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Mammalian cell models to advance our understanding of wound healing: a review

Jerneja Vidmar, MSc, MD,[a,b,c] *Constance Chingwaru, BSc,*[d] *and Walter Chingwaru, PhD*[b,c,d,*]

[a] *Department of Plastic and Reconstructive Surgery, University Medical Centre Maribor Maribor, Slovenia*
[b] *Institute Ceres/Zavod Ceres Celje, Slovenia*
[c] *Maribor Institute of Biomedical Sciences, Maribor, Slovenia*
[d] *Department of Biological Sciences, Faculty of Science, Bindura University Science Education, Bindura, Zimbabwe*

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ABSTRACT

Rapid and efficient healing of damaged tissue is critical for the restoration of tissue function and avoidance of tissue defects. Many *in vitro* cell models have been described for wound healing studies; however, the mechanisms that underlie the process, especially in chronic or complicated wounds, are not fully understood. The identification of cell culture systems that closely simulate the physiology of damaged tissue *in vivo* is necessary. We describe the cell culture models that have enhanced our understanding, this far, of the wound healing process or have been used in drug discovery. Cell cultures derived from the epithelium, including corneal, renal, intestinal (IEC-8 cells and IEC-6), skin epithelial cells (keratinocytes, fibroblasts, and multipotent mesenchymal stem cells), and the endothelium (human umbilical vein endothelial cells, primary mouse endothelial cells, endodermal stem cells, human mesenchymal stem cells, and corneal endothelial cells) have played a pivotal role toward our understanding of the mechanisms of wound healing. More studies are necessary to develop co-culture cell models which closely simulate the environment of a wound *in vivo*. Cell culture models are invaluable tools to promote our understanding of the mechanisms that regulate the wound healing process and provide a platform for drug discovery.

Introduction

Wound healing is a dynamic process that involves coordinated action of both resident and migratory cell populations within the extracellular matrix (ECM) and the accompanying cytokines.[1] Wound healing is achieved through four stages, namely hemostasis, inflammation, proliferation, and remodeling (Fig. 1).[3] Chronic injury, however, often triggers maladaptive wound healing responses that culminate into tissue fibrosis and organ malfunction.[4] To facilitate normal wound healing, the use of appropriate wound therapy and wound care interventions (bandages and negative pressure wound therapy) is necessary.[5] Cytokines, growth factors, and chemokines play an important role in the wound healing process.[6] Inflammation is known to initiate the healing process, as such its regulation forms an integral part of the wound management process.[7] Inflammation involves the activation of platelets and the recruitment of neutrophils, macrophages (Mf), and fibroblasts to the wound site.[8] Although the phases of normal wound healing are well defined, the pathogenesis of

* *Corresponding author*. Department of Biological Sciences, Faculty of Science, Bindura University Science Education, P. Bag 1020, Bindura, Zimbabwe. Tel.: +263 7777 66606.
E-mail address: wchingwaru@yahoo.co.uk (W. Chingwaru).
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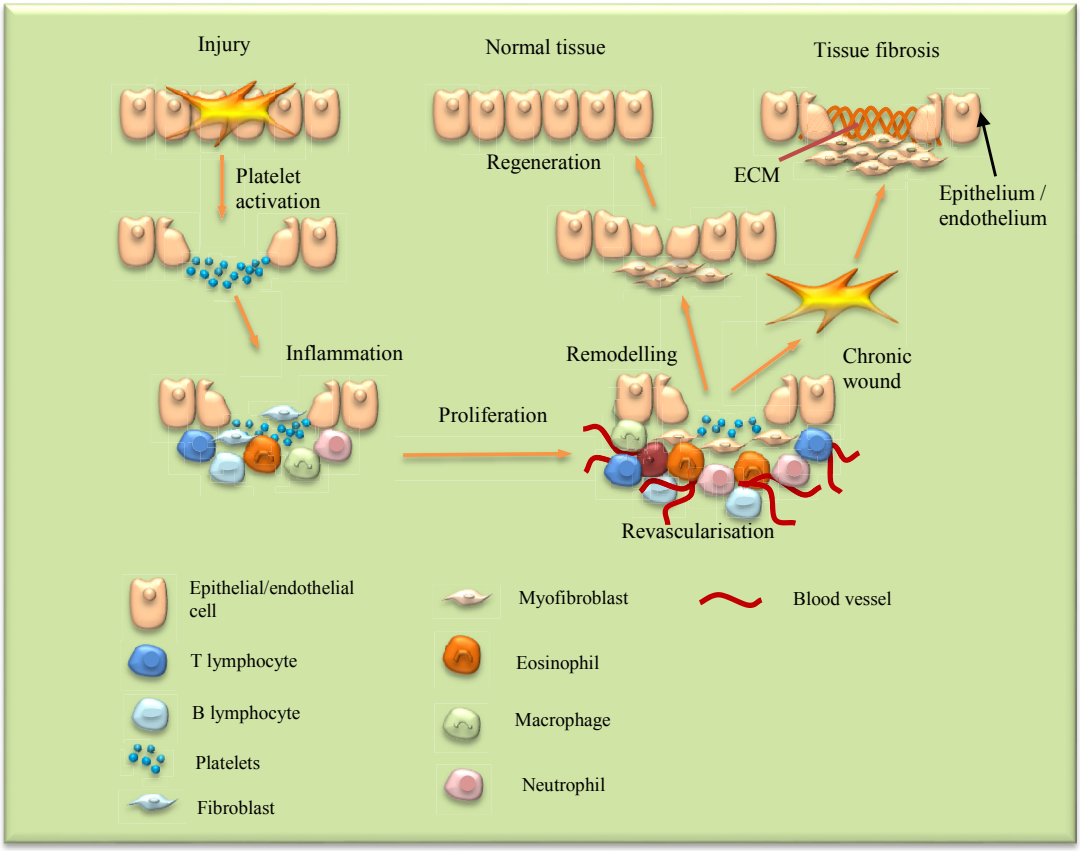

Fig. 1 – A general model of wound repair. Adapted from Forbes and Rosenthal (2014).[2] (Color version of figure is available online.)

chronic wounds, particularly those linked to diabetes, remains largely undefined.[9] In addition, the mechanisms that underlie the healing of delicate tissues organs, especially the central nervous system, are far from being understood. Impaired reepithelialization underlies the progress of chronic wounds.[10] Cell cultures have become gold standard for preclinical studies which have led to important findings in drug discovery[11] and mechanistic and toxicity studies.[12,13] Despite the advances enjoyed in other sectors of science, our understanding of wound repair mechanisms has remained poor because of lack of robust cell culture models for wound healing. A number of cell culture models with potential for use in studies of and interventions for wound healing have been described. This treatise summarizes the spectrum of cell culture models and assesses the potential of such cultures for wound healing studies.

Injury can occur in any tissue of the body, including damage to the epidermal, endodermal, glial, connective, and bone tissues. The ideal models for wound healing should include all the cell types and molecules that take part in the process. For example, the healing of a damaged epidermis requires the participation of epithelial cells including keratinocytes and fibroblasts, and the recruitment of myofibroblasts and blood cells, namely platelets, macrophages, eosinophils, T lymphocytes and B lymphocytes. A model of wound repair demonstrating the participation of different cells in the process is shown in Figure 1. Given the complexity of the wound healing process, the availability of co-culture models that include combinations of all the cells that take part in the process would be ideal. However, the setup of such co-culture systems is not without challenges because the different cell species may not be grown to equal extents under cell culture conditions. Co-culture setups that involve the growth to confluence of different cell types separately and allowing the cells to communicate through pores in a membrane dividing the cells ideally provide us with relevant information on the wound healing process than we would get with monoculture models. However, monoculture models provide initial information that allows us to understand the wound healing process. Furthermore, a number of cell cultures are available as therapies to promote the healing process. This article summarizes the developments in the area of cell cultures, including mono- and co-culture cell models that have promoted our understanding wound healing or are available as therapies to promote the wound healing.

The blood vessel: a highway facilitating wound healing

The wound healing process, being complex, often is initiated after the recruitment of specialist blood cells, including platelets, Mf, and eosinophils, to the wound site (Figs. 2 and 3). A number of molecules such as cytokines and growth factors