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Making the right choice: Biomechanical design making in tumor invasion

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Little is known about the complex interplay between the extracellular mechanical environment and the mechanical properties that characterize the intracellular environment during various stages of tumor metastasis. To date, most studies have focused on artificial 2D environments that are unrealistic and far from in vivo. In order to elucidate the cell-matrix relationship in cancer progression, we probe the intracellular and extra-cellular mechanical and biochemical environments to understand how tumor cells navigate the complex 3D environments. We simultaneously focus on cytoskeletal mechanics and intracellular signaling pathways as a function of dynamic matrix environments. Our results a non-linear dependence of focal adhesion protein (FAK) phosphorylation on matrix cross-linking and matrix mechanics. Increase in FAK phosphorylation is associated with actin cross-linking, changes in cell morphology and increased production of matrix degrading enzymes or MMPs. This production, in turn, affects adhesion through another feedback mechanism where MMPs regulate integrin expression and hence control cell shape, attachment and migration. Together, these two competing mechanisms control how cells respond to mechano-chemical changes in their local environment during single and collective migration in natural 3D environments. Our results highlight the interconnectivity of mechanical and chemical processes during 3D tumor invasion and identify key controllers of the cell decision process during tumor invasion.