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AUTOIMMUNITY AND GENE THERAPY
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The nemesis of autoimmunity

N Giannoukakis and M Trucco

In a very recent review, we outlined the current status of gene therapy approaches in autoimmune, type 1 diabetes mellitus (T1DM).[1] This disorder of glucose homeostasis most frequently affects children. Underlying the condition is a chronic inflammation of the pancreatic islets of Langerhans, ultimately resulting in the destruction of insulin-producing beta cells. The immunopathogenesis of the disease unequivocally implicates T-cell-mediated destruction of the beta cells, primed by defects of central and peripheral tolerance to beta cell-specific antigens. While immunosuppressive drugs can suppress the ongoing inflammation, recent advances have demonstrated the feasibility of re-establishing tolerance through cell therapy methods like chimerism induction, immunomodulatory antibody therapy and transplantation of allogeneic islets.[1]

Islet transplants have long been attractive for insulin replacement, but a considerable number of hurdles, mostly immunologic, have impeded the progress of islet transplantation until recently. While the development of a corticosteroid-free immunosuppressive regimen has improved the likelihood of islet transplantation as a clinical option, previously unforeseen logistical issues as well as determinants of primary graft failure have raised new questions regarding its utility.[1] To circumvent these problems, many investigators have focused on engineering allogeneic islets to resist primary graft failure, acute and chronic allorejection and recurrence of autoimmunity in a diabetic host, most often the non-obese diabetic (NOD) mouse.

While a large number of genes have been examined as candidates to prolong islet allograft survival, only two, perhaps three vectors, have demonstrated good transduction efficiency: adenovirus being the most popular and the most efficient, followed at a distance by the HIV-1-based lentiviral vector. While many of these studies are still in the proof-of-principle stage of development and optimization, more recently the promise offered by recombinant AAV (rAAV) as a do-it-all vector 'infected' the arena of T1DM gene therapy.

rAAV was considered an attractive vector for a number of reasons: (1) it seems to be practically non-immunogenic, unlike adenoviral vehicles; (2) it can stably integrate into the host genome under certain conditions; and (3) it can transduce nondividing cells, like pancreatic islet cells. These features were exploited in a number of studies aimed at restoring insulin production,[2–4] at facilitating islet transplantation[5,6] and at inducing immunoregulation in prediabetic NOD mice.[7,8] Perhaps the most crucial determinant of high-level transgene expression from these vectors was the serotype. Generally, it has been challenging to achieve high-efficiency transduction of intact human and murine islets with first-generation AAV serotypes 1 and 2. Recent engineering of serotype 2 into a modified vector, however, did result in efficient transduction of intact islets, albeit at high multiplicity of infection.[8,9]

The report by Zhang and colleagues in this issue of *Gene Therapy*[10] uncovers an important, hitherto unknown determinant that should help those interested in AAV-mediated gene transfer in the context of diabetes mellitus to better understand the interaction between the vector recipient and the vector with its encoded transgene product. On a global scale, the data should encourage further research into host genome–vector interactions in autoimmune disorders, and perhaps transplantation, at least in approaches where the vector is administered systemically. In this report, the authors conclusively demonstrate that autoimmunity can be an impediment for successful gene transfer using rAAV. It is not known whether the effect is genomically determined in the host, at loci that concurrently affect autoimmunity susceptibility and the host immune response against the vector; this merits further investigation. However, these data raise more important questions. Firstly, does the state of immune activation/suppression of the host affect the outcome of transduction efficiency and gene expression levels from different viral vectors? This question is certainly relevant not only to the autoimmunity field, but to gene therapy aimed at manipulating the immune system in eradicating tumors, viruses and other foreign pathogens. Secondly, what are the effects of genetic background of vector recipients on the outcome of systemic gene therapy *versus* gene expression from *ex vivo*-transduced cells and tissues?

The complexity of host genome–vector interactions has not been thoroughly considered and it would be of interest to study well-defined populations in whole-genome screens for vector responses, at the immunological level and at the level of toxicity. The studies could focus initially on differences among well-defined mouse strains and congenic lines, eventually including humans.

Considerable attention has focused on the toxicity associated with viral vectors (adenovirus and herpes vectors) as well as with the potential for oncogenesis (retroviruses). There is no question that vector features are a key determinant in toxicity and oncogenic potential; however, it is possible that the genetics of the host could influence vector integration site and copy number of integrants (for example, *cis*-acting sequences and chromosomal variegation effects determined by the host genome). Additionally, transcription of the vector backbone and/or translation/stability of the primary transcript could also be susceptible to host genome effects, where toxicity could be affected by the level of transcription/translation factors in the host cell, all being genetically programmed.

Autoimmune disorders, especially T1DM, have been attractive candidates for gene therapy. The

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data by Zhang and colleagues are timely and important as they alert the field to host genetic background being as important a consideration as the choice of the vector itself in determining the success of the transduction strategy. Moreover, unreported failures of systemic viral gene transfer approaches for autoimmune disorders should now be revisited, keeping in mind the potential for genetic background effects on vector performance and antivector/transgene immunity. Furthermore, these findings should emphasize the necessity of combining gene therapy approaches with tolerance induction strategies to prevent the possible recurrence of autoimmunity, while concurrently surmounting host immune responses to the gene delivery vehicle and its genetic payload in allografts or recipient tissues.

Why the autoimmune background had such a profound effect in this study is presently unclear, but in line with the authors' conclusion, we speculate that autoimmunity may become a nemesis from the perspective of the therapist. We enthusiastically suggest, however, that mouse models of human autoimmune disorders will become a treasure trove for the geneticist interested in determining the interplay between genes and immune cells responsible for host genome-antivector/transgene phenomenon. ■

Nick Giannoukakis and Massimo Trucco are at the Diabetes Institute of the University of Pittsburgh, Rangos Research Center, Pittsburgh, CA, USA. e-mail: mnt@pitt.edu

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