Role of cellular interactions during epithelial defence against cancer.

Offered by: Medhavi Vishwakarma (Joining Centre for Biosystems Science and Engineering in July 2021).

Background of the problem: Tumour is a mass of over-proliferating cells burdened by oncogenic mutations. However, if mutations alone drove cancer, then trillions of new mutations that our cells acquire every day, greatly increase our probability of getting cancer. Yet a majority of people live cancer-free for decades. How? Recent studies suggest that our tissues exhibit a defence mechanism against cancer, which, to some extent override the ability of oncogenic cells to form tumour[1]. In this view, the fate of an incipient tumour is largely determined by the competitive interactions between host cells and tumour cells[2]. Such interactions allow host-cells to recognize and remove misfit oncogenic cells - epithelial defence against cancer (EDAC) [3] (Fig.1). Instead, when tumour is fitter than the host, similar interactions could lead to host-cell death, allowing for tumour growth and expansion [2, 4] (Fig.1). *Cellular interactions which lead to EDAC remain largely unknown. It also remains elusive how oncogenic cells gain competitive advantage over host cells to impair EDAC?*

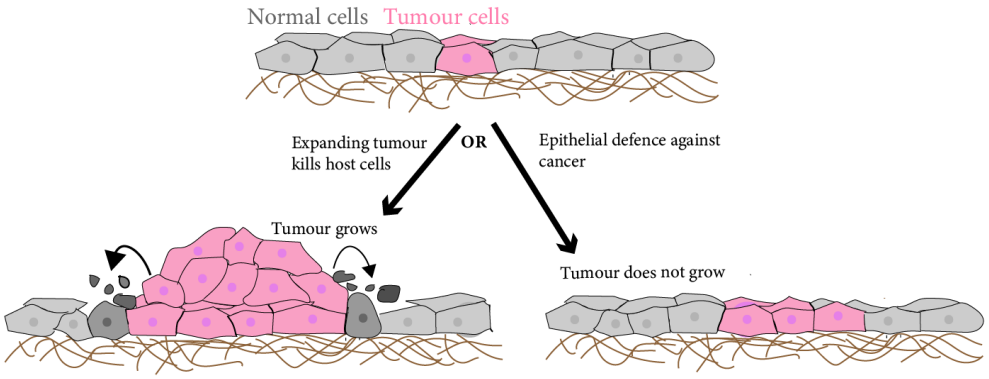

Figure 1. Epithelial defence against cancer: Cellular interactions determine the fate of an incipient tumor.

Project Detail: Cellular behaviour within epithelial tissues is a convoluted response driven by both physical and biochemical interactions between cells. We will use tools of cell biology and biophysics to understand the bio-physical interactions between oncogenic cells and host epithelial cells (Figure 2). More specifically, gene editing, and high-resolution microscopic techniques will be used to modify and study dynamics of cell adhesion molecules live during EDAC. Additionally, we will also use biophysical tools, such as traction force microscopy and monolayer stress microscopy to determine how cell-cell and cell-substrate signalling link to active cellular forces during Epithelial defense against cancer (Figure 2).

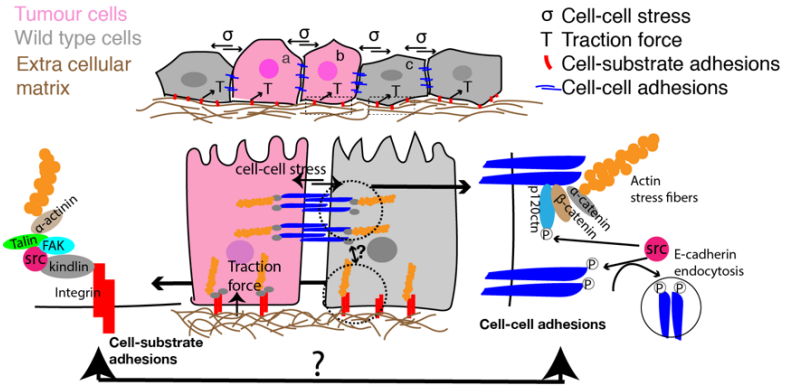

Figure 2. Deciphering role of cell-cell and cell substrate interactions in EDAC. *We will investigate how cell-cell and cell-substrate adhesions cross talk to modulate cellular cytoskeleton in both host and tumour cells in order to suppress or promote tumour growth. Using traction force and monolayer stress microscopy, we will investigate if cells use active forces during tumour-host interactions and how these forces are sensed and transduced to generate the required tumour suppressive or tumour promoting response.*

Impact of the problem: On the long term, a comprehensive understanding on Epithelial defence against cancer will be used to generate novel anticancer therapies harnessing the protective barrier of host epithelial cells against cancer[2]. This

approach would complement the current approach to therapy, which focusses solely on apoptosis to kill the tumour cells[5] and have long lasting side effects on the patient.

Prerequisite: A strong background in cell and molecular biology and basic understanding of physics.

Technical skills acquired in this project: Cell culture, Gene knockout and over expression, Lentiviral gene delivery, Microscopy (Confocal and inverted fluorescence microscopy), Traction force and monolayer stress microscopy, Image analysis using ImageJ .

Literature:

1. Bissell, M.J., and Hines, W.C. (2011). Why don't we get more cancer? A proposed role of the microenvironment in restraining cancer progression. Nat Med *17*, 320-329.
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3. Kajita, M., and Fujita, Y. (2015). EDAC: Epithelial defence against cancer-cell competition between normal and transformed epithelial cells in mammals. J Biochem *158*, 15-23.
4. Suijkerbuijk, S.J., Kolahgar, G., Kucinski, I., and Piddini, E. (2016). Cell Competition Drives the Growth of Intestinal Adenomas in Drosophila. Curr Biol *26*, 428-438.
5. Carneiro, B.A., and El-Deiry, W.S. (2020). Targeting apoptosis in cancer therapy. Nat Rev Clin Oncol.