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## Geometric Control of YAP-dependent Mechanotransduction: A Proposed Model

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Abstract: Geometric Control of YAP-dependent Mechanotransduction: A Proposed Model  
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The Billiar lab is interested in the interplay between mechanical tension and programmed cell death (namely, apoptosis) in cells growing on micro-contact printed aggregates. The Billiar lab uses a bioinspired hydrogel to develop an *in vitro* model for mechanosensitive signaling in mammalian cells. The micro-contact printed cell aggregates experience a loss of tensional homeostasis at the center of the aggregates, which results in selective cell death at the center, but not periphery of the aggregates, followed by calcification, similar to excised diseased aortic valves. However, the subcellular mechanisms responsible for transducing the mechanical cues from the loss of tensional homeostasis to pro-apoptotic signaling have yet to be elucidated; the Billiar lab is interested in finding this link.

Mechanotransduction is the functional link between mechanical cues and the consequent subcellular biochemical response.<sup>1</sup> Cells sense and respond to their physical surroundings via cell-cell junctions, cell-matrix adhesions, and intracellular actin networks.<sup>1</sup> For example, in epithelial cells, restriction of cell growth to spatially patterned circular arrays leads to (1) increased proliferation and (2) higher tractional stresses at the periphery than at the center.<sup>2-3</sup> Proliferation at the periphery of these circular cell aggregates is YAP-dependent, with nuclear localization of YAP at the periphery.<sup>4</sup> Transcriptional co-activator YAP is (1) a nuclear relay of mechanical signals,<sup>5</sup> (2) the main transcriptional effector of the Hippo pathway,<sup>6</sup> and (3) involved in both proliferation (via TEAD promoter) and apoptosis (via p73 promoter).<sup>7</sup> Cell competition is an apoptosis-dependent cell communication phenomenon based on cell fitness comparisons, and which creates “loser” cells that die via apoptosis and “winner” cells that survive.<sup>8-9</sup> For example, co-culture of TEAD-activity-manipulated fibroblasts with WT induces cell competition, in which cells with higher TEAD activity “won,” and cells with lower TEAD activity “lost” (underwent apoptosis).<sup>10</sup>

**Hypothesis: Culture of fibroblasts in geometrically constrained, circular cell aggregates induces cell competition via the formation of “winner” and “loser” cell populations due to differences in tensional homeostasis experienced at the periphery vs. center of the aggregates.**

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