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The β2-Adrenergic Receptor Is a Global Regulator of Wound Healing *In Vivo*

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1 Introduction

Wound healing is a complex process, requiring the coordinated, temporal orchestration of numerous processes, including galvanotaxis, to repair damaged tissue. Over the past five years, we have established a role for the β2 adrenergic receptor (β2-AR) in regulating skin wound healing by investigating the effect of β2-AR activation and blockade on the cellular processes of both human keratinocytes (K) and dermal fibroblasts (DF) in vitro and on wound healing in ex-vivo human skin models (1-6). Our prior research suggests that an endogenous catecholamine/ β2-AR network might regulate wound healing in vivo. In this study, we established colonies of FVB β2-AR +/+ (wild-type, WT) and FVB β2-AR -/- (knock-out, KO) mice to investigate the role of the β2-AR in murine wound healing in vivo.

2 Materials and Methods

Murine K and DF were isolated from both WT and KO neonates and the effect of β2-AR ligands on murine cell migration, ERK phosphorylation and galvanotaxis was studied as previously described (1-6). Two 6mm full-thickness wounds were created on the shaved backs of WT and KO mice, treated daily, topically, with gel alone or gel containing 0.1% β2-AR agonist or antagonist (n = 5). Wounds were photographed daily then excised after either 3 or 5 days, fixed, embedded and sectioned for both hematoxylin/eosin and smooth muscle α-actin (SMαA) immunostaining.

3 Results

β2-AR activation decreased both ERK phosphorylation and the migratory capacity of WT murine K, while blinding them to an applied electric field (EF). β2-AR blockade increased ERK phosphorylation, migration rate and galvanotaxis in WT murine K. KO murine K did not respond to β2-AR ligands but migrated faster and more directionally in an EF than their WT counterparts. In contrast, both β2-AR activation and blockade increased ERK phosphorylation and speed of migration in WT murine DF, while KO murine DF did not respond to β2-AR ligands but migrated faster than WT. Finally, we detected catecholamine synthesis enzymes and measured epinephrine in both WT and KO K extracts.

β2-AR agonist treatment delayed while β2-AR antagonist treatment or loss of the β2-AR accelerated wound closure. β2-AR activation decreased wound re-epithelialization by 15% while blockade or loss of receptor increased re-epithelialization by 30% in wounds excised 5 days post wounding. Wound contraction correlates with the appearance of SmαA expressing myofibroblasts in the granulation tissue. WT mice exhibited dense staining for SmαA within the dermis below the hyperproliferative epithelial wound margin. SMαA staining was markedly reduced in ß-AR agonist-treated WT wounds (by 62%) and markedly increased in β2-AR antagonist-treated WT wounds (2.2 fold) and KO wounds (27%).

4 Conclusion

In summary, we have demonstrated that β2-AR agonist treatment significantly delays, while β2-AR antagonist treatment significantly augments wound healing in vivo by modulating both re-epithelialization (K) and wound contraction (DF). Additionally, the fact that wound healing is

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accelerated in β2-AR KO mice provides convincing evidence that the β2-AR/catecholamine network regulates the rate of wound healing. Our work demonstrates that β2-AR blockade could be a potential therapy for promoting healing in chronic wounds.

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References

1. Pullar, C. E., Chen, J., and Isseroff, R. R. (2003) *J . Biol. Chem.* **278**, 22555-22562.
2. Pullar, C. E., Grahn, J. C., Liu, W., and Isseroff, R. R. (2006) *FASEB J.* **20**, 76-86.
3. Pullar, C. E., and Isseroff, R. R. (2005) *J. Cell. Sci.* **118**, 2023-2034.
4. Pullar, C. E., and Isseroff, R. R. (2005) *Wound. Repair. Regen*. **13**, 405-411.
5. Pullar, C. E., and Isseroff, R. R. (2006) *J. Cell. Sci.* **119**, 592-602.
6. Pullar, C. E., Rizzo, A., and Isseroff, R. R. (2006) *J. Biol. Chem*. **281**, 21225-21235.