Library
Indian Institute of Science Education and Research
Mohali

DSpace@IISERMohali / Thesis & Dissertation / Doctor of Philosophy (PhD) / PhD-2017

Please use this identifier to cite or link to this item: http://hdl.handle.net/123456789/5902

Title:	Reversal of immunosenescence by Rab8a empowered dendritic cells
Authors:	SINGH, SUDHAKAR
Keywords:	cells dendritic cells vaccination
Issue Date:	Feb-2024
Publisher:	IISER Mohali
Abstract:	Aged population exhibits enhanced susceptibility to viral infection and responds poorly to vaccination. This necessitates devising immune enhancing strategies for this group. Dendritic cells (DCs) because of their unique morphological features and strategic location at tissue sites serve as the sentinels of the immune system and can effectively prime antigen specific cytotoxic T lymphocytes (CTLs), a fraction of which further differentiates into lasting memory. Anamnestic response of memory cells confers to the host a quick protection during a subsequent exposure with homologous infection. Given the critical role of DCs in linking the innate and adaptive immune system, the study was undertaken to gain insights into DCs' biology and their role in immunosenescence. Genome-wide RNAseq analysis of conventional DCs (CD11b + CD11c + cells) isolated from unmanipulated young and aged mice revealed a severely compromised type I interferon signaling in the latter group. Type I IFNs serve as one of the first anti-viral response. Furthermore, DCs of aged animals were severely impaired in antigen presentation and mounted poor response of CTLs in vitro and in vivo. Genes of PI3K/MtorC1 signaling pathway such as Rab8a, Akt1 and S6K were downregulated in the aging cells. Therefore, the role of Rab8a, a small GTPase downstream to growth factor receptors such as CSF2Ra and IGFR, was evaluated in DCs. Rab8a depleted bone marrow precursors of young animals failed to efficiently differentiate into functionally competent DCs while those from aged animals following reconstitution with Rab8a regained functionality. Accordingly, the Rab8a reconstituted DCs generated a strong anti-viral IFN response when stimulated with two of the viruses viz., IAV and a gamma-herpesvirus (MHV68). Antigen-pulsed DCs enhanced activation of CTLs in vitro and mounted a potent primary and memory response of antigen specific CTLs to efficiently control a respiratory infection caused byInfluenza A Virus. Rab8a in conjunction with Rab11 promoted formation of endosomal recycling compartment (ERC) enriched with peptide loaded class I MHC complexes and such complexes were more efficiently displayed on the surface of DCs to engage with antigen specific CTLs. Therefore, the study uncovers a critical role of Rab8a in regulating differentiation and functionality of DCs and that a Rab8a reconstitution of DCs of an aging host could provide a viable approach to achieve immune sufficiency. These observations also have clinical implication in managing viral infections, enhancing vaccine efficacy as well as promoting anti-tumor response in the aging population.
URI:	http://hdl.handle.net/123456789/5902
Appears in Collections:	PhD-2017

Files in This Item:

File	Description	Size	Format	
Sudhakar Singh_ Final PhD thesis_13022024.pdf		9.05 MB	Adobe PDF	View/Open

Show full item record

Admin Tools

Edit...
Export Item
Export (migrate) Item
Export metadata