Multiparameter Optimization of the Extracellular Matrix: A Novel Approach to Controlling Cancer

Pal, Antara (School: Acton Boxborough Regional High School)

Cancer originates from genetic and non-genetic alterations which induce not only abnormal cell proliferation, but also abnormal migration. Local invasion involves motile cancer cells advancing through the extracellular matrix (ECM) by secreting Matrix Metalloproteinase (MMP) and contributes to over 90% of cancer mortalities. Thus, it is critical to develop novel approaches to limiting local cancer invasion by studying cancer cell-ECM interactions. ECM microenvironments differ in cell-matrix adhesions and fiber rigidities. To understand the roles these ECM parameters play in local invasion, the Cellular Potts Model (CPM) was used to simulate local invasion through parallel linear ECM configurations of varying cell-matrix adhesions and fiber rigidities. ECM fibers with strong cell-matrix attachments were found to generate cell pseudopodia, which aid in increasing local invasion rate, while weaker attachments prevent the cells from forming protrusive regions, limiting invasion. ECM arrays with rigid fibers elongate the cell body, allowing the cells to form cell protrusions, resulting in increased cancer invasiveness. Conversely, soft fibers stimulate cell rounding, which is associated with limited migration. Combining the weakest cell-ECM attachments and softest ECM fibers decreased local invasion by over 90%. To the best of my knowledge, this is the first time multi-parameter optimization has been applied to ECM parameters. Understanding the interactions between the ECM and cancer cells may provide insight into novel therapeutic approaches to prevent cancer migration and improve survival.

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