

NEWS AND COMMENTARY

Autoimmunity Beyond the immune system

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Since lymphocytes are the active contributor of an immune response, it is usually assumed that genetic susceptibility to autoimmune disease is determined by defects in mechanisms that ensure lymphocyte tolerance. Lonyai *et al.*¹ challenge the assumption that the target organ remains invariant, and propose a role for genetic polymorphisms in target organ development and function in determining the susceptibility of an individual to autoimmune disease.

In this study, Lonyai *et al.* use the non-obese diabetic (NOD) inbred mouse model, which has a genetic predisposition for the spontaneous development of T-cell-dependent autoimmune diabetes. NOD mice are also prone to multiple other autoimmune disorders, spontaneously developing sialitis and dacryoadenitis and have increased susceptibility to experimentally induced autoimmune encephalitis, gastritis, thyroiditis, prostatitis and haemolytic anaemia, among other diseases. This multi-organ susceptibility has led to the investigation of defects in general immune tolerance mechanisms that could affect multiple targets, such as defective thymic negative selection.

Despite the abundance of data for immune tolerance defects in NOD mice, a role for additional target organ-intrinsic polymorphisms in directing autoimmunity towards specific organs has not been excluded. Several recent studies have suggested that for the pancreatic β islets at least, the target organ may be defective and that these defects may be involved in diabetes development. NOD.scid mice were used to test for autoimmune-independent NOD traits. These studies revealed abnormal development of the pancreatic tissue, increased insulin production and profound insulin resistance.^{2,3} NOD pancreatic islets also show an intrinsic resis-

tance to CD8⁺ T-cell-mediated destruction, a trait which is genetically linked to *TNFR2* within the diabetogenic *Idd9* loci.⁴ Another diabetogenic loci, *Idd4*, alters sensory neuronal control over the response of β islet cells to inflammatory infiltrate.⁵

The paper published by Lonyai *et al.* extend these findings to additional organs. As well as known defects in the pancreas, they observe structural defects in the cochlea, salivary glands and the tongue of NOD mice. As these defects are also observed in NOD.scid mice, they appear to be primary developmental defects rather than secondary changes due to autoimmunity. The developmental defects in the cochlea are severe enough to result in near-complete deafness, while the functional defects in the pancreas, salivary glands and tongue are subclinical in the absence of the adaptive immune system.

Intriguingly, Lonyai *et al.* note that the pancreas, salivary glands, cochlea and tongue are all dependent on Hox11 for development, raising the spectre that the developmental defects observed in NOD mice have a common genetic causality. As the pancreas and salivary glands represent two early targets of spontaneous autoimmunity in NOD mice, these structural defects may be involved in the susceptibility of the organs to autoimmune attack. Potential mechanisms by which structural defects could increase susceptibility to autoimmunity include increased immune priming or reduced resistance to inflammation. Enhanced levels of immune priming could occur through altered barrier permeability allowing increased leukocyte traffic through the tissue, or by increased spontaneous apoptosis in the tissue seeding the draining lymph nodes with an enhanced antigen load. A reduced resistance to inflammation could occur through decreased cellular fitness, where individual constituent cells die at a lower level of inflammatory pressure, or through reduced tolerogenic potency,

wherein tolerance inducing pathways within the tissue are impaired.

The authors note that in humans, type I diabetes and Sjogren's syndrome frequently co-occur and are commonly associated with both hearing loss and taste abnormalities, recapitulating the Hox11-dependent tissue quartet. These effects could be due to secondary consequences of autoimmunity against a primary target. However, the results from NOD mice raise the possibility that genetic variation in target organ development may contribute to the susceptibility to autoimmunity in human populations (Figure 1). This question has not yet been directly addressed, but there is, however, three independent lines of epidemiological and genetic data that indicates that in autoimmune diabetes, at least, polymorphisms in pancreatic function may contribute to disease progression.

First, within the population of children who develop autoimmune diabetes, progression from subclinical to clinical autoimmunity is more rapid in obese children.⁶ Second, 10% of all patients that first present with metabolic type II diabetes progress to autoimmune type I diabetes within 5 years, with linkage to the same genetic polymorphisms that are associated with type I diabetes.⁷ Third, gestational diabetes is caused by metabolic pancreatic dysfunction during the stress of pregnancy and has familial linkage to both autoimmune type I and metabolic type II diabetes.^{8,9} While none of these findings are definitive, they are suggestive of the existence of genetic polymorphisms (and environmental factors) that impair pancreatic development or function and thus contribute to the incidence of autoimmune type I diabetes. The correlation of Hox11 expression with organ defects in both the NOD mice and in humans suggests that common polymorphisms could be altering the susceptibility of multiple target organs simultaneously, resulting in the observed quartet of comorbidity. Hox11

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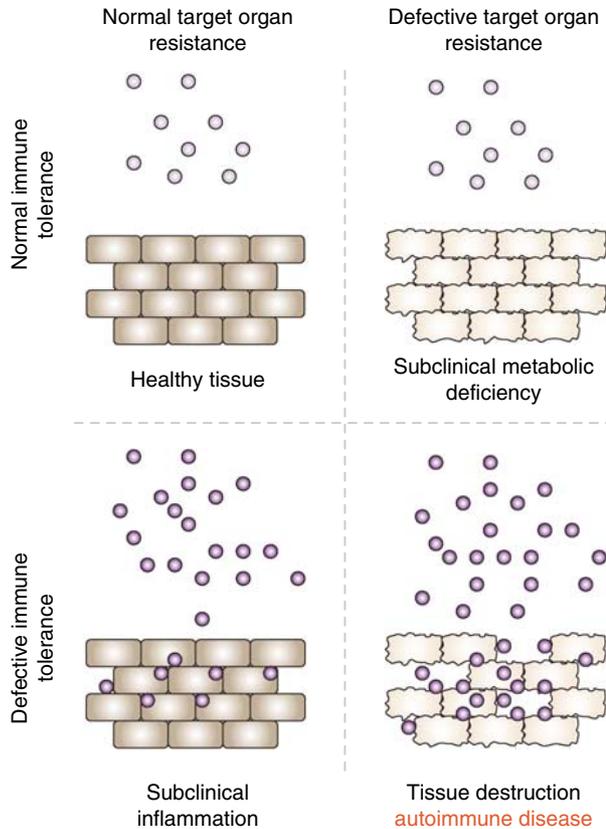


Figure 1 Synergistic effects of defects in immune tolerance mechanisms and target organ resistance. Under a synergistic model of autoimmune susceptibility, genetic defects in immune tolerance lead to inflammation, while genetic defects in target organ function or development lead to metabolic deficiency. Either alone present with subclinical effects, however the combination allows the otherwise subclinical inflammation to destroy the weakened tissue and precipitate clinical autoimmune manifestations.

itself, however, is a poor candidate, as it has not been linked to diabetes in either NOD mice or humans.

Beyond diabetes, there are several examples where polymorphisms in target organ function have been formally associated with susceptibility to autoimmune disease. The obese strain chicken develops autoimmune thyroiditis, with genetic susceptibility dictated by a combination of dominant polymorphisms involved in immune tolerance failure and recessive polymorphisms that determine thyroid susceptibility to immune destruction.¹⁰ Another example is the association of Crohn's

disease with polymorphisms in CARD15. These polymorphisms result in defective function of resident intestinal cells in recognizing commensal microflora, and increase the risk of development of autoimmune gastrointestinal disease.¹¹

Despite the attractiveness of the hypothesis, caution is warranted when interpreting the contribution of any particular NOD defect in the development of autoimmunity. It would certainly be an unlikely coincidence if the developmental defects in multiple target organs of NOD mice were completely independent of the susceptibility of these organs

to autoimmunity. However, from the NOD mice we have learnt to expect unlikely coincidences, and the literature abounds with NOD defects which ended up being unrelated to their susceptibility to autoimmunity. The next stage of research will be to test whether these organ-intrinsic abnormalities have pathological consequences during the development of autoimmunity.

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