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The microRNA expression signature on modified titanium implant surfaces influences genetic mechanisms leading to osteogenic differentiation

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ABSTRACT

Topographically and chemically modified titanium implants are recognized to have improved osteogenic properties; however, the molecular regulation of this process remains unknown. This study aimed to determine the microRNA profile and the potential regulation of osteogenic differentiation following early exposure of osteoprogenitor cells to sand-blasted, large-grit acid-etched (SLA) and hydrophilic SLA (modSLA) surfaces. Firstly, the osteogenic characteristics of the primary osteoprogenitor cells were confirmed using ALP activity and Alizarin Red S staining. The effect of smooth (SMO), SLA and modSLA surfaces on the TGF-β/BMP (BMP2, BMP6, ACVR1) and non-canonical WNT/Ca^{2+} (WNT5A, FZD6) pathways, as well as the integrins ITGB1 and ITGA2, was determined. It was revealed that the modified titanium surfaces could induce the activation of TGF-β/BMP and non-canonical WNT/Ca^{2+} signaling genes. The expression pattern of microRNAs (miRNAs) related to cell differentiation was evaluated. Statistical analysis of the differentially regulated miRNAs indicated that 35 and 32 miRNAs were down-regulated on the modSLA and SLA surfaces respectively, when compared with the smooth surface (SMO). Thirty-one miRNAs that were down-regulated were common to both modSLA and SLA. There were 10 miRNAs up-regulated on modSLA and nine on SLA surfaces, amongst which eight were the same as observed on modSLA. TargetScan predictions for the down-regulated miRNAs revealed genes of the TGF-β/BMP and non-canonical Ca^{2+} pathways as targets. This study demonstrated that modified titanium implant surfaces induce differential regulation of miRNAs, which potentially regulate the TGF-β/BMP and WNT/Ca^{2+} pathways during osteogenic differentiation on modified titanium implant surfaces.

1. Introduction

Titanium has long been considered the preferred material for implants in dentistry and orthopedics owing to its physical, chemical and biocompatibility features. Increasing clinical use of implants has necessitated the need for improved healing, especially in sites where bone quality and quantity is less than ideal. Surface topography and chemistry have been shown to be important factors influencing the osteogenic properties of implant surfaces [1,2].

Micro-roughened surfaces, such as the widely studied sand-blasted, large grit, acid-etched (SLA) titanium surfaces, potentially mimic the micro-rough biological bone tissue environment. The activities and characteristics of progenitor cells are influenced by their interaction with the implant surfaces [3]. Chemical modification of SLA, resulting in a hydrophilic surface (modSLA), has been shown to further improve osteogenic differentiation in vitro and osseointegration in vivo [4–11]. Investigation of the underlying molecular mechanisms responsible for the enhanced osteogenic properties of modified surfaces has been the focus of significant recent attention, and in vivo and in vitro gene expression studies have revealed differences in osteogenesis associated gene expression in response to SLA and modSLA [12–16]. Furthermore, studies investigating the associated biological mechanisms suggest that the TGF-β/BMP and WNT signaling pathways are triggered early in the interaction between osteoprogenitors and implant surfaces [2,13,14,17]. However, the detailed molecular mechanisms that regulate osteogenesis on these surfaces are still elusive and require further investigation.

The activation and de-activation of key regulatory genes is crucial to the process of differentiation of progenitor cells. Micro-RNAs (miRNAs) have been shown to influence the pattern of gene expression by translational repression and gene silencing [18] and are vital regulators of the differentiation process [19]. MiRNAs have been found to be critical in the development of organisms and

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