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Biological response of human suture mesenchymal cells to Titania nanotube-based implants for advanced craniosynostosis therapy

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ABSTRACT

Titania nanotubes (TNTs) engineered on titanium (Ti) surfaces (i.e. TNT/Ti) and loaded with specific drugs have been recognised as a promising solution for localised therapeutic delivery to address several medical problems not feasible with conventional drug administration. We propose the use of TNT/Ti protein-releasing implants to treat paediatric craniofacial abnormality in craniosynostosis caused by premature fusion of cranial sutures. In this study, we have analysed the biological response of human suture mesenchymal cells (SMCs), extracted from two different patients undergoing craniofacial reconstruction surgery, at the TNT/Ti implant surface. The experimental groups included large-diameter TNT/Ti implants, with and without biopolymer surface coating (Chitosan and Pluronic-F127) while the controls comprised of flat Ti disc and tissue culture plastic. The non-loaded implant surfaces and the cellular interactions at the implant-cell interface were characterised using scanning electron microscopy (SEM). The SMC adhesion, viability and proliferation were determined by MTT assay and manual cell counting at day 1 and day 3 of cell incubation. SEM showed significant reduction in initial attachment and adhesion of SMCs at TNT-cell biointerface compared with the control Ti discs. Subsequent cell proliferation results also revealed a decrease in the number of viable cells on the TNT surfaces. The nanotopography and structural features along with the surface chemistry dictated the cellular response, with nanotubular surfaces (with and without polymer coating) impeding cell adhesion and proliferation. Our findings hold promise for the use of TNT-based cranial implants as a delivery system to prevent sutural bone growth for advanced craniosynostosis therapy.

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1. Introduction

Craniosynostosis is a paediatric craniofacial abnormality caused by premature fusion of cranial sutures [1]. It is a largely unknown but fairly common pathology occurring in approximately 1 in 2500 live births [1]. The early suture closure (Fig. 1) can be associated with morphologic abnormalities such as dysmorphic head and asymmetric facial features, causing raised intracranial pressure and impaired cerebral blood flow leading to significant morbidity [2–4]. The conventional management of this disease relies on invasive surgical reconstruction of the cranial vault. Although the prematurely fused bones are excised and reshaped to increase the intracranial volume, patients often require repetitive interventions as the brain grows [5,6]. Depending on the severity and cause, patients can have single or multiple fused sutures [7].

The suture pathophysiology is related to abnormal proliferation and differentiation of cells at the osteogenic fronts within a growing skull [8]. The current goal of craniosynostosis research is to design therapeutic implants that can alter/delay premature suture fusion by altering the events at the cellular level, thus avoiding the multiple operations.

Medical implants made from Titanium (Ti) and its alloys have extensively been explored for orthopaedic, dental and craniofacial applications by virtue of their bioinertness and biocompatibility

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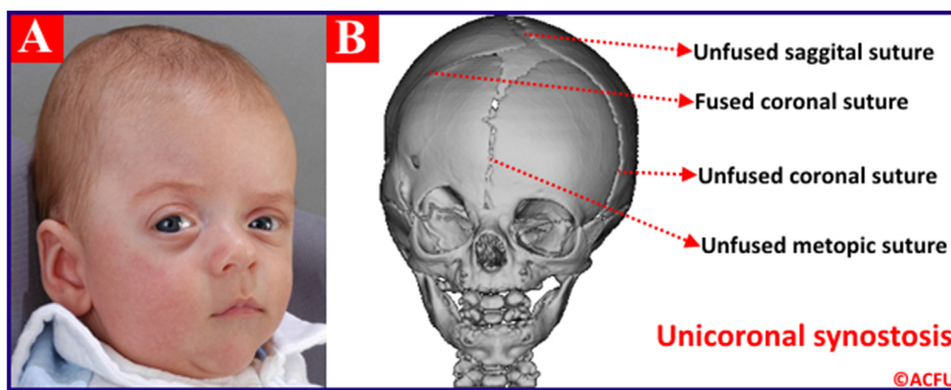

Fig. 1. A digital (A) and radiological (B) image of an infant skull with unicoronal synostosis (i.e. suture fusion on the right side) before undergoing a cranial vault reconstruction surgery at the Australian Craniofacial Unit (ACFU).

properties [9,10]. Moreover, numerous surface modifications and micro- and nano-structuring techniques have been explored in the last two decades to avoid post-implantation infection and implant rejection [11,12]. Previous studies have confirmed the relevance of both chemical and structural modification of Ti implants at micro and nano scales to modulate the cellular response and bioactivity [13–16]. One of the simplest and most efficient approaches to generate nanostructured surfaces is to electrochemically anodise Ti to grow an oxide layer with Titania nanotubes (TNTs) [17,18]. The concept of TNT/Ti drug-releasing implants has been established as a superior localised therapeutic-delivery platform in treating bone-related diseases due to their outstanding chemical and mechanical properties as well as easily tuneable dimensions and loading capacity [11,12,16,19]. These implants have been successfully applied for slow and extended release of therapeutics with varied chemistries and solubilities, triggered on-demand release of externally stimulated payloads and sequential release of multiple drugs and carriers [20–23]. Numerous studies have demonstrated the capabilities of TNTs to release substantial amount of drugs (antibiotic, anticancer, antibacterial), proteins, genes and RNAs catering to bone-implant challenges [12,19,24]. Extending this approach to craniosynostosis therapy, TNT/Ti cranial implants present a promising platform for localised delivery of proteins (bone antagonists), prohibiting sutural bone formation in a murine model.

The TNT/Ti implants are polymer-coated (with Chitosan and Pluronic-F127) in order to modulate the implant interactions, and to extend the release of loaded proteins in vivo. Both Chitosan and Pluronic-F127 are biodegradable polymers with low toxicity, high biocompatibility and weak immunogenic properties which make them ideal for tissue engineering and drug delivery applications [25,26].

For successful clinical implantation and optimal functioning of the TNT/Ti implant, it is essential to understand the events at suture cell-biomaterial interface. Human primary suture cells or suture mesenchymal cells (SMCs) are a complex population derived from bone-forming tissues of the skull calvarial plates. The tissue complex comprises of cells at different stages of differentiation including mesenchymal cells, osteoprogenitor cells, preosteoblasts, osteoblasts, osteocytes and cells from other developmental lineages [8,27]. Previous research based on an in vitro model of explant human calvarial suture tissue culture has identified the cellular mechanisms involved in abnormal bone growth during suture morphogenesis [27–29]. Experimental evidence shows that the cranial osteoblasts potentially de-differentiate into pre-osteoblastic cells when cultivated in the absence of osteogenic cues, making them ideal candidates for studying cell behaviour at the TNT/Ti implant surface [30]. In addition, they are likely to behave as stem cells cultured on TNTs [31,32].

Owing to their nanotopographical surface features (closely mimicking the natural extracellular matrix/bone morphology), TNT/Ti implants are known to modulate and control cell behaviour and surface interaction. In addition to nanoscale surface morphology, cell adhesion and subsequent proliferation, migration and differentiation are highly dependent on TNT porosity and pore dimensions. Surface roughness, chemistry, wettability, charge and the crystal phase also affect cell physiology. TNTs with variable dimensions and surface properties have been shown to influence the behaviour of a variety of cell types cultured on the surface, e.g. osteoblasts, fibroblasts, chondrocytes, myocytes, keratinocytes, endothelial cells and mesenchymal stem cells (MSCs). However, the cellular response of different cell types to similar TNT morphologies (diameters) is conflicting [13,14,31–35].

The events succeeding an *ex vivo*/clinical implantation involve the immediate adsorption of extracellular matrix (ECM) proteins (vitronectin and fibronectin) from the media or the body serum onto the implant surface. The protein adsorption and subsequent unfolding expose the functional groups and provide anchorage sites to the surrounding cell surface receptors (integrins), which cluster to form a focal adhesion complex, thereby controlling cell adhesion, spreading and function [34–36].

The response of different phenotypic cell lines to the TNTs with variable topographical characteristics (diameters) is not universal. In some studies, 30 nm TNTs show good MSC adhesion, while in others 70–100 nm TNT surfaces promote elongation and expression of osteogenic differentiation markers [37]. Comparisons also indicate that 15 nm diameter TNTs promote MSC activity, integrin clustering and focal formation while 100 nm TNTs impair cell functions and induce cell death [31]. Furthermore, 30–100 nm [15], 50 nm [38] and 70 nm [38,39] TNTs are known to significantly enhance osteoblast cell growth and function, contradicting the findings of impaired osteoblastic function when the nanotube diameter is larger than 50 nm [31].

Considering all the ambiguities about the varied cellular behaviour on TNTs, our aim was to evaluate the in vitro performance of large-diameter TNT/Ti implants on the adhesion, proliferation, viability and morphology of human suture mesenchymal cells. Since the TNT/Ti implants show promise in treating paediatric craniofacial abnormality (i.e. craniosynostosis), the SMCs (primary cells) extracted from affected patients undergoing crainectomy gives this novel study an opportunity to broaden the existing knowledge base. Our specific objectives were (i) to fabricate TNT/Ti implants and to investigate the initial human SMC interaction at the implant surfaces, (ii) to compare the human SMC behaviour (adhesion, spreading and proliferation) within and between the polymer-coated (with Chitosan and Pluronic-F127) and uncoated TNT surfaces (i.e. three experimental groups), includ-

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