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Complement Receptor 3 Blockade Promotes IL-12-Mediated Clearance of Porphyromonas gingivalis and Negates Its Virulence In Vivo

Authors:

Abstract: The ability of certain pathogens to exploit innate immune function allows them to undermine immune clearance and thereby increase their persistence and capacity to cause disease. Porphyromonas gingivalis is a major pathogen in periodontal disease and is associated with increased risk of systemic conditions. We have previously shown that the fimbriae of P. gingivalis interact with complement receptor 3 (CR3; CD 11b/CD18) in monocytes/macrophages, resulting in inhibition of IL-12p70 production in vitro. The in vivo biological implications of this observation were investigated in this study using a CR3 antagonist (XVA143). XVA143 was shown to block CR3 binding of P. gingivalis fimbriae and reverse IL-12p70 inhibition; specifically, CR3 blockade resulted in inhibition of ERK1/2 phosphorylation and up-regulation of IL-12 p35 and p40 mRNA expression. Importantly, mice pretreated with XVA143 elicited higher IL-12p70 and IFN-? levels in response to P. gingivalis i.p. infection and displayed enhanced pathogen clearance, compared with similarly infected controls. The notion that CR3 is associated with reduced IL-12p70 induction and impaired P. gingivalis clearance was confirmed using i.p. infected wild-type and CR3-deficient mice. Moreover, XVA143 dramatically attenuated the persistence and virulence of P. gingivalis in experimental mouse periodontitis, as evidenced by reduced induction of periodontal bone loss. Therefore, CR3 blockade may represent a promising immunomodulatory approach for controlling human periodontitis and possibly associated systemic diseases.