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Review

Vitamin D and calcium regulation of epidermal wound healing

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ABSTRACT

Wound healing is essential for survival. This is a multistep process involving a number of different cell types. In the skin wounding triggers an acute inflammatory response, with the innate immune system contributing both to protection against invasive organisms and to triggering the invasion of inflammatory cells into the wounded area. These cells release a variety of cytokines and growth factors that stimulate the proliferation and migration of dermal and epidermal cells to close the wound. In particular, wounding activates stem cells in the interfollicular epidermis (IFE) and hair follicles (HF) to proliferate and send their progeny to re-epithelialize the wound. β-catenin and calcium signaling are important for this activation process. Mice lacking the VDR when placed on a low calcium diet have delayed wound healing. This is associated with reduced β-catenin transcriptional activity and proliferation in the cells at the leading edge of wound closure. These data suggest that vitamin D and calcium signaling are necessary components of the epidermal response to wounding, likely by regulating stem cell activation through increased β-catenin transcriptional activity.

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Contents

1. Introduction

Chronic skin wounds are estimated to affect 6.5 million patients in the US at a cost of over $25 billion [1]. Moreover, skin wound repair leads to the additional burden of scarring, a $12 billion annual market [1]. This does not take into account the psychologic damage caused by disfiguring lesions that such skin wounds can cause.

Wound healing is a multistep process involving a number of cell types and processes [2,3]. The initial stages involve blood clotting and an inflammatory response. The innate immune system plays an important role in initiating the inflammatory response. Cells null for VDR or CYP27B1 (the enzyme producing $1,25(OH)_2D_3$) cannot mount this innate immune response [4], and we have

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recently shown that cells null for the calcium sensing receptor (CaSR) are likewise deficient [5]. Wounding also leads to the activation of a number of signaling pathways (review in [6]). In particular, developmental pathways including wnt/β-catenin, TGFβ1, notch, and sonic hedgehog have all been implicated in the repair of skin wounds.

Following the initial inflammatory reaction, and in response to the cytokines and growth factors expressed following wounding, the epidermal and dermal cells proliferate and migrate to fill the wound with matrix enabling the keratinocytes to re-epithelialize and subsequently reform the epidermal barrier. Stem cells in the bulge region and infundibulum of the hair follicle (HF) and in the interfollicular epidermis (IFE) play critical roles in this process. Under normal circumstances the stem cells in the IFE maintain the epidermis, the stem cells in the infundibulum maintain the infundibulum and sebaceous gland, and the stem cells in the bulge and secondary hair germ maintain the cycling portion of the hair follicle [7,8]. However, when the skin is wounded the progeny of stem cells from all regions of the HF and IFE contribute at least initially [9,10], although to variable extent. Ito et al. [11] labeled the stem cells in the bulge of the adult mouse using an inducible K15-crePR/R26R transgenic and found that after wounding approximately 25% of the cells in the newly formed epidermis originated from the bulge. However, these cells did not persist. Levy et al. [12] labeled the stem cells throughout the follicle including the infundibulum with a Shh cre/R26R transgenic and confirmed that cells from other regions of the follicle also contributed to re-epithelialization after wounding, and noted that these cells persisted in the regenerated epidermis. However, stem cells in the IFE make the greatest and most lasting contribution [10]. Moreover, the stem cells from the HF are not absolutely required for re-epithelialization. Langton et al. [13] evaluated wound healing in a mouse model lacking HF, and observed that although healing was delayed, re-epithelialization did eventually occur.

Alopecia is a well described characteristic of mice and humans lacking VDR [14–16] due to failure to regenerate the cycling lower portion of the hair follicle after the initial developmental cycle is completed [5]. Cianferotti et al. [17] attributed this to a gradual loss of the proliferative potential in the bulge stem cells, which they attribute in part to the loss of VDR. However, this conclusion has been challenged by Palmer et al. [18], who attributed the failure of HF cycling in the VDR null mouse in part to a failure of the bulge stem cells' progeny to migrate out of the bulge rather than their loss of proliferative potential suggesting a loss of activation.

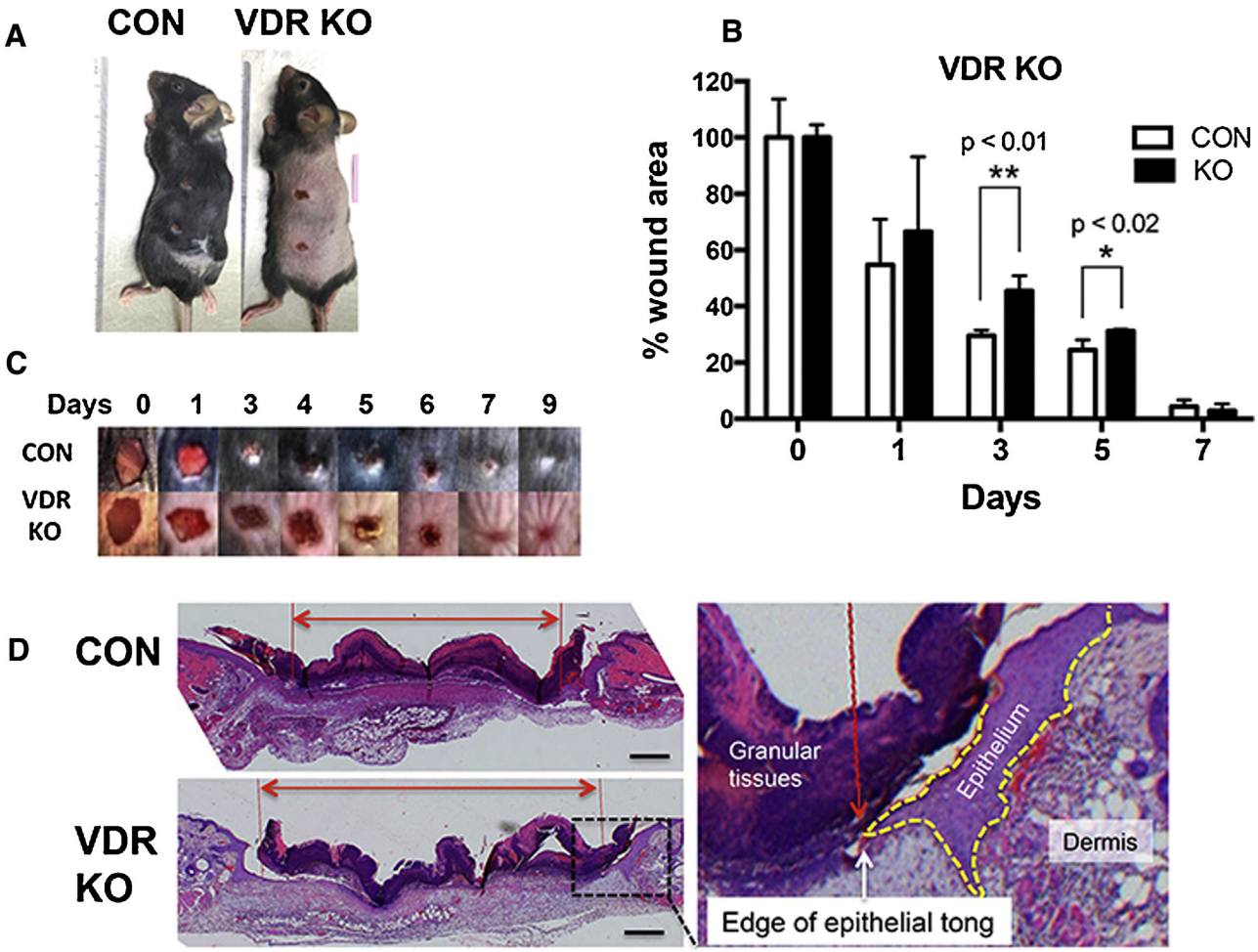

Fig. 1. The impact of keratinocyte specific deletion of VDR on wound healing.
(A) 3 months old ^{epi}VDRKO mice and their control littermates (CON) underwent 6 mm full thickness skin biopsies. (B) The wound area was calculated by measurement of wound size each day, and shown as percent of 0 time control. The bars enclose mean +/− SD, $^{*}p < 0.05$ ($n = 7–8$). (C) Photographs were taken of the wounds daily through 9 days. Representative photographs from KO and control mice are shown. (D) 3 mm wounds excised at day 3 were examined histologically to evaluate re-epithelization. The representative H&E stained sections across the anterior/posterior diameter of the wounds are shown. The yellow dotted line outlines the epidermal tongue. The red lines show the edges of the epidermal tongues crossing the wound, and the red double headed arrow shows the distance to be traveled to close the wound. Percentage re-epithelialization was defined as the distance traveled by both epithelial tongues divided by the distance needed to travel to fully re-epithelialize the wound. Bar = 400 μm. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).