REGIONAL CENTRE FOR BIOTECHNOLOGY

Seminar series

"The Small Arf-like GTPase Arl8b Regulate Lytic Granule Polarization and Cell-Mediated Cytotoxicity in Natural Killer Cells"

Amit Tuli , PhD

Harvard Medical School (HMS)/Brigham and Women's Hospital (BWH)
Boston, MA, USA

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A key mechanism that immune cells including Natural killer (NK) cells and cytotoxic T-lymphocytes employ to kill infected or transformed target cells is through regulated exocytosis of lytic granule contents towards the target cell membrane. Although the mechanism by which lytic granules kill the target cells is well understood, the preceding molecular steps including their movement on microtubules and polarization towards the immunological synapse (IS) is less clear. Here we describe a role for Arl8b in the exocytic events required for effective NK cell-mediated cytotoxicity. Arl8b is a small GTPase of the Arl (Arf-like) family. Though little is known about Arl8b function, proteomic studies have localized it to lysosomes and subsequent work utilizing overexpressed tagged forms of Arl8b have shown that changes in its expression influenced lysosome motility. We found endogenous Arl8b co-localized with perforin and granzyme containing lytic granules in both ex vivo NK cells and immortalized NK cell lines. Moreover, Arl8b-deficient NK cells clearly demonstrated a significant loss of cytolytic activity compared with control cells. To gain insight into the mechanism of Arl8b action, we assessed which step during lytic granule exocytosis is impaired upon Arl8b knockdown. It was previously reported that the microtubule organizing centre (MTOC) translocates towards the immunological synapse (IS) as it matures. This reorientation is essential for the movement and polarization of the granules to the site of release. We examined the role of Arl8b in these processes using Arl8b-deficient cells. Interestingly, compared to the control knockdown, in NK cells lacking Arl8b, lytic granules and MTOC failed to polarize at the IS and remained almost at the opposite pole to that of the IS. Together these results mark Arl8b as a novel regulator of the lytic granule polarization and cell-mediated cytotoxicity, implicating this GTPase in lymphocyte function.