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Subversion of Innate Immunity by Periodontopathic Bacteria via Exploitation of Complement Receptor-3

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Abstract: The capacity of certain pathogens to exploit innate immune receptors enables them to undermine immune clearance and persist in their host, often causing disease. Here we review subversive interactions of Porphyromonas gingivalis, a major periodontal pathogen, with the complement receptor-3 (CR3; CD 11b/CD18) in monocytes/macrophages. Through its cell surface fimbriae, P. gingivalis stimulates Toll-like receptor-2 (TLR2) inside-out signaling which induces the highaffinity conformation of CR 3. Although this activates CR3-dependent monocyte adhesion and transendothelial migration, P. gingivalis has co- opted this TLR2 proadhesive pathway for CR3 binding and intracellular entry. In CR3-deficient macrophages, the internalization of P. gingivalis is reduced 2-fold but its ability to survive intracellularly is reduced 1000-fold, indicating that CR3 is exploited by the pathogen as a relatively safe portal of entry. The interaction of P. gingivalis fimbriae with CR3 additionally inhibits production of bioactive (p70) interleukin-12, which mediates immune clearance. In vivo blockade of CR3 leads to reduced persistence of P. gingivalis in the mouse host and diminished ability to cause periodontal bone loss, the hallmark of periodontal disease. Strikingly, the ability of P. gingivalis to interact with and exploit CR3 depends upon quantitatively minor components (FimCDE) of its fimbrial structure, which predominantly consists of polymerized fimbrillin (FimA). Indeed, isogenic mutants lacking FimCDE but expressing FimA are dramatically less persistent and virulent than the wild-type organism both in vitro and in vivo. This model of immune evasion through CR3 exploitation by P. gingivalis supports the concept that pathogens evolved to manipulate innate immune function for promoting their adaptive fitness.