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Details of the Collaborative Activity

2018-19

Name of the Collaborating Institute: Laboratory of Translational Medicine, School of Life Sciences, University of Hyderabad, Hyderabad-500046, Telangana, India

Name of the Collaborating Department: YU-IOB Center for Systems Biology and Molecular Medicine.

Activities:

Joint Research: YU-IOB Center for Systems Biology and Molecular Medicine and School of Life Sciences, University of Hyderabad collaborated and published a research article.

Joint Publication:

Nadella V, Mohanty A, Sharma L, **Yellaboina S**, Mollenkopf HJ, Mazumdar VB, Palaparthi R, Mylavarapu MB, Maurya R, Kurukuti S, Rudel T, Prakash H, Inhibitors of Apoptosis Protein Antagonists (Smac Mimetic Compounds) Control Polarization of Macrophages during Microbial Challenge and Sterile Inflammatory Responses. *Frontiers in Immunology.* 2018; 8, 1792.10.3389/fimmu.2017.01792

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Inhibitors of Apoptosis Protein Antagonists (Smac Mimetic Compounds) Control Polarization of Macrophages during Microbial Challenge and Sterile Inflammatory Responses

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Apoptosis is a physiological cell death process essential for development, tissue homeostasis, and for immune defense of multicellular animals. Inhibitors of apoptosis proteins (IAPs) regulate apoptosis in response to various cellular assaults. Using both genetic and pharmacological approaches we demonstrate here that the IAPs not only support opportunistic survival of intracellular human pathogens like *Chlamydia pneumoniae* but also control plasticity of iNOS+ M1 macrophage during the course of infection and render them refractory for immune stimulation. Treatment of Th1 primed macrophages with birinapant (IAP-specific antagonist) inhibited NO generation and relevant proteins involved in innate immune signaling. Accordingly, birinapant promoted hypoxia, angiogenesis, and tumor-induced M2 polarization of iNOS+ M1 macrophages. Interestingly, birinapant-driven changes in immune signaling were accompanied with changes in the expression of various proteins involved in the metabolism, and thus revealing the new role of IAPs in immune metabolic reprogramming in committed macrophages. Taken together, our study reveals the significance of IAP targeting approaches (Smac mimetic compounds) for the management of infectious and inflammatory diseases relying on macrophage plasticity.

Keywords: apoptosis, macrophages immunobiology, inflammation mediators, polarization, infection, hypothalamus

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INTRODUCTION

Deregulated host cell apoptosis leads to destructive inflammatory responses which are deleterious in nature as seen in septic shock, auto-immunity, cancer, and episode of chronic bacterial infections. Resistance to apoptosis relies on the increased expression and stability of anti-apoptotic proteins namely inhibitors of apoptosis proteins (IAPs). *Chlamydia pneumoniae*, a Gram-negative