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Disease-specific role for β-arrestin-1 in inflammatory disease pathogenesis

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β-arrestins (β-arrestin-1 and 2) are scaffolding proteins originally identified as critical regulators of G-protein coupled receptor (GPCR) desensitization. More recent studies indicate that the functions of β-arrestins are much broader and include a wide variety of cell signaling functions including their role in biased signaling from GPCRs. Studies from our lab and others demonstrate a critical role for β-arrestins in non-GPCR signaling including receptors involved in inflammation, such as TLRs. In previous studies, we found that β-arrestin1 (β-arr1) is a critical mediator of endotoxemia in mouse model. Consistent with that, we also found that the β-arr1 deficient mice are protected from intestinal inflammation. Accordingly, β-arr1 deficient mice also exhibited significantly low levels of IL-6 compared to wild type mice during colitis. By generating bone marrow chimeras, we further found that deficiency of β-arr1 in the hematopoietic compartment is sufficient to prevent colitis-induced weight loss. Surprisingly however, we found that β-arr1 deficient mice are strikingly more susceptible to polymicrobial sepsis induced by cecal ligation and puncture. This opposing phenotype also correlated with enhanced levels of IL-6 in the β-arr1 knockout mice. Intriguingly, we further found that the negative regulatory role of β-arr1 in the polymicrobial sepsis model is attributable to regulation of IL-6 by β-arr1 in the non-hematopoietic cells. Together our results suggest that β-arr1 in different cellular compartments have selective and unique roles depending on the instigating stimuli in terms of inflammatory disease.

Biography

Narayanan Parameswaran obtained his Veterinary Medicine degree from Madras Veterinary College, India and a PhD from Michigan State University, East Lansing. After a Post-doctoral fellowship at Thomas Jefferson University, he started his independent career at Michigan State University in 2006. He has published more than 45 peer-reviewed manuscripts in reputed journals. He currently serves as editorial board member for Genes and Immunity and is also an appointed member of the Innate Immunity and Inflammation study section at the National Institutes of Health. In addition, he has served on several other grant review panels including the American Heart Association.

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