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Nuclear innate sensor IFI16 recognition of hepresviral genomes and inflammasome and IFN-β responses

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The innate immune system NOD-like and AIM2-like receptors are cytoplasmic inflammasome sensors of foreign molecules, including DNA and elicit pro-inflammatory IL-1β, IL-18 or interferon β (IFN-β) responses. We have shown that IFI16, a sequence-independent nuclear innate sensor, recognizes the episomal dsDNA genomes of herpes viruses such as KSHV, EBV, and HSV-1 in the infected cell nuclei, forms an inflammasome complex with ASC and procaspase1, and relocates into the cytoplasm leading into Caspase-1 and IL-1β generation. IFI16 also induces IFN-β during HSV-1 infection via the cytoplasmic STING-IRF3 pathway. Whether IFI16 recognizes foreign DNA directly or utilizes other host protein(s), and the mechanisms of IFI16-inflammasome formation, cytoplasmic redistribution and STING activation were not known. Our studies demonstrate that BRCA1 is in complex with IFI16 in the host cell nucleus, and their association increases in the presence of nuclear viral genomes during *de novo* KSHV, EBV and HSV-1 infection, and in latent KSHV or EBV infection. Our findings highlight that BRCA1 plays a hitherto unidentified innate immunomodulatory role by facilitating nuclear foreign DNA sensing by IFI16, assembly and cytoplasmic distribution of IFI16-inflammasomes, IL-1β and IFN-β formation. Our studies also demonstrate that recognition of herpesvirus genomes in the nucleus by IFI16 leads into its interaction with histone acetyltransferase p300 and IFI16 acetylation resulting in IFI16-ASC interaction, inflammasome assembly, cytoplasmic redistribution, caspase-1 activation, IL-1β production, interaction with STING, and IFN-β production. Collectively, our studies identify the increased nuclear acetylation of IFI16 as a dynamic essential post-genome recognition event in the nucleus that is common to the IFI16-mediated innate responses of inflammasome induction and IFN-β production during herpesvirus infections.

Biography

Bala Chandran received his MS from JIPMER, Pondicherry and his PhD degree from AIIMS, New Delhi, India in 1979. His Postdoctoral experience includes positions at the Cancer Research Group at McMaster University, Hamilton, Ontario, Canada and at the University of Florida, Gainesville. He was appointed as an Assistant Professor in the Department of Microbiology, University of Kansas Medical Center in 1986 and then Professor in 1996. He joined the Department of Microbiology and Immunology at Rosalind Franklin University of Medicine and Science on July 1, 2005 as Professor and Chair. He has published more than 150 papers.

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