Bioactive Glass and Deferoxamine Synergistically Promote Angiogenesis and Myogenesis in vitro: Implications for Skeletal Muscle Regeneration

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INTRODUCTION: Successful skeletal muscle regeneration depends on coordinated angiogenesis and myogenesis. Bioactive glass (BG) releases ionic products that modulate inflammation, while deferoxamine (DFO), a hypoxia-inducible factor-1α (HIF-1α) stabilizer, enhances angiogenic signaling. This study investigated the combined effects of BG and DFO on murine endothelial (SVEC) and myoblast (C2C12) cells to establish an in vitro foundation for future translational applications.

METHODS: SVEC and C2C12 cells were cultured with BG extracts (10 mg/mL), DFO (1, 5, 10, 20, 50, and 100 μg/ml), or their combination (BG+DFO). In SVEC cells, cell viability and angiogenic activity was assessed by CCK-8 assay, tube formation assay, and scratch assay. In C2C12 cells, cell viability (CCK-8 assay, 24 h) and myogenic differentiation (MHC immunofluorescence, fusion index after 7 days, and qPCR) were evaluated. Data were analyzed using one-way ANOVA with Tukey's post hoc test.

RESULTS SECTION: SVEC cells were sensitive to DFO, with viability significantly reduced at 5 μg/mL. However, when co-treated with BG and DFO, BG markedly improved SVEC viability. DFO alone enhanced SVEC migration, and the BG+DFO group showed a similar effect, indicating that BG did not impair the pro-migratory activity of DFO. In tube formation assay, DFO significantly promoted capillary-like structure formation, whereas BG alone showed no effect. Importantly, BG did not interfere with DFO function, as the BG+DFO group also displayed enhanced tube formation (Figure 1). In C2C12 cells, viability decreased significantly when DFO concentration reached 50 μg/mL, whereas BG extract solutions increased cell viability. BG treatment significantly promoted C2C12 differentiation, yielding more mature myotubes and a higher maturation index compared with control. The BG+DFO combination further enhanced myotube formation and differentiation capacity (Figure 2).

DISCUSSION: The present study demonstrates that BG and DFO exert complementary effects on endothelial and myoblast function in vitro. Consistent with our hypothesis, DFO strongly promoted angiogenic behaviors of SVEC cells, including migration and tube formation, while BG provided a protective role by rescuing SVEC viability that was otherwise impaired by DFO, indicating a synergistic interaction. In C2C12 myoblasts, BG significantly enhanced cell viability and promoted differentiation into mature myotubes, while the combined BG+DFO treatment further improved myogenic maturation, suggesting that the dual therapy supports both angiogenesis and myogenesis. A limitation of this study is that all data were obtained in vitro, using immortalized cell lines, which may not fully recapitulate the complex in vivo environment of skeletal muscle regeneration. Additionally, the potential dose-dependent cytotoxicity of DFO highlights the importance of optimizing delivery strategies for future applications. In conclusion, our findings support the synergistic potential of BG and DFO in promoting angiogenesis and myogenesis, providing an early proof-of-concept for a dual-therapy regenerative approach. Future studies will validate these effects in animal models of muscle injury to further establish translational relevance.

SIGNIFICANCE/CLINICAL RELEVANCE: (1-2 sentences): The synergistic activity of BG and DFO addresses a critical unmet need in regenerative medicine by targeting both angiogenesis and myogenesis, two processes essential for functional muscle recovery. Clinically, this strategy could advance therapeutic options for patients with severe muscle injuries, where current treatments often result in incomplete repair and functional deficits.

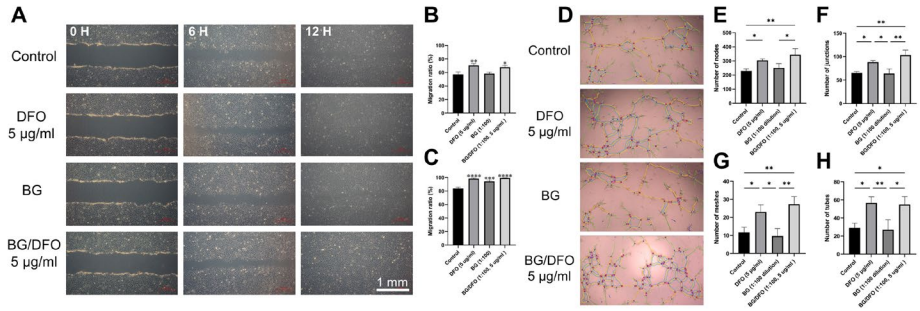

Figure 1. Effects of DFO and BG on the migration and tube formation of SVEC. (A) The scratch assay of SVEC. (B and C) The quantification of SVEC migration after 6h and 12h, respectively. (D) The tube formation assay of SVEC. (E-H) Quantitative evaluation of tube formation (nodes, junctions, meshes, and tubes) after different treatments.

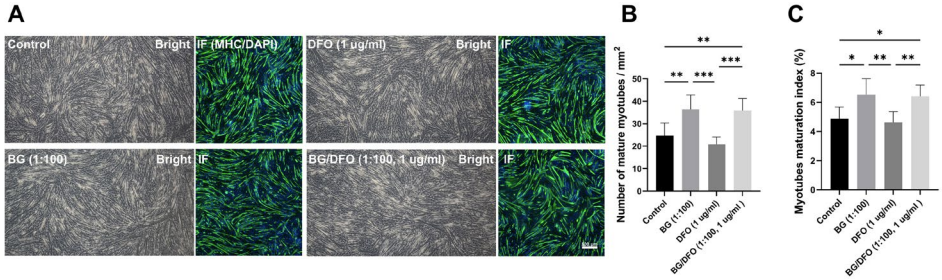

Figure 2. Effects of DFO and BG on the differentiaiton of C2C12. (A) The morphology of C2C12 after 7 days differentiation and MHC IF staining. (B) Quantitative evaluation of mature myotube formation. (C) The myotube maturation index.