Gene-environment interaction in type 1 diabetes mellitus

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Type 1 diabetes (T1D) mellitus can best be characterized as a disorder of gluco-regulation due to the insufficient production of a single critical hormone: insulin. Since the middle of the last century the most efficient pharmacologic solution has been to administer the hormone to the patient daily. Increasingly sophisticated dosing schedules together with the availability of recombinant variants of the hormone have succeeded in granting normal lifespan to type 1 diabetics. Nevertheless, no matter the degree of sophistication, current even aggressive regimens have not proven capable of faithfully recapitulating the normal performance of the endogenous insulin producing beta cells in response to glucose. This limit leads to the inevitable principal causes of morbidity and mortality associated with T1D, namely the complications of kidney and heart together with ocular and neural diseases.

While insulin replacement continues to be the primary treatment, the need to establish physiologic gluco-regulation in order to avoid complications has led to multiple avenues of alternative interventions, most of which are at the experimental stage. What all of these interventions have in common, however, is the hurdle imposed by the immune system at the level of ongoing autoimmunity and, in some cases, at the level of transplant rejection by the host1,2. Autoimmunity in T1D is characterized by an inflammatory response against the insulin-producing beta cells of the pancreas, a chronic inflammation around and in the pancreatic islets of Langerhans termed “peri-insulitis” and “insulitis”, respectively. As studied in the two classic rodent models of the disease (diabetes-prone BioBreeding, DP-BB, rat and non obese diabetic, NOD, prone mouse), early on in the acute phase of the immune attack the islets exhibit an abundant cell infiltration by mononuclear cells, macrophages and dendritic cells (DC). With time, T-cells become the major constituent of the insulitis and are responsible for the greatest beta cell damage and destruction. The clinical onset manifests once the number of surviving beta cells cannot secrete sufficient insulin to satisfy the body’s needs.

A strong genetic predisposition is a conditio sine qua non of T1D and a large body of studies support that key genetic susceptibility loci affect the genesis, function and survival of immune cell subsets. To understand the critical role played by the genetic predisposition in T1D, it is necessary to consider the processes that shape
molecules so that even strongly self-reactive T cell clo-
tive selection are altered by the disease-associated HLA
cular interactions that normally drive positive and nega-
with a suboptimal functional groove. In fact, the mole-
of the non-Asp57 alleles constituting class II molecules
due at the same position (Asp57). The importance of this
the disease was found to be associated with the inheri-
tance of an HLA-DQ allelic form with an aspartic resi-
due at the same position (Asp57). The importance of this
ano acid change has to do with the physical structure of
the non-Asp57 alleles constituting class II molecules with
a suboptimal functional groove. In fact, the mole-
cular interactions that normally drive positive and nega-
tive selection are altered by the disease-associated HLA
molecules so that even strongly self-reactive T cell clo-
es are allowed to escape to the periphery. 

Evidence of beta cell regeneration promoted by bone
marrow or stem cell allo-transplantation in new-onset
disease NOD mice has been observed by several
groups. On this basis we were not surprised to see that
in the NOD mouse as well, abrogation of autoimmu-
ity is sufficient to promote regeneration or rescue of the
insulin-producing beta cells in the host endocrine pan-
creas even after the onset of the disease. These studies
suggest that, although the physiological state of islet
cells tends towards a fully differentiated phenotype,
the lack of autoimmune aggression, together with the
“danger” signals generated by massive beta cell de-
struction may trigger processes inside progenitors (whe-
ter islet-resident or ductal epithelium-resident) that
result in some degree of islet cell regeneration. T1D
pathogenesis is then a dynamic process. Once self tol-
erance is lost and beta cells begin to be destroyed, the
system reaches a new equilibrium in which the newly-
differentiated beta cells are in turn eliminated by the
ongoing autoimmune process.

Interestingly, we have recently shown that the in vi-
tro treatment of DC with CD40, CD80, and CD86 an-
tisense oligodeoxyribonucleotides (AS-ODN), reduce
co-stimulatory molecule levels at their surface, produ-
cing functionally-immature DC capable of preventing
or reversing new onset diabetes in the NOD mouse. This
was accomplished while maintaining T-cell res-
ponsiveness to alloantigens in animals that received
repeated injections of modified DC. Co-stimulatory
depleted DC also augmented the number of T regu-
ulatory cells (Treg) that were CD4+ CD25+ Foxp3+
through short-range IL-7 signaling. We also are cu-
cently conducting an NIH-funded, FDA-approved
phase I clinical trial that is designed to test the safety
of AS-ODN-treated autologous DC into T1D patients
with established disease. Leukocytes of the pa-
ent are obtained by apheresis and DC are generated in
vitro from them and engineered in GMP facilities with
the addition of AS-ODN. In turn, these DC, which ex-
press low levels of CD40, 80, and CD86, are injected
into the patient by intradermal administration at an
anatomical site proximal to the pancreas. DC will
migrate to the nearest, i.e., pancreatic, lymph nodes,
where they are able to interrupt the vicious circle that
maintains islet-specific inflammation, i.e., insulitis. In
the pancreas, DC acquire beta cell specific antigens
from apoptotic cells, leading to the eventual display of
these antigens to naïve T-cells in the pancreas-draining
lymph nodes. The lack of co-stimulatory molecules
will result in an anergizing signal to the T-cells, induce
regulatory immune cells (like Foxp3+ Treg), and inter-
rupt the T-cell mediated anti-beta cell epitope-spre-
ding phenomenon. Within the endocrine pancreas,
thus far, we have not observed adverse events of any
sort, nor did the patients experience even subjective discomforts; the hematological and immunologic profiles after DC administration in all of the first six treated diabetic patients are similar if not identical to those measured at baseline pre-screening; there is no evidence of latent viral activation; there is no evidence of induction of any additional autoimmune reaction; there is no worsening of glycemia or increased insulin requirements; physical examinations and all biochemistry is within the normal range.

**Conflict of interest**

The author declares he has no conflict of interest.

**REFERENCES**


