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pGlcNAc nanofibers derived from a marine polymer stimulate regenerative wound repair via activation of a TLR4/type-I IFN pathway in combination with an integrin/Akt1 dependent pathway

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The structural balance between elastin, collagen and other extracellular matrix components is absent in adult wound repair resulting in misaligned and excessive collagen deposition that contributes to scar formation. Our findings show that a marine derived pGlcNAc nanofiber stimulates tensile strength and elasticity of wounded skin so that it is equal to that of uninjured skin. Nanofibers promote cellular alignment, secretion of aligned collagen fibers and increased tropoelastin expression. Nanofiber-dependent reductions in scar formation are, in part, due to activation of an integrin/Akt1-dependent pathway. In addition to the activation of Akt1, our deep sequencing results suggest a role for a TLR4/type-I interferon (IFNαβ) pathway in the nanofiber-driven anti-fibrotic phenotype. Here we show that pGlcNAc nanofibers specifically stimulate type-I IFN (IFNαβ) expression via activation of Toll-like receptor 4 (TLR4), in the absence of TLR4-induced NFκB-dependent inflammatory responses in normal human fibroblasts and endothelial cells. TLR4 null animals fail to respond to nanofiber treatment, which can be rescued by addition of IFNα2A to the wound bed. Indeed, inhibition of type-I IFN activity using a blocking antibody against the type-I IFN receptor inhibits nanofiber induced tissue repair. Our findings support a model where nanofiber stimulation of TLR4 preferentially favors the IFNαβ response over an inflammatory response mediated through MyD88. As inflammatory responses lead to increased TGF-β production, increases in myofibroblast production and fibrotic, disorganized collagen deposition. Our findings suggest that reductions in inflammatory cell recruitment or activation results in reduced scar formation and increased tensile strength and elasticity of healed wounds. The marked difference in collagen deposition and increased elastogenesis in nanofiber treated wounds suggests that the nanofibers are specifically stimulating a more regenerative type of tissue repair.

Biography

Robin C Muise-Helmericks is currently an Associate Professor in the Department of Regenerative Medicine and Cell Biology, Member of the Hollings Cancer Center and Adjunct Associate Professor in the Departments of Oral Health at the Medical University of South Carolina.

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