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Chromatin outside the cell: A new paradigm in biology

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1 10^9 - 10^{12} cells die in the adult human body daily and much of the fragmented chromosomes in the form of cell-free chromatin (cfCh) are released into the extracellular compartment of the body, including into the circulation. Our research has shown that cfCh have extraordinary and diverse local and systemic damaging effects on host cells that may form the basis of many human maladies. cfCh can freely enter into healthy cells, accumulate in their nuclei, trigger a DNA damage repair response and integrate into their genomes by a unique mechanism. Genomic integration of cfCh leads to dsDNA breaks, inflammation, chromosomal instability, senescence and apoptosis of recipient cells. These pathologies are integral to ageing and ageing-related disorders such as cardio-vascular diseases, diabetes, stroke and neurodegenerative disorders. cfCh induced inflammation and DNA damage may play a key role in infection and sepsis as well as autoimmune disorders and cancer. cfCh isolated from cancer patients can readily transform NIH3T3 cells by inducing DNA damage, inflammation and chromosomal instability and up-regulating multiple hallmarks of cancer. The transformed cells form tumors when inoculated into immune-deficient mice. Cell-free DNA isolated from sera of cancer patients are inactive, suggesting epigenetic mechanisms underlying the oncogenic process. When cancer cells are injected intravenously into mice, they die rapidly upon reaching distant organs to release cfCh particles which localize in nuclei of target cells to induce dsDNA breaks, inflammatory cytokines and up-regulating cancer hallmarks. Fluorescent phosphorylated H2AX signals and those of NF κ B and cancer hallmarks are frequently activated simultaneously in the same target cells suggesting that such cells have a high propensity for oncogenic transformation. These findings suggest that cfCh from dying cancer cells can transform cells of the microenvironment both locally and in distant organs providing a novel mechanism of tumor invasion and metastasis.

Biography

Indraneel (Neel) Mitra is Ernest Borges Chair in Translational Research and Professor Emeritus Department of Surgical Oncology, Tata Memorial Centre, Mumbai. He has obtained his Medical Degree from University of Delhi, is a Fellow of the Royal College of Surgeons of England and holds a PhD degree from University of London. He has completed his Post-doctoral research with Dr. Renato Dulbecco, Nobel Laureate, at the Imperial Cancer Research Laboratories in London. His current research interests are in the area of biology of extracellular nucleic acids and their role in ageing, inflammation, degenerative disorders and initiation and meta-stasis of cancer. He has published in high impact journals such as Nature, Cell, Lancet and Br Med J. He is a Fellow of the Indian National Science Academy and Indian Academy of Sciences.

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