

Tissue-Engineered Oral Mucosa Constructs for *In Vitro* Research and Clinical Applications



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Received: February 12, 2018; **Published:** February 19, 2018

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Mini Review

Monolayer cultures of epithelial or gingival fibroblasts have been used for the study of oral mucosa and the effect of external stimuli, such as different types of dental materials. However, monolayer models lack polarized cell phenotype and systemic components, which affect their function and response to stimuli [1,2]. Several tissue-engineered oral mucosa models have been developed to overcome these limitations with applications in different fields [2-4]. These 3D cultures provide a higher degree of complexity than monolayer cell cultures being closer to explant cultures, providing an *in vitro* model resembling the *in vivo* situation [2]. At least two tissue-engineered oral mucosa models are commercially available, Skin Ethic™ Oral Epithelium and Gingival Epithelium constructs from EPISKIN (Lyon France), or the Epi Oral™ and Epi Gingival™ constructs from Mat Tek Corporation (Ashland, MA, USA). Other commercial skin tissue models are validated to be used as an alternative to animal testing to proof cosmetics safety [5]. Thus, it could be envisaged that in the near future oral tissue models might be approved to test cosmetic dental raw materials or formulations such as tooth pastes or mouthwashes. However, the existing commercial models lack a fibroblast/collagen matrix component, which is critical in human oral mucosa [2].

In order to produce a full thickness tissue-engineered mucosa with epithelial and fibroblasts components, several strategies have been followed using different scaffolds or cells from different origin (Table 1). These differences in scaffold and cell origin are very important depending on the aim of the study or the application of the oral system. *In vivo* clinical applications include both intra-oral graftings (i.e., for use in reconstructions of the oral cavity

after tumor resection or the treatment of gingival recession) and extra-oral applications (i.e., for use in urethroplasty, grafting of burn wounds or eyelid reconstruction) [1,6]. For these applications, human primary cells (from the same patient if possible) are used in the fabrication of the oral graft [6]. Besides, *in vitro* applications include cosmetic testing or study of different dental materials such as titanium implants [7]. These 3D cultures can also be used in oral cancer research to facilitate the study of mechanistic aspects of the disease, early invasion, tumor growth, new treatments or diagnostic tests [8]. For *in vitro* applications, the use of immortalized cells is preferred, since primary cells are difficult to maintain for a long period of time and results can differ for every cell donor. Buccal carcinoma cell lines may not represent normal epithelial cells; since the results produced using these cells should be interpreted with caution and validated with other cells [2]. Another *in vitro* application is the use of tissue-engineered oral mucosa as model for the emerging research field that studies soft tissue interaction with dental implant abutments. Human primary oral keratinocytes and human primary oral fibroblasts have been used to produce constructs for this purpose [9,10]. In addition, a three-dimensional tissue engineered bone-oral mucosal model has been produced to assess both soft and hard tissue integration on titanium implants [11].

Conclusion

In conclusion, the use of tissue-engineered oral mucosa constitutes both a therapeutic and a research tool that depending on the given application shall be constructed by a different strategy.

Table 1: Summary of different strategies (scaffolds and cell types) used to develop tissue-engineered oral mucosa.

Scaffold	Cell type	Application	Reference
Acellular dermis			
Alloderm® (LifeCell)	Primary human keratinocytes and Immortalized fibroblasts (3T3)	Clinical application for intraoral grafting procedures	[12,13]
	Primary human oral keratinocytes and fibroblasts	<i>In vitro</i> testing	[10]
Deepidermalized dermis	Primary canine oral keratinocytes and Immortalized fibroblasts (3T3)	Graft for dog cleft palate repair	[14]
	Keratinocytes derived from human oral palate	<i>In vitro</i> preparation of bioartificial mucosa. The authors conclude that a plate scaffold should be used	[15]
Amniotic membrane			
Human amniotic membrane	Primary rabbit oral epithelial cells	Cornea autologous transplantation in rabbits	[16]
Collagen			
Collagen type-I	Human oral immortalized keratinocytes and immortalized fibroblasts (3T3)	<i>In vitro</i> testing	[2]
	immortalized human oral keratinocytes and primary human oral fibroblasts	<i>In vitro</i> testing	[17]
Collagen-chitosan	Primary human oral keratinocytes	<i>In vitro</i> testing	[18]
Collagen-elastin	Primary human gingival keratinocytes and primary fibroblasts	Clinical application in periodontal therapy	[19]
	Primary human palatal mucosa keratinocytes and primary human fibroblasts	<i>In vitro</i> testing	[20]
Collagen-GAG-chitosan	Primary human palatal mucosa and primary human fibroblasts	<i>In vitro</i> testing	[20]
CollaCote®(Zimmer Dental)	Primary human oral epithelial cells and human gingival fibroblasts	<i>In vitro</i> testing	[21]
Fibrin			
Fibrin matrix	Primary human fibroblasts and keratinocytes from oral mucosa	Clinical application for ankyloglossia	[22,23]
	Primary human fibroblasts and keratinocytes from oral mucosa	Clinical application for hemifacialmicrosomia and ankyloglossia	[24]
Synthetic Scaffolds			
Poly (ethylene terephthalate)	Primary human palatal mucosa keratinocytes and primary human fibroblasts	<i>In vitro</i> Testing	[20]
Polycarbonate membrane			
Electro-spun poly L-lactic acid			
Electro-spun polystyrene			
Polylactic glycolic acid	Primary dog epidermal keratinocytes	Clinical application for mucosa prosthesis	[25]

Acknowledgement

This work was supported by the Ministerio de Educación Cultura y Deporte (contract to M.A.L.G; FPU15/03412), the Instituto de Salud Carlos III (contract to J.M.R; CP 16/00124.) and the Ministerio de Empleo y Seguridad Social with the Sistema de Garantía Juvenil (contract to M.M.B).

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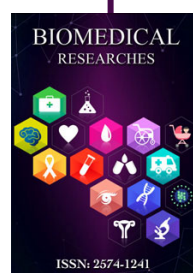
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