Tata Institute of Fundamental Research
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Webinar

Oncogenes and their role in shaping the tumor microenvironment

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The proto-oncogenes are essential for normal cell growth, but they permanently turn on cell proliferation when they mutate or amplify their expression. When this happens, the cell grows out of control, and it leads to cancer. The oncogenes drive tumour initiation, growth, metastasis, and drug-resistance. Their mechanism of carcinogenesis could be cell-intrinsic or cell-extrinsic. I try to find novel oncogenes and understand their mechanism of action to design targeted cancer therapies.

The cell-intrinsic mechanism of oncogenic signalling activates the cell survival pathways. We identified a proto-oncogene Dll1, a Notch ligand, promoting normal mammary gland development (Science 2018). The expression of Dll1 goes up in tumours and even more in metastatic tumours. Higher expression of Dll1 makes cells resistant to chemotherapy, whereas blocking of Dll1 significantly reduces tumour growth and metastasis in vivo (Oncogene 2019, Nature Communications 2021).

The cell-extrinsic oncogenic mechanism is where the interaction of tumour cells with stromal cells is crucial. The epithelial/tumour-stromal interactions are essential for normal development and cancer. In normal development, we found epithelial cells interact with macrophages (immune cells) and drives the mammary gland's growth (Science 2018). Likewise, we discovered how breast cancer cells recruit myeloid-derived suppressor cells (MDSC; immune cells), and their interactions help cancer cells to promote tumour growth and metastasis. Understanding these interactions intrigued us to target them for further investigation. The inhibition of these interactions resulted in decreased metastatic events in mouse models (JCI, 2018).

In conclusion, targeting the tumour microenvironment with a standard of care therapy (such as chemotherapy or radiotherapy) could be vital for treating patients. I plan to reveal additional oncogenes and mechanisms for cancer therapy.

References:

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