National Institute of Technology Rourkela

Defence Seminar

Seminar Title	: Understanding the role of Ac-93253 iodide in apoptosis as an anti-mycobacterial response in macrophages
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Venue	: LS Seminar Hall
Date and Time	: 29 Feb 2024 (5:00 PM)
Abstract	: Recent studies suggest that host defense mechanisms like autophagy, inflammation, oxidative stress and apoptosis in macrophages plays a significant role in host defense against intracellular pathogens like viruses, fungi, protozoan, and bacteria, including *Mycobacterium tuberculosis* (*M. tb*). It is still unclear if micromolecules inducing host defense mechanisms could be an attractive approach to combat the intracellular burden of M. tb. Hence, the present study has investigated the anti-mycobacterial effect of apoptosis mediated through phenotypic screening of micromolecules Shows Ac-93253 a potent candidate against the mycobacteria in THP-1 cells. Through MTT and trypan blue exclusion assay, 0.5 &muM of Ac-93253 was found to be noncytotoxic even after 72 h of treatment in phorbol 12-myristate 13-acetate (PMA) differentiated THP-1 (dTHP-1) cells. We have found that Ac-93253 treatment does not affect autophagy regulation, ROI, or RNI generation in uninfected and mycobacteria-infected dTHP-1 cells. At the same time point and same concentration, inflammation was also not affected upon Ac-93253 treatment. Significant regulation in the expression of various pro-apoptotic genes like Bcl-2, Bax, and Bad and the cleaved caspase 3 was observed upon treatment with a non-cytotoxic dose of Ac-93253. Ac-93253 treatment also leads to DNA fragmentation and increased phosphatidylserine accumulation in the plasma membrane's outer leaflet. Further, Ac-93253 also effectively reduced the growth of mycobacteria in infected macrophages, Z-VAD-FMK a broad range apoptosis inhibitor significantly brought back the mycobacterial growth in Ac-93253 treated macrophages. Ac-93253 treatment manipulates the mitochondrial membrane potential, CsA a mitochondrial membrane potential stabilizer, substantially inhibits the apoptosis and abrogates the anti-mycobacterial effect of Ac-93253. These findings suggest apoptosis may be the probable effector response through which Ac-93253 manifests its anti-mycobacterial property.

Keywords: Tuberculosis Mycobacteria Ac-93253 Host directed therapy Mitochondrial membrane potential Apoptosis