Cytokine 62 (2013) 1–21

Contents lists available at SciVerse ScienceDirect

Cytokine

journal homepage: www.journals.elsevier.com/cytokine

Review Article

A review of the influence of growth factors and cytokines in in vitro human keratinocyte migration

Philip V. Peplow [a,*], Marissa P. Chatterjee [b]

[a] Department of Anatomy, University of Otago, New Zealand
[b] Department of Prosthetic Dentistry, BIOMAT Research Cluster, KU Leuven, Belgium

ARTICLE INFO

Article history:
Received 5 November 2012
Received in revised form 4 February 2013
Accepted 11 February 2013
Available online 11 March 2013

Keywords:
Growth factor
Cytokine
Keratinocyte
Cell migration
In vitro

ABSTRACT

Objective: Keratinocyte migration from the wound edge is a crucial step in the reepithelization of cutaneous wounds. Growth factors and cytokines, released from cells that invade the wound matrix, play an important role, and several in vitro assays have been performed to elucidate this. The purposes of this study were to review in vitro human studies on keratinocyte migration to identify those growth factors or cytokines that stimulate keratinocyte migration and whether these assays might serve as a screening procedure prior to testing combinations of growth factors or cytokines to promote wound closure in vivo.
Methods: Research papers investigating effect of growth factors and cytokines on human keratinocyte migration in vitro were retrieved from library sources, *PubMed* databases, reference lists of papers, and searches of relevant journals.
Results: Fourteen different growth factors and cytokines enhanced migration in scratch wound assay and HGF together with TGF-β, and IGF-1 with EGF, were more stimulatory than either growth factor alone. HGF with TGF-β1 had a greater chemokinetic effect than either growth factor alone in transmigration assay. TGF-β1, FGF-7, FGF-2 and AGF were chemotactic to keratinocytes. EGF, TGF-α, IL-1α, IGF and MGSA enhanced cell migration on ECM proteins.
Conclusion: Many growth factors and cytokines enhanced migration of keratinocytes in vitro, and certain combinations of growth factors were more stimulatory than either alone. These and other combinations that stimulate keratinocyte migration in vitro should be tested for effect on wound closure and repair in vivo. The scratch wound assay provides a useful, inexpensive and easy-to-perform screening method for testing individual or combinations of growth factors or cytokines, or growth factors combined with other modalities such as laser irradiation, prior to performing wound healing studies with laboratory animals.

© 2013 Elsevier Ltd. All rights reserved.

1. Introduction

In the repair of cutaneous wounds it is essential for the wound to be resurfaced as quickly as possible in order to regain structural and functional integrity and to serve as a protective barrier to prevent desiccation and invasion by pathogenic microorganisms. This is achieved by proliferation and directional migration of keratinocytes from the edges of the wound. For migration to occur there needs to be disruption of intercellular junctional complexes. The migration of keratinocytes occurs initially over a provisional matrix that forms within and fills the wound bed. Fibrin, fibronectin and vitronectin together with platelets are components of this matrix [1] and it provides a scaffold or mesh for neutrophil, macrophage, lymphocyte, endothelial cell, and fibroblast localization at the wound site. Fibrinogen and fibronectin when covalently linked by factor XIII of the blood coagulation system promote the adherence of fibroblasts to tissue culture dishes [2] and fibronectin coating of plates increases the adherence of endothelial cells [3,4]. As wound repair progresses, the provisional matrix becomes replaced by one consisting of collagen fibers synthesized by fibroblasts, and of proteoglycans such as hyaluronic acid, heparan sulfate, chondroitin sulfate, dermatan sulfate and which contribute to the extracellular matrix (ECM). The wound healing process is orchestrated by growth factors and cytokines released by a variety of cells that accumulate within the provisional matrix and ECM (e.g. platelets, neutrophils, fibroblasts, endothelial cells, macrophages, lymphocytes).

The ECM can directly bind to and release certain growth factors (e.g. heparan sulfate binding to fibroblast growth factor-2, FGF-2) which may serve to sequester and protect growth factors from degradation and/or enhance their activity. Indirect interactions include binding of cells to ECM via integrins, which enables cells to respond to growth factors (e.g. integrin binding is necessary for vascular endothelial growth factor (VEGF)-induced angiogenesis) and can induce growth factor expression (e.g. adherence of

* Corresponding author. Tel.: +64 3 479 7374; fax: +64 3 479 7254.
E-mail address: phil.peplow@stonebow.otago.ac.nz (P.V. Peplow).

1043-4666/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.cyto.2013.02.015

monocytes to ECM stimulates the synthesis of platelet-derived growth factor, PDGF) [5].

Tight junctions are considered to be crucial for the barrier function of the mammalian skin and have been shown to be present in the epidermis of wild-type mice [6], and immunofluorescence labeling and immunoelectron microscopy with antibodies to ZO-1 and occludin demonstrated the presence of tight junction antigens in adult and developing human epidermis [7]. Interkeratinocyte adherens junctions have also been shown in human epidermis [8]. Release from tight and adherens junctions causes the loss of epithelial cell polarity and enables migration of keratinocytes. Adult epidermal keratinocytes migrate by crawling, a process that requires protrusion of the plasma membrane at the front of the cell and contraction of the cell body at the rear [9]. Lamellipodia are sheet-like extensions of cytoplasm that form transient adhesions with the cell substrate, enabling the cell to move along the substrate. Formation of lamellipodia requires ruffling along the plasma membrane and reorganization of the actin cytoskeleton [10,11]. Various growth factors can influence keratinocyte shape differently. For example, insulin-like growth factor-1 (IGF-1) stimulates membrane protrusion and facilitates cell spreading, while epidermal growth factor (EGF) induces contraction of keratinocytes [12]. The effects of each growth factor on keratinocyte shape are mediated by distinct signal transduction pathways.

Growth factors and cytokines play an important role in the wound healing process. They induce proliferation and migration of cells within the wound environment, and also regulate the ECM by stimulating the synthesis of collagen and fibronectin in a variety of cell lines [13] as well as many other ECM components [14]. Keratinocyte proliferation and migration are essential for the formation of skin appendages and epidermal repair after wounding, and many growth factors investigated so far have been shown to stimulate these functions [15]. The question arises as to whether there are specific contributions of individual growth factors and cytokines to particular keratinocyte functions. This review has searched published in vitro human studies and analyzed and compared various growth factors and cytokines for their potential to regulate the shape and spreading of individual keratinocytes, stimulate migration in scratch wound assay and in Boyden and transwell chambers, and to influence migration with specific ECM proteoglycans as substrate.

2. Materials and methods

2.1. Literature review

A systematic review of the relevant literature was performed. Original research papers investigating the effects of growth factors and cytokines on the shape, spreading and migration of human keratinocytes in vitro, and published up to December 2011 were retrieved and used for this review. Relevant papers were sought and obtained from library sources and the online database *PubMed* using *EndNote* X1 (Thomson Reuters, Carlsbad, USA) or the web database accessed at www. pubmed.com. Search terms were ‘‘keratinocyte’’, ‘‘growth factor’’, ‘‘cytokine’’, ‘‘chemokine’’, ‘‘effect of growth factor’’, ‘‘effect of cytokine’’, ‘‘effect of chemokine’’, ‘‘scratch wound’’, ‘‘migration’’, and ‘‘in vitro’’. Additional secondary sources of information included reference lists from retrieved papers, and pertinent papers identified by hand searches of relevant journals not found from the databases.

2.2. Inclusion/exclusion criteria

We included studies that met the following c riteria: (i) growth factor or cytokine was investigated as the primary intervention (independent variable); (ii) the growth factor or cytokine together with dose and exposure time were defined; (iii) at least one outcome or index of cellular expression of shape or migration was identified; (iv) studies were performed with human keratinocyte cells or cell lines in vitro; (v) studies were related to epidermal regeneration and wound repair.

Studies excluded from this study were: (i) in vitro studies involving keratinocytes from animals other than humans; (ii) in vivo studies involving human patients or whole animals, not isolated keratinocyte cells or cell lines; (iii) studies performed with cells other than keratinocytes; (iv) reviews and meta-analyses; (v) studies for which only an abstract was available; (vi) studies reported in languages for which no English language translation was available; (vii) in vitro studies which did not examine the effect of growth factors or cytokines on keratinocyte migration.

2.3. Retrieved articles

The process followed for retrieving articles from the literature search is summarized in Fig. 1.

2.4. Items for data extraction

Literature searches were carried out by both authors and the findings were combined. Articles for inclusion and exclusion were identified independently, and confirmed, thereby minimizing bias.

For included articles, the following data were extracted and tabulated: *research method*: (in vitro studies – controls, minimizing variability in experimental conditions); *cell type:* (human keratinocyte cells; donor tissue source or established cell lines); *description of cells:* (normal cells, cell lines, number of replicates); *growth factor or cytokine exposure parameters; experimental outcomes:* (cell shape, cell spreading, migration); *study conclusion*: (results of exposure of keratinocytes to growth factor or cytokine).

Studies were then critically reviewed in terms of methodology, appropriateness of growth factor and cytokine parameters, and contributions of individual growth factors and cytokines to particular keratinocyte functions.

3. Results

Results from the literature search are summarized in Fig. 1. In total, 24 publications were included in this review [12,16–38] and are summarized in Tables 1–6. Several of the publications had performed more than one type of study (e.g. scratch wound assay and transmigration assay using chambers).

3.1. Migration of keratinocytes in scratch wound assay or similar procedure (Tables 1 and 2)

There were 11 studies in which the cell monolayer was wounded with a pipette tip or spatula, two studies where half of the monolayer was removed with a razor blade, and one study where cell monolayer was denuded by a rubber policeman. Seven of the studies had used HaCaT cell line, one with NHEK cell line, and six using keratinocytes grown from donor tissue. All of the studies had used cells cultured to complete or almost complete confluence, and in five of the studies the cells were incubated with mitomycin C to arrest proliferation prior to wounding. The cells were starved prior to scratch wounding or removing part of the monolayer, and the extent of migration of cells into the scratch wound area or the area cleared of cells determined at times that varied from 4 to 72 h (mean 31 h). With prior starvation and without mitomycin treatment or added growth factor or cytokine, keratinocyte migration achieved only a very small extent of wound

Download English Version:

https://daneshyari.com/en/article/5897864

Download Persian Version:

https://daneshyari.com/article/5897864

Daneshyari.com