

## Abstract

TLR3 is a key receptor for recognition of double-stranded RNA and initiation of immune responses against viral infections. However, hyperactive responses can have adverse effects, such as virus-induced asthma. Strategies to prevent TLR3-mediated pathology are therefore desired. We investigated the effect of single-stranded DNA oligonucleotides (ssDNA-ODNs) on TLR3 activation. Human monocyte-derived dendritic cells up-regulate maturation markers and secrete proinflammatory cytokines on treatment with the synthetic TLR3 ligand polyinosine-polycytidylic acid (poly I:C). These events were inhibited in cultures with ssDNA-ODNs. Poly I:C activation of nonhematopoietic cells was also inhibited by ssDNA-ODNs. The uptake of poly I:C into cells was reduced in the presence of ssDNA-ODNs, preventing TLR3 engagement from occurring. To confirm this inhibition *in vivo*, we administered ssDNA-ODNs and poly I:C, alone or in combination, via the intranasal route in cynomolgus macaques. Proinflammatory cytokines were detected in nasal secretions in the poly I:C group, while the levels were reduced in the groups receiving ssDNA-ODNs or both substances. Our results demonstrate that TLR3-triggered immune activation can be modulated by ssDNA-ODNs and provide evidence of dampening proinflammatory cytokine release in the airways of cynomolgus macaques. These findings may open novel perspectives for clinical strategies to prevent or treat inflammatory conditions exacerbated by TLR3 signaling.