Ryan Moseley

Cardiff University, UK

Development of epoxy-tigliane pharmaceuticals as novel therapeutics for dermal fibrosis

Excessive dermal scarring/fibrosis poses major challenges to Healthcare Services worldwide, confounded by existing therapies being unsatisfactory at treating fibrosis. Therefore, there is significant need for novel anti-fibrotic therapies with improved efficacy. We are evaluating the novel healing properties of epoxy-tiglianes (EBC-46, EBC-211), isolated from the Fontain's Blushwood Tree indigenous to Queensland's tropical rainforest. EBC-46 possesses potent anti-cancer properties and stimulates exceptional healing following tumour destruction, manifested as accelerated wound re-epithelialisation, closure and minimal scarring. To elucidate their anti-scarring properties, we assessed epoxy-tigliane effects on fibroblast proliferation, migration; and transforming growth factor-β1 (TGF-β1)-driven myofibroblast differentiation/behaviour. Dermal fibroblasts were treated with EBC-46 or EBC-211 (0-10μg/ml). Cell cycle progression/proliferation were assessed by Flow Cytometry and MTT assay. Migration was assessed using in vitro scratch wounds/Time-Lapse Microscopy. TGF-β1-driven, fibroblast-myofibroblast differentiation was examined by immuno-cytochemical/QRT-PCR detection of α-smooth muscle actin (α-SMA) expression/stress fibre formation. Epoxy-tigliane-induced gene expression changes were quantified by Microarrays, confirmed by protein level analyses. Both epoxy-tiglianes significantly retarded fibroblast proliferation, although neither affected migration. Although α-SMA expression/stress fibre organization and myofibroblast formation were unaffected at 0.001-0.01μg/ml or 1-10μg/ml EBC-46, EBC-46 significantly inhibited α-SMA expression/stress fibre formation at 0.1μg/ml, with cells retaining normal fibroblast morphologies. EBC-211 induced similar effects at 10μg/ml. Epoxy-tiglianes up-regulated proteinase, anti-fibrotic matrix component and TGF-β1 inhibitor genes; and down-regulated proteinase inhibitors, pro-fibrotic matrix component and TGF-β1 signalling genes. Epoxy-tiglianes also increased high molecular weight hyaluronan synthesis. Therefore, epoxy-tiglianes modulate fibroblast proliferation, differentiation and matrix composition/turnover, inducing scar resolution. Findings support epoxy-tigliane development as novel anti-fibrotic therapeutics against dermal scarring/fibrosis.

Biography

Ryan Moseley graduated from Swansea University with a BSc (Honours) Degree in Biochemistry. Later, he obtained his PhD from the School of Dentistry, University of Wales College of Medicine, examining the role of oxidative stress in periodontal disease. He continues his research at Cardiff University, where he is currently a Reader in Tissue Repair and Director of the CITER MSc Programme in Tissue Engineering. He research focuses on the mechanisms underlying dermal and oral wound healing during health and disease; and the development of stem cell, biomaterial and pharmaceutical based strategies to address impaired healing in these tissues. He has been supported by funding bodies worldwide, including the MRC, NHMRC and Wellcome Trust, culminating in numerous published papers, filed patents with industrial partners in the dermal wound healing sector (Convatec, Systagenix Wound Management, Peplin/LEO Pharma, QBiotics); and many conference prizes.

MoseleyR@cardiff.ac.uk

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