TiO_2 nano-dimensioned surfaces modulate host inflammation via mediating macrophage M1/M2 polarization

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Statement of Purpose: For restoration of human function, application of endosseous implant is indispensable to modern medicine. However, kinds of implantable biomaterials displayed controversial osteo-genic activities in vitro and in vivo due to perpetuating inflammation elicited by themselves, which may be highly related the performance of implant. Besides, polarization of macrophages, key member of host innate inflammatory responses, is highly related to tissue fate: classically activated M1 macrophages often result to chronic inflammation and impeded bone formation whereas alternatively activated M2 macrophages are benefit to bone regeneration. In this work, we built different scales of TiO_2 implant nano-dimensioned surface to modulate host inflammation and macrophage polarization.

Methods: Human primary macrophages were collected from peripheral blood and purified by immune-magnetic beads assay($CD14^+$). HF-based anodization method was used to construct TiO_2 nano-dimensioned surface and specimens were grouped by anodization voltages(polished Ti, 5V and 20V). SEM and immunofluorescence staining were applied for cell morphological observation. Cytokines secretion and macrophage polarization were identified by ELISA and flow cytometry assay(FCM).

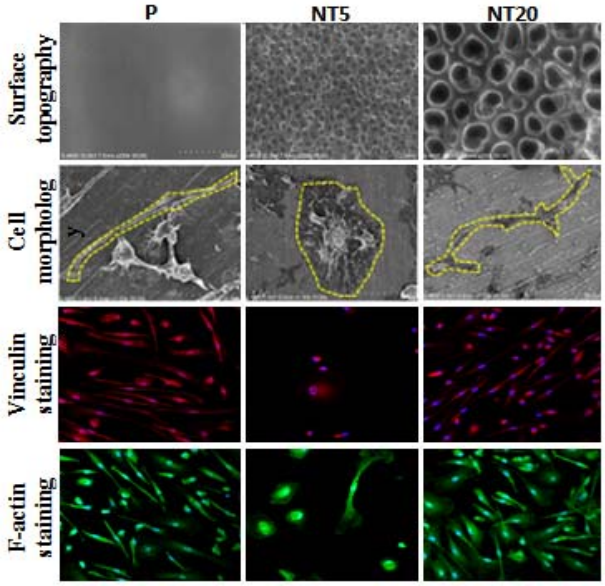

Figure.1. TiO_2 nano-dimensioned surface control the morphologic change of human macrophages.

Results: Surface topography of TiO_2 nano-dimensioned surfaces and morphology of macrophages are displayed in Figure1: stretched macrophages on P and NT20 exhibited an evidence of activation whereas oval shaped cells on NT5 showed a static status. Focal adhesion formation and F-actin distribution yield to the similar phenomenon described above(Figure.1.): NT5 surface suppressed focal adhesion formation and stretching of cytoskeleton.

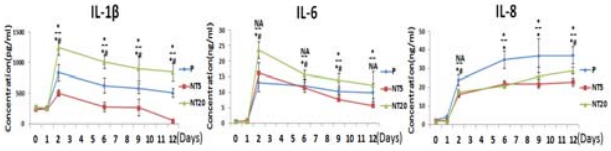

Figure.2. Inflammatory mediators released from macrophages on modified surfaces

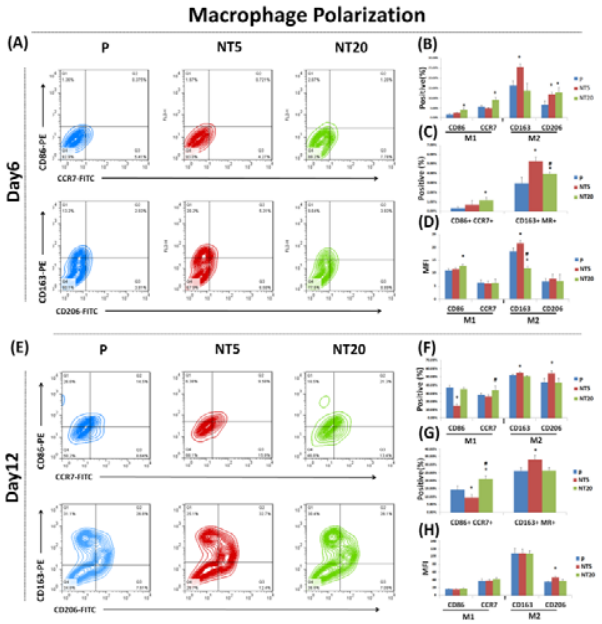

Figure.3. Polarization of macrophages on different TiO_2 nano-dimensioned surfaces

Through cytokines secretion determination(Figure.2), we found that activated macrophages on NT20 secreted the highest level of IL-1β and IL-6 whereas NT5 produce the lowest. Both NT5 and NT20 inhibited IL-8 production. FCM analysis(Figure.3) also showed that NT5 induced macrophages polarizing to anti-inflammatory M2 phenotype ($CD163^+CD206^+$) whereas NT20 enhanced pro-inflammatory M1 polarization($CD86^+CCR7^+$).

Conclusions: Small scale of nano-dimensioned TiO2 surface(NT5,30nm in diameter) help to maintain the static status of macrophage and to induce macrophage polarizing to anti-inflammatory M2 phenotype, which is benefit to inflammation resolution and bone regeneration. Manipulating nano-scales of surface topography can effectively regulate host innate inflammation and probably be a new strategy to improve performance of implanted biomaterials. However, additional research is still need to clarify the mechanism of surface-induced intracellular signal pathway.

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