Base-metal dental casting alloy biocompatibility assessment using a human-derived three-dimensional oral mucosal model

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A R T I C L E   I N F O

Article history: Received 8 June 2011 Received in revised form 15 August 2011 Accepted 17 August 2011 Available online 24 August 2011

Keywords: Biocompatibility Dental casting alloys Inflammation Oxidative stress ICP-MS

A B S T R A C T

Nickel–chromium (Ni–Cr) alloys used in fixed prosthodontics have been associated with type IV Ni-induced hypersensitivity. We hypothesised that the full-thickness human-derived oral mucosa model employed for biocompatibility testing of base-metal dental alloys would provide insights into the mechanisms of Ni-induced toxicity. Primary oral keratinocytes and gingival fibroblasts were seeded onto Allo-derm™ and maintained until full thickness was achieved prior to Ni–Cr and cobalt–chromium (Co–Cr) alloy disc exposure (2–72 h). Biocompatibility assessment involved histological analyses with cell viability measurements, oxidative stress responses, inflammatory cytokine expression and cellular toxicity analyses. Inductively coupled plasma mass spectrometry analysis determined elemental ion release levels. We detected adverse morphology with significant reductions in cell viability, significant increases in oxidative stress, inflammatory cytokine expression and cellular toxicity for the Ni–Cr alloy-treated oral mucosal models compared with untreated oral mucosal models, and adverse effects were increased for the Ni–Cr alloy that leached the most Ni. Co–Cr demonstrated significantly enhanced biocompatibility compared with Ni–Cr alloy-treated oral mucosal models. The human-derived full-thickness oral mucosal model discriminated between dental alloys and provided insights into the mechanisms of Ni-induced toxicity, highlighting potential clinical relevance.

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1. Introduction

Two-dimensional (2-D) oral keratinocyte [1–3] and gingival fibroblast [4–6] cell monolayers have been employed to determine dental casting alloy biocompatibility. Oral keratinocytes are the primary tissue target of nickel ions and have been associated with the proinflammatory response elicited by the oral mucosa during nickel hypersensitivity reactions in vivo [7]. However, the ability of cell monolayer structures to faithfully replicate the complexities of full-thickness human oral mucosal tissue have been questioned [7–9]. Cell monolayer structures possess deficiencies in cell differentiation [10,11], since anatomically cell monolayers fail to represent complex three-dimensional (3-D) native human oral mucosal tissue. Cell differentiation modifies a cell’s ability to respond to chemical and hormonal signals due to changes in gene expression [12]. Additionally, cell monolayers lack supporting connective tissue, basement membranes and extracellular matrix [13], which can lead to increased toxin susceptibility and inappropriate immune responses.

Recent advances in tissue engineering have led to oral mucosal equivalent development with an in vitro translational advantage for biocompatibility testing [8,13–15]. Moharamzadeh et al. [15] incorporated primary gingival fibroblasts and immortalised TR146 oral keratinocytes into a human-derived scaffold structure (Allo-derm™) and identified cell differentiation, manifest as a cytokeratin expression profile similar to native human oral mucosal tissue, comprising cytokeratins 5, 10 and 19, indicative of cell type and epithelial differentiation status [15]. However, the Moharamzadeh et al. [15] study could not be described as a primary cell-based structure as immortalised rather than primary oral keratinocytes were employed.

Nickel–chromium (Ni–Cr) dental alloys were developed as a cost-effective alternative to Weinstein’s high-gold patented alloy [16] in response to rising gold prices from 1968 [17]. Co–Cr dental alloys possess similar elastic moduli, strength and hardness as Ni–Cr dental alloys, but are less ductile compared with their Ni–Cr counterparts [18,19] and are accordingly not as widely employed in clinical dentistry. Today Ni–Cr alloys are used extensively in fixed prosthodontics [20,21] where appliances can remain in situ, adjacent to the oral mucosa, for substantial periods of time and have been associated with Ni allergy—indicative of a type IV Ni-induced hypersensitivity response [22]. Nickel allergy has been