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AAV-based cytokine/interferon gene delivery into immune cells reveals new attributes of activity previously unrecognized: Cytokine tropisms and intracrine activities are uncovered

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Adoptive transfer of antigen-specific cytotoxic T lymphocytes (CTL) holds significant promise in treating cancer and Th1 response cytokines are critical for their stimulation. We reported that, using adeno-associated virus type 2 (AAV2) gene delivery, interleukin 7- (IL-7) and interferon gamma- (IFN-γ) autocrine/T cell gene delivery resulted in superior ex vivo CTL stimulation over paracrine/DC delivery. Moreover, we have reported that IL-2 gene delivery provides no benefit into any cell type for CTL generation. However, IL-12 is yet another important Th1 cytokine which affects both DC and T cells. Here, again using AAV2 gene delivery, IL-12-paracrine/DC gene delivery gave significantly superior stimulation of carcinoembryonic antigen (CEA)-specific CTL killing over that induced by autocrine gene delivery (or exogenous IL-12 addition). This is surprising as both AAV2/IL-12-treated T cells and DC secreted approximately the same level of IL-12. Paracrine IL-12 gene delivery also resulted in highest IL-12/IL-10 secretion ratio by DC and highest CD40, CD80, CD83 and CD86 expression. Moreover, AAV2/IL-12-DC stimulated the highest T cell IFN-γ production, highest T cell proliferation, highest CD69+/CD8+ levels, and lowest level of CD25+/CD4+ Treg. These data strongly suggest that the primary activity of IL-12 during CTL generation is upon the DC. These data are also consistent with there being novel activity for IL-12 within the DC itself, not involving its surface receptor; an "intracrine" activity. Given the plethora of IL-12 studies, these data also suggest that this gene delivery comparison approach could be useful for uncovering new cytokine activities and mechanism(s) of action gone unrecognized by conventional immunologic assays. Finally, these data further suggest AAV2/IL-12 intracrine gene delivery into DC may have utility in immunotherapy protocols involving antigen-specific CTL.

Biography

Paul Hermonat received his Ph.D. from the University of Florida in 1984. There he mutationally mapped the genes of AAV and carried out the first AAV-based gene transfer experiments. Now at the University of Arkansas for Medical Sciences, he has 141 publications and has helped lay the foundation of knowledge on AAV molecular biology and its use in gene therapy. Presently he studies AAV-based gene therapy for treating cardiovascular disease and cancer, and studies the use of helper genes for AAV production.

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