Milestone 4

Animal models of T1D

Animal models of type 1 diabetes (T1D) enable the study of mechanisms underlying its pathogenesis and the development of therapeutic interventions. One of the most widely used models of the disease is the spontaneous diabetic Wistar rat, commonly referred to as the BB rat, which was first described in 1974 and then more extensively reported on in 1978 by Nakhooda and colleagues.

This group performed a longitudinal study of 51 weanlings from insulin-treated diabetic male and non-diabetic female parents with the specific aim of tracking the evolution from normoglycaemia to overt diabetes. In order to characterize the disease onset and early development, they monitored daily food and water intake, as well as body weight, and collected urine and blood samples. These samples were collected biweekly as diabetes was left untreated until the animals' condition mandated sacrifice, at which point the pancreas was removed for histological staining.

Changes in analysed parameters were referenced to the onset of overt diabetes, defined as the first day of detected glycosuria. They found that 9 of 51 animals became overtly diabetic, but the time of onset varied considerably (40–87 days), as did incidence between litters (9–50%). They also noticed that the onset of glycosuria was accompanied by rapid weight loss. Concurrently, the researchers measured a sharp increase in plasma levels of glucose and glucagon, as well as a decrease in insulin levels, for all 9 overtly diabetic animals. This dysregulation of glucose homeostasis was also detected via significant increases in plasma free fatty acid and total blood ketone concentrations.

Furthermore, oral glucose tolerance tests showed abnormal glycaemic responses in 6 of 9 rats compared with age-matched non-littermate controls. Finally, histological staining revealed that islets of select diabetic rats were smaller, less numerous and composed mostly of non β-cells; however, end-stage morphologies differed considerably.

One of the main take-home messages of this study was the recognition that disease onset and progression are rapid, occurring on the timescale of hours to days, but also heterogeneous. Many other groups would use the BB rat model in the coming decades to study T1D, including in the context of genetics, environmental factors and autoimmunity.

This article would certainly not be complete without mentioning the non-obese diabetic (NOD) mouse model, which was first described by Makino and colleagues in 1980. Along with the BB rat, this mouse model has proven useful for preclinical T1D research and is associated with several advantages linked to its better-defined genome, greater availability of lab reagents and imaging tools, and lower maintenance costs.

The first NOD mouse was generated during routine breeding of CTS mice, and discovered owing to its abnormal polyuria and glycosuria, accompanied by rapid weight loss. Although this first mouse died within 1 month, the researchers were able to establish the NOD strain via selective breeding, specifically by using its offspring to generate eight mating pairs tested for spontaneous diabetes and reproductive ability — a huge effort that involved more than 1,500 mice in total.

It is important to point out that, although other groups had previously generated hereditary diabetic mouse strains suitable for the study of maturity-onset diabetes or juvenile-onset diabetes induced by a virus or chemical, the NOD mouse was the first spontaneous non-obese diabetic strain.

Researchers tracked body weight and water intake, as well as urine volume, food consumption, plasma and urine glucose levels, and plasma cholesterol over time, defining the onset of diabetes based on a commercial urine glucose test. Interestingly, they found much higher incidence rates in females (80%) than in males (10%), the latter also featuring later disease onset. Histological analyses revealed lymphocyte infiltration into pancreatic islets, as well as a reduction in the number of β-cells and size of islets.

These two animal models of T1D have advanced our understanding of disease pathophysiology. Still, clinical translation of therapeutics has remained challenging, as curative success is dependent on treatment dose, timing and other parameters. Researchers in the field now agree that, although useful, these remain mere models and insights gained cannot be directly applied to humans. In fact, clinical trials have shown that numerous therapeutic interventions that were effective in animals later proved ineffective for patients with diabetes. Much work has focused on this issue and more remains to be done for the development of bona fide models to guide translation and more accurately predict therapeutic outcomes in humans.

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Milestone studies
Nakhooda, A. F. et al. The spontaneously diabetic Wistar rat (the "BB" rat). *Diabetologia* **14**, 199–207 (1978) | Makino, S. et al. Breeding of a non-obese, diabetic strain of mice. *Exp. Anim.* **29**, 1–13 (1980)

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