Medical Hypotheses 81 (2013) 883–886

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Physical forces make rete ridges in oral mucosa

Xuepeng Xiong [a,b,*], Tianfu Wu [a], Sangang He [b]

[a] Department of Oral Maxillofacial-Head Neck Oncology, School and Hospital of Stomatology, Wuhan University, Wuhan 430079, People's Republic of China
[b] The State Key Laboratory Breeding Base of Basic Science of Stomatology (Hubei-MOST) and Key Laboratory of Oral Biomedicine Ministry of Education, School and Hospital of Stomatology, Wuhan University, Wuhan 430079, People's Republic of China

ARTICLE INFO

Article history:
Received 5 March 2013
Accepted 3 July 2013

ABSTRACT

Rete ridge has important functions in the epidermis, but the current tissue engineered oral mucosa or skin equivalents are generally lack of this structure. To regenerate a rete ridge structure in the oral mucosa equivalents, we firstly attempted to make clear how rete ridge is formed in the oral mucosa and the preliminary study disclosed the mechanical stress evoked the morphogenesis of rete ridge. In this paper, we make a hypothesis that the morphogenesis of rete ridge is elicited by the physical forces and proceed with the internal pushing forces derived from the keratinocyte division, among these process, the activated ERK and PC cascades, accompanied with the MMPs liberated growth factors are working together to induce the keratinocyte proliferation, these cell divisions produced internal forces, which not only push the keratinocyte stem cells and progenitor cells to migrate in the contrary directions but also in turn to activate the ERK and PC cascades, meanwhile, the activated MMPs degrade the ECM of lamina propria, under these internal pushing forces and the remodeling of lamina propria, rete ridge is gradually formed. This hypothesis gives us the possibility to regenerate the rete ridge structure in the tissue engineered oral mucosa or skin equivalents through simulating the morphogenesis of rete ridge.

Introduction

Oral mucosa is a mucous membrane lines the oral cavity and consists of oral epithelium and lamina propria, by which the undulating basement membrane divided. Under health conditions, oral mucosa is in a constant state of resurfacing, with the basal epidermal stem cells asymmetric dividing to generate progenitor cells and the differentiated corneocytes shedding off through desquamation. Rete ridges are epithelial projections and furcations that penetrated into the dermis or lamina propria of the skin or oral mucosa, and play two main functions: (i) through enlarging the contacted area between the epithelium and the dermis or lamina propria, rete ridges enhance the adhesion between these two layers and help scatter external forces and masticatory stresses to which skin or oral mucosa is constantly exposed; (ii) to be physical protective niches where keratinocyte stem cells resided and these cells are usually provided at the bottom of rete ridges [1–3]; and some other uncategorized roles do not excluded.

Till now, Innovations in the field of oral mucosa and skin tissue engineering have generated the equivalents exhibited several resemblance to the native skin and oral mucosa tissues [4,5], among them, the structure of rete ridge has been partially replicated through microfabrication of an analog of basal lamina in a bioengineered skin equivalent [6,7] and on the empty hair follicles of an acellular porcine dermal matrix in our previous constructed oral mucosa equivalent [8], it is found the profiles of rete ridge had influenced the stratification and differentiation of the epithelium.

Recently, we preliminarily pointed out that the morphogenesis of rete ridge in oral mucosa is a consequence of physical forces, during this process, extracellular regulated protein kinase 1/2 (ERK1/2) was mechanically activated to promote the proliferation and migration of the keratinocytes [1]. This understanding further inspires us to explore the complexity of the morphogenesis of rete ridge in oral mucosa, for this knowledge will benefit our future researches on the tissue engineering of oral mucosa or skin. At here, we will make a thorough hypothesis about the morphogenesis of rete ridge in oral mucosa and how the signaling cascades regulate this process.

Mechanical stress and rete ridge

To know the morphological features of rete ridge from the different period, the palatal mucosa tissues of mice from the fetus to neonatal in different developmental stages were retrieved to study their histological characteristics. It is found that the palatal mucosa of mouse fetus in embryonic 14.5 days (E14.5D) only has

* Corresponding author. Address: 237# Luoyu road, Hongshan District, Wuhan City, Hubei Province, People's Republic of China. Tel.: +86 27 87686215; fax: +86 27 87873260.
E-mail address: xiongxuepeng@qq.com (X. Xiong).

0306-9877/$ - see front matter Crown Copyright © 2013 Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.mehy.2013.07.005

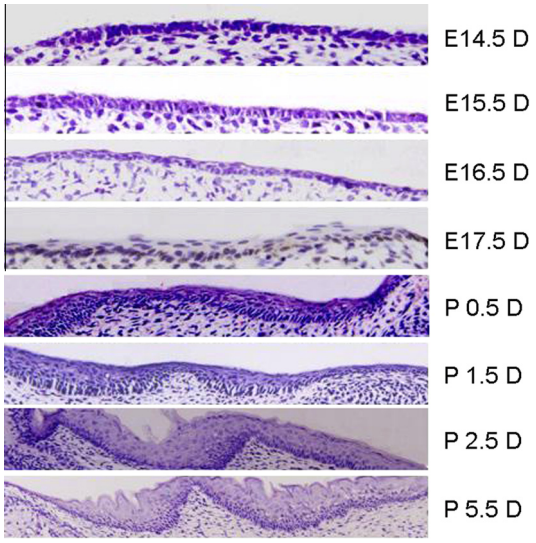

Fig. 1. Rete ridge profiles of mouse palatal mucosa of different stages of embrogenesis and postnatal period. (E = embrogenic period, P = postnatal period; D = day).

one single epithelial cell layer, and the connected area between the epithelium and the lamina propria is a straight line. As the fetus growing up and after birth, the epithelium of palatal mucosa gradually became multilayered and the structure of rete ridge emerged progressively (Fig. 1). It demonstrates that the rete ridge is not a connate topography, but develops accompanied with the general development.

The responses of cells to mechanical stresses account for the tissue morphogenesis [9]. Oral sucking, usually begins before birth, is the earliest external mechanical stimuli applied on the oral mucosa. Thereafter, oral mucosa is constantly exposed to various types of mechanical stimuli during chewing, speaking and sucking, and the masticatory mucosa, lines the jaws and does not have elasticity, usually bears more strength than the lining mucosa. From our previous study, the rete ridges of masticatory mucosa are longer than that of the lining mucosa [1] (Fig. 2). Thus, it is suggested that the length of rete ridge is positively correlated with the strength of mechanical stresses.

Mechanically activated signaling cascades and epithelium development

In the epidermis, epidermal stem cell, transient amplifying cells and keratinocytes constitute the epidermal proliferation unit (EPU), the cells migrate from the bottom to top of the epidermis and desquamate finally. Among EPUs, most of the epidermal stem cells reside in the bottom of rete ridges, and the transient amplifying cells, which proliferate with high frequency, are on the top of the epidermal stem cells and outnumber another two cell types. In the EPUs, the migration route of the keratinocyte is nearly perpendicular to the surface of epidermis [10].

Mechanical stimuli and the evoked signaling cascades play pivotal roles in the development of epithelial tissues [11]. Once the skin or mucosal tissues perceive the physical forces, several signaling cascades (ERK1/2, p38 and JNK) in the keratinocytes are activated, and then the mechanical stimuli are finally transformed into molecular signals to increase the proliferation of keratinocytes. Extracellular matrix metalloproteinases (MMPs) are also stimulated by the mechanical stimuli, the activated MMPs then liberate growth factors in the extracellular space for further inducing the proliferation of keratinocytes [12] and degrade the extracellular matrix for benefiting the migration of keratinocytes [13]. Except for sensing the external mechanical stresses, keratinocytes could also perceive the internal forces derived from cell division, this in turn further activates the signaling cascades to accelerate the proliferation of keratinocytes.

Protein C (PC) is an autocrine growth factor of keratinocytes and usually secreted during the proliferation period, it in turn activates the ERK1/2 and the downstream cascades for facilitating the proliferation and migration of keratinocytes [14,15].

In brief, it is possibly that external physical forces initiate or increase the proliferation of keratinocytes, and then the division of these keratinocytes produced the internal forces in turn inducing the proliferation of themselves, wherein several activated signal cascades take part in these processes.

Hypothesis

In considering to these aforementioned data, we firstly raised that the morphogenesis of rete ridge in oral mucosa is an outcome

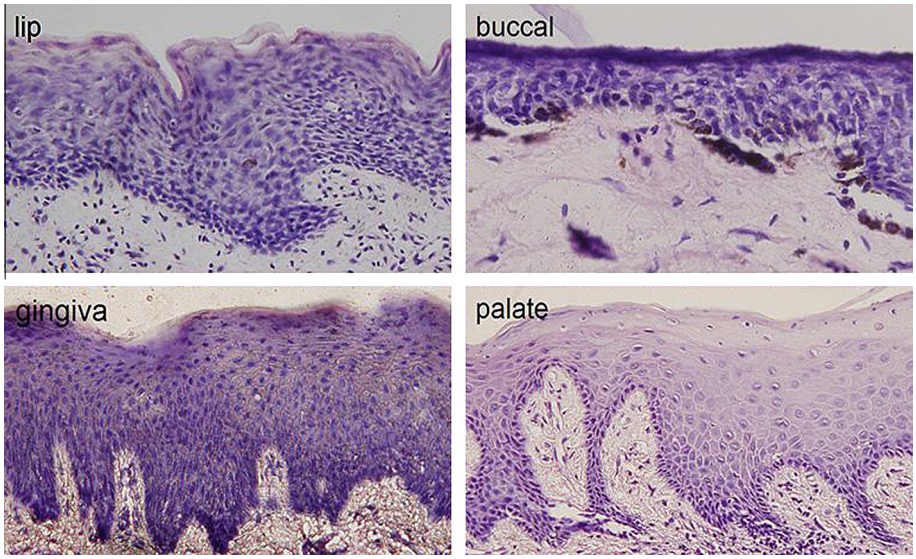

Fig. 2. Rete ridge profiles of human oral mucosa from different site, and generally, masticatory mucosa has longer rete ridge than lining mucosa.