SHIFTS TOWARD AEROBIC GLYCOLYSIS PRODUCE PHYSIOLOGICAL RESPONSES TO INJURY RESULTING IN DIVERSE WOUND REPAIR

Faruk, Fayiz [1], Walker D Short[2], Benjamin W Padon[2], Tanuj J Prajaparti[2], Sonya Keswani[2], Aditya Kaul[2], Hui Li[2], Ling Yu[2], Sundeep G Keswani[2], Cristian Coarfa[1], Swathi Balaji[2]

[1] Baylor College of Medicine, Department of Surgery, Pediatric General Surgery

[2] Texas Children's Hospital, Surgery, Pediatric General Surgery

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Background: Identical dermal injuries can heal with varying degrees of fibrosis in different patients. Wound repair is an energy-intensive process that is fueled by oxidative phosphorylation(OXPHOS) and glycolysis. As proliferation of fibroblasts to rebuild the dermis relies on increased lactate production, a prelude to aerobic glycolysis, we hypothesize differences in fibroblast bioenergetic metabolism underlie differential scarring in patients.

Materials/Methods: We created a biorepository of fibroblasts from abdominoplasty samples derived from patients with low scar(LS)/ high scar(HS) phenotypes. Expression of Pyruvate Kinase M2(PKM2) and lactate dehydrogenase(LDHA) were measured in patient skin(IHC). OXPHOS(OCR), glycolysis(ECAR), and ATP at resting, under stress, and TGFb treatment were analyzed in fibroblasts(seahorse assays), along with expression of PKM2 and LDHA(Protein simpleWES). LS/HS human fibroblasts(106 cells/wound) were transferred to 6mm full-thickness stented wounds on SCID mice(8-10wk; F). Wounds were harvested at d7/d28, wound closure(H/E), aSMA, PKM2 and LDHA(staining), inflammatory profile(Luminex;IHC), collagen expression(trichrome) were analyzed.n=3 biologic replicates/group, p-values by ANOVA.

Results: Expression of PKM2/LDHA was markedly higher in normal skin/scar tissue from HS. In vitro, RNA sequencing revealed altered metabolic pathways in HS vs. LS normal skin fibroblasts. HS fibroblasts had higher basal OCR/ECAR than LS($p<0.01$), suggesting more bioenergetic metabolism in HS. HS fibroblasts responded to stress(FCCP/Oligomycin treatments) with a significant increase in SRC and GRC than LS($p<0.01$), along with an increase in phospoPKM2($p<0.05$). In vivo, murine wounds with HS fibroblasts showed expedited wound closure at d7 with reduced IL-10, IL-17, MIP-1a/b, and G-CSF expression via immunoplexing and increase in aSMA(25-fold) gene expression and staining. At d28, there was marked increase in PKM2+ and LDHA+ spindle-shaped cells in wounds with HS, along with pronounced collagen staining and thick epidermis.

Conclusions: Fibroblasts of different scarring phenotypes display characteristic bioenergetic metabolism profiles and produce distinct scarring in murine wounds. Our data suggests that a shift to aerobic glycolysis(Warburg effect) is associated with increased fibrosis(high scar).

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