Let's celebrate us Postdocs!

UMPA Postdoc Spotlight Series

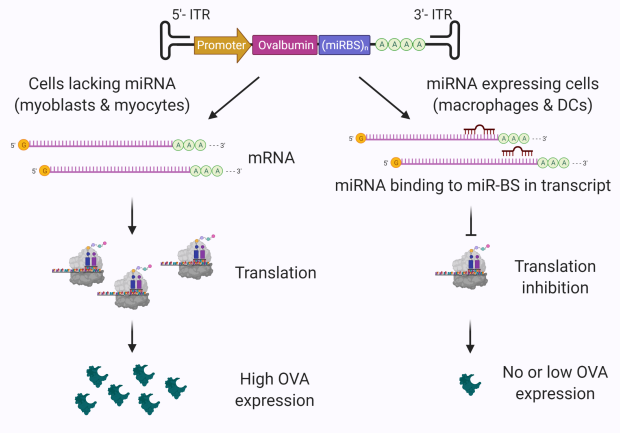
Spring Edition

The Journal of Clinical Investigation REVIEW

Overcoming innate immune barriers that impede AAV gene therapy vectors

Manish Muhuri,[1,2,3] Yukiko Maeda,[1,3,4] Hong Ma,[1] Sanjay Ram,[5] Katherine A. Fitzgerald,[6] Phillip W.L. Tai,[1,2,3] and Guangping Gao[1,2,7]

[1]Horae Gene Therapy Center, [2]Department of Microbiology and Physiological Systems, [3]UMDE Program, [4]Department of Medicine, [5]Division of Infectious Diseases and Immunology, [6]Program in Innate Immunity, Department of Medicine, and [7]Li Weibo Institute for Rare Diseases Research, University of Massachusetts Medical School, Worcester, Massachusetts, USA.



miRNA mediated detargeting entails the utilization of differential miRNA expression in different cell types to selectively inhibit transgene expression in "unwanted immune cells". When the AAVs infect cell types that possibly do not express the miRNA of interest, transcription and translation of the vector genome leads to production of transgene (OVA). However, in other cell types like APCs that express high levels of the miRNAs against which binding sites have been designed lead to transcript degradation and unsuccessful OVA production. As a result, these APCs are unable to process OVA peptides on MHCs for B and T cell activation.

Recombinant adeno-associated viruses (rAAV) vectors have emerged as promising and attractive tools for in vivo gene therapy. In this manuscript, we have discussed the current obstacles that innate immunity poses for the successful implementation of rAAVs as reliable gene therapy medications (*JCI, 2021*). Development of these drugs requires that we consider a balance between the promise of a lifesaving treatment and the related risks, known or unknown. In the last few years, a series of studies have reported novel rAAV-related inflammatory toxicities in nonhuman primates (NHPs) and more recently, deaths of human subjects in clinical trials. it was presumed that innate immunity against rAAVs is inconsequential. However, the innate immune system is the first line of defense against foreign pathogens and provides activation signals that are critical for adaptive immunity. We have reviewed the innate immune pathways implicated in response to rAAV infection. Thereafter, we have also presented selected strategies that show promise for overcoming the innate immune barriers to human gene therapy.

Manish Muhuri, PhD

Gao Lab

Horae Gene Therapy Center

I received my Ph.D. in developmental and RNA biology at NTU, Singapore. My doctoral studies were focused on dissecting the function of microRNA miR-124 in mice brain development as well the mechanism of biogenesis of intronic miRNAs. This was followed with a stint at A-STAR (Agency for Science Technology and Research), Singapore working on elucidating oncogenic biomarkers for aggressive cancers. I'm currently working in Horae Gene Therapy Center (HGTC) and exploring novel vector engineering strategies to reduce the immunogenicity of recombinant adeno associated viral (rAAV) vectors for treatment of genetic and infectious diseases in addition to improving their tissue targeting properties.

rAAV vectors have emerged as one of the leading tools for facilitating gene therapeutics for rare monogenic diseases. The host immune response, however, is one of the most critical roadblocks limiting effective and long-term transgene expression. AAV-delivered transgene products can stimulate host immune responses, and can lead to the generation of transgene-specific antibodies and cytotoxic T lymphocytes. rAAV transduction of professional APCs, like dendritic cells (DCs), macrophages, and B cells culminates in cytotoxic T cell-mediated clearance of infected cells. Detargeting transgenes from specific cell types via endogenously expressed miRNAs can also be used to limit spurious transgene expression from non-target cells. We have previously shown that miR-142-mediated APC detargeting boosts transgene levels and inhibits antibody formation and cytotoxic T cell response (*JCI Insight, 2019*). We have further identified two miRNAs, miR-223-3p and miR-652-5p, whose expression is enriched in APCs in mice. We have further also demonstrated that a combination of tandem miRNA binding sites designs effectively improve transgene expression, blunt antibody response against the transgene, and reduce the activation of T cells (Th1, Th17 and memory T cells). Our findings not only reiterate the therapeutic potential of miRNA-mediated detargeting cassettes, but also demonstrate that a combination of different miR-BSs might have an additive or synergistic effect on inhibition of transgene immunity (*Frontiers in Immunology, 2021*).