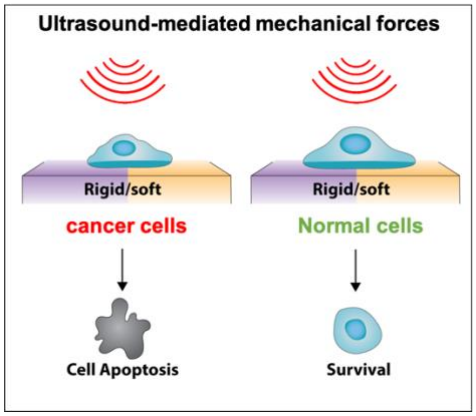
Investigating the effect of nanoscale ligand spacing on mechanical force-induced cancer cell killing

Background

Cells interact with extracellular matrix (ECM) using transmembrane receptors, integrins, that activate signalling pathways to control cell functions.[1] Recent studies highlighted that physical properties of ECM like rigidity, topography, protein fibre diameter and spatial distribution of cell binding domains on protein fibres affect the integrin-mediated signalling pathways.[2] The size of these ECM properties are found to be in the order of tens of nanometres. Thus, while studying cell-ECM interaction at nanoscale level, it becomes imperative to consider the nanoscale spacing between binding domains present on ECM through which cell-ECM binding occurs. Recent reports revealed the range of nanoscale spacing observed between periodic binding domains present on proteins. For instance, collagen exhibits periodic binding domains every after 70 nm which is considered to be length scale at which cells adhere to collagen fibre.[3] For fibronectin, periodic binding domains were observed to be around 42 nm.[4]



It is well established that cells recognize nanometre-scale changes and respond them by altering size and distribution of focal adhesions, stress fibre formation and traction force generation to activate appropriate signalling pathways.[5] Ultimately, these nanoscale changes affect several cellular activities including spreading, migration, differentiation and survival. In the context of cancer, nanoscale ligand spacing has been shown to affect cancer cell plasticity, chemoresistance development[6] and tumorigenicity[7]. Recently it was reported that cancer cells are mechanosensitive and apoptosed when subjected to physiologically relevant mechanical forces.[8-10] Thus, here we are interested address a question, **does nanoscale ligand spacing affect mechanical force-induced cancer cell killing and what is the molecular mechanism behind it.**

Experimental design

We will develop gold nanodot platforms to mimic nanoscale ligand spacing observed in ECM. Also, we will fabricate custom-built ultrasound device to apply ultrasound-mediated mechanical forces on the cells. Cancer cells grown on biofunctionalized nanodot platforms will be treated with mechanical force to measure the level of apoptosis as a function of level of nanoscale ligand spacing. Cell and molecular biology techniques along with high-resolution imaging will be implemented to characterize the biomechanical properties of the cells and to establish the link between the nanoscale ligand spacing-mediated cellular changes and the mechano-induced cancer cell killing.

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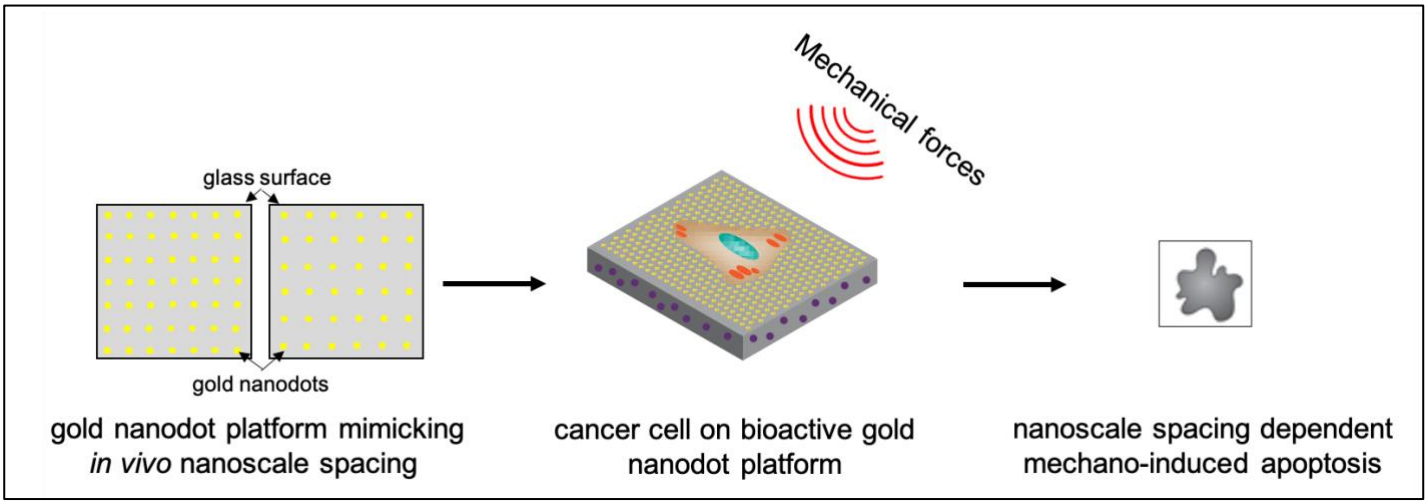

Figure: Schematic depicting steps to study the effect of nanoscale ligand spacing on the mechanical force-induced apoptosis

Significance of the study

This study will provide better understanding of ECM nanoscale ligand spacing that can influence mechano-induced apoptosis and help us to optimize the ultrasound parameters to maximize apoptosis in tumor cells based on tumor ECM composition.

Collaboration

This work will be done in collaboration with **Prof. Jennifer Young**, Mechanobiology Institute, Singapore.

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