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The effect of titanium on the expression and activity of Matrix metalloproteinase 7 in differentially activated macrophages

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Implant material is widely used in medical fields such as orthopedics, odontology or cardiology. Due to its excellent properties regarding corrosion resistance and biocompatibility, titanium has been used successfully for decades. However, in the orthopedic field, studies report failure rates between 3,4-9%. One of the main reasons for implant failure is aseptic implant loosening which has been reported to be responsible for 80% of revision surgeries. Matrix metalloproteinase and especially MMP-7 play a significant role in the pathology of implant failure. MMP-7 has, due to the lack of its hemopexin domain, one of the broadest substrate spectrums among all MMPs. It can degrade the extracellular matrix as well as activate a large number of cytokines. These cytokines, in turn, can cause numerous pathologies (e.g., fibrosis or chronic inflammation). Macrophages are the principal cell type involved in the orchestration of the foreign body response. In order to analyze the foreign body response to titanium, which is one of the most used materials for implants in humans, the aim of this work was to examine the effect of human primary macrophage exposure to titanium on the MMP-7 production. Using Affymetrix microarray assays it was previously identified in our laboratory, that titanium induces MMP-7 gene expression in macrophages (79). The specific aims of the current project included 1) quantification of titanium induced changes in gene expression and secretion of MMP-7 in human primary M0, M1 and M2 macrophages; 2) comparative analysis of titanium induced MMP-7 production on 3 different levels (mRNA, protein secretion, activity); and 3) analysis of TIMP-3 and CD151, regulators of MMP-7 activity, in response to titanium stimulation. Analysis of differential effects of porous and polished titanium on MMP-7 production by M0, M1, and M2 was performed in the model system established in our laboratory where human primary M0, M1, and M2 macrophages are differentiated out of peripheral blood monocytes cultured on titanium disks was used. RT-PCR analysis revealed that both polished and porous titanium up-regulate MMP-7 mRNA in M0 and M2 macrophages. Additionally, polished titanium was able to induce MMP-7 in M1 macrophages. Protein analysis by ELISA confirmed that secretion of MMP-7 correlates with the up-regulated levels of mRNA in M0 and M2. Analysis of active MMP-7 demonstrated that titanium induced release in M0 and M2 in some donors, however without statistical significance. The inducing effect of titanium on MMP7 production was differential on each level of regulation with a principal induction on mRNA and protein level. It was shown that MMP-7 increased by the time of incubation both under titanium stimulation as well as without titanium. The maximum MMP-7 levels were detected on day 6 of incubation. Exposure of macrophages to titanium resulted in changes of expression of the MMP-7 regulators TIMP3 and CD151 in some donors, however without statistical significance, suggesting that there are also other mechanisms responsible for the post-translational regulation of MMP-7. Collectively, the results demonstrate that MMP-7 is statistically significant induced in human primary macrophages by titanium on mRNA and protein levels, and in part of donors on the levels of released active MMP-7. MMP-7 production was induced in macrophages by both porous and polished titanium, while the strongest effect was found in M2 macrophages. As the up-regulation of MMP-7 may be essential for the success of the integration of a titanium implant, a macrophage-based model system is suggested as a predictive tool for implant failure enabling a personalized therapeutic approach.