Type 1 and Type 2 Diabetes Susceptibility in Mice: Is There Genetic Overlap?

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My 34 year career at The Jackson Laboratory has focused on the interaction between genetic and environmental factors that predispose inbred mouse strains to develop diabetes: both autoimmune and non-autoimmune forms of Type I insulin-dependent diabetes (T1D), and Type 2 diabetes (T2D), associated with insulin resistance and obesity ("diabesity"). The premiere mouse model for autoimmune, T-cell mediated T1D, the NOD mouse, has a female sex bias whereas nearly all the diabesity models of T2D in mice are male sex-limited. Despite the sex differences, it seems intuitive that T2D-associated genes contributing to obesity, to impaired glucose tolerance/weaker beta cell function, or to impaired endocrine signaling could, in certain mouse strain combinations, synergize to produce a more rapid onset autoimmune T1D. My lecture will examine this question, using studies published by others in the literature as well as by genetic outcrosses done in my own laboratory. The findings argue that there is little or no genetic overlap . Indeed, a spontaneous mutation in the extracellular domain of the leptin receptor in NOD/ShiLtJ mice superimposed an insulin resistant diabesity syndrome onto a model destined to exhibit autoimmune destruction of the beta cells. Although the superimposed diabesity syndrome elicited a much earlier development of hyperglycemia, the autoimmune syndrome was suppressed, and many of the obese mutant NOD mice, especially females, actually underwent spontaneous remission from hyperglycemia while pancreatic beta cell mass continued to increase. Hence, in the mouse at least, the metabolic disturbances associated with a T2D syndrome fail to promote an earlier onset autoimmune attack on the beta cells, but rather retard or prevent it.