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Title: IN VITRO MODEL OF VALVULAR FIBROSIS: VALVE INTERSTITIAL CELLS OF ORYCTOLAGUS CUNICULUS INDUCED BY TRANSFORMING GROWTH FACTOR- β1, INTERLEUKIN-1β, INTERLEUKIN-6, AND TUMOR NECROSIS FACTOR-α

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Background & Aims: Fibrosis, the transformation of valve interstitial cells (VICs) into activated VICs (aVICs), is characterized by myofibroblast differentiation, represents a multifaceted pathological process influenced by a plethora of growth factors, cytokines, and hormones, including transforming growth factor- B1 (TGF-B1), tumor necrosis factor-A (TNF-A), interleukin-1B (IL-1B) and interleukin-6 (IL-6). A-smooth muscle actin (A-SMA) expression serves as a hallmark of myofibroblast differentiation.

Methods: This study investigated the effects of IL-1B, IL-6, TGF-B1, and TNF-A as inducers of myofibroblast differentiation in VICs to established an in vitro model of myofibroblast differentiation. This was an in vitro laboratory experiment posttest only control group design. The VICs were isolated from heart valves of New Zealand rabbits (Oryctolagus cuniculus), which were induced by using (1) IL-1B at 10 ng/mL; (2) IL-6 at 50 ng/mL; (3) TGF- B1 at 5 ng/mL; and (4) TNF-A at 10 ng/mL. Myofibroblast differentiation was observed by immunocytochemistry based on A-SMA expression. T-test using the p-value < 0.05 as the significance limit was used.

Results: Immunochemical staining demonstrated that cells were completely differentiated into myofibroblasts with mean of A-SMA expression differences in IL-1B, IL-6, TGF-B1, and TNF-A compared to control groups were 5.066 ± 0.106, 8.822 ± 0.898, 8.582 ± 0.744, and 7.438 ± 1.407 respectively ($p<0.001$). The greatest mean differences between inducer groups and control groups were found in IL-6 and TGF-B1.

Conclusions: IL-1B, IL-6, TGF-B1, and TNF-A induced myofibroblast differentiation of valve interstitial cells differentiation of Oryctolagus cuniculus expressed by A-SMA and can be used as an in vitro model of myofibroblast differentiation.