonella typhimurium* (Stm). The action of PF is via a cAMP-dependent protein kinase A (PKA)-mediated effect on T cells. PF inhibits activation-mediated loss of superantigen-reactive CD4 as well as CD8 T cells in vivo without significantly affecting their activation, and inhibits activation-induced death and caspase induction in stimulated CD4 as well as CD8 T cells in vitro without preventing the induction of activation markers. Consistent with this ability to prevent activation-induced death in not only CD4 but also CD8 T cells, PF also enhances the persistence of CD8 T cell responses in vivo. Thus, specific inhibition of activation-induced T cell apoptosis transiently during immune priming is likely to enhance the persistence of CD4 and CD8 T cell responses to vaccination, and pharmacological modulators of the cAMP pathway already in clinical use can be exploited for this purpose as immunological adjuvants.