Type 1 Diabetes

Sefina Arif, King's College, London, UK

Type 1 diabetes (**T1D**) is a chronic **T-cell mediated disease** that leads to the destruction of the insulin-secreting islet **β-cells** (**Figure 1**) resulting in absolute insulin deficiency and hyperglycaemia.

Epidemiology

Type 1 diabetes (T1D) accounts for about 5-10% of all patients with diabetes and the worldwide incidence is increasing by ~3 % every year. There is considerable geographical variation in the prevalence of the disease with the highest incidence seen in Finland and Sardinia and the lowest in Venezuela.

Pathology

The clinical presentation of T1D is preceded by an asymptomatic period lasting from months to years which is characterised by **autoantibodies** against islet β-cell components. Insulin autoantibodies are amongst the first to appear, followed by autoantibodies to glutamic acid decarboxylase (GAD) and then spreading to IA-2 (insulinoma-associated tyrosine phosphatase protein) and ZnT8 (zinc-transporter 8); indeed, the presence of multiple autoantibodies is diagnostic of stage 1 of T1D (Fig 1).

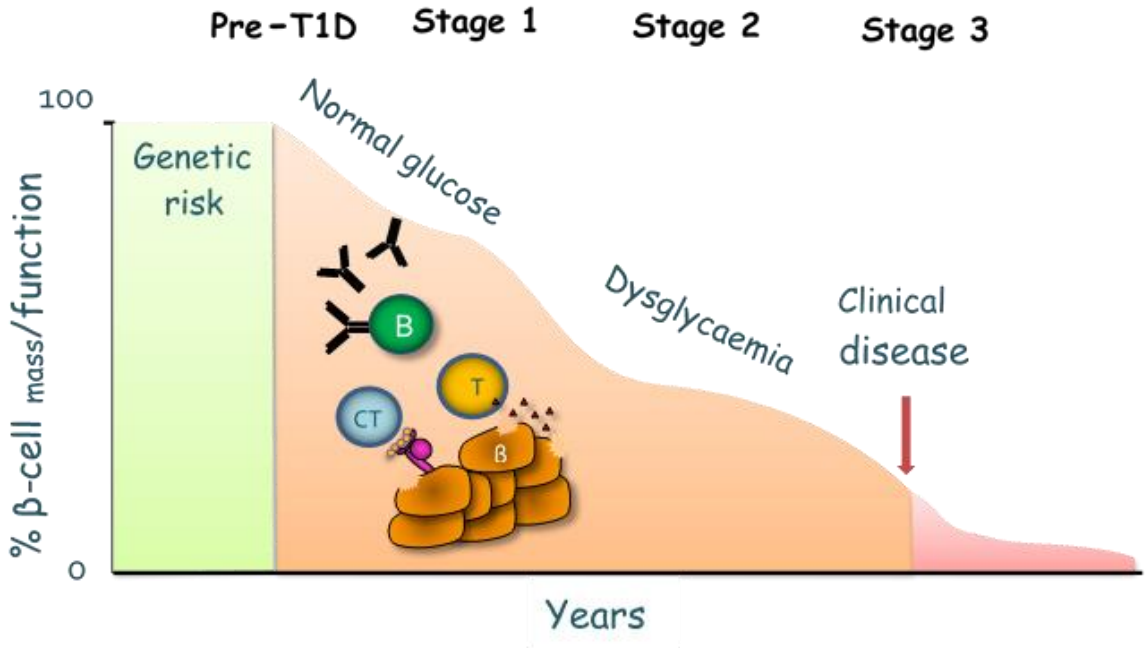

Figure 1. Progression to T1D. A possible environmental trigger can activate an autoimmune response in individuals with a genetic predisposition to T1D, resulting in the production of autoantibodies followed by insulitis which impairs β-cell function leading to clinical disease onset.

Type 1 Diabetes

Sefina Arif, King's College, London, UK

The destruction of the islet β-cell in T1D is the result of a complex interplay between multiple players of both the innate and adaptive immune system; immunohistochemical analysis of islet inflammation from pancreata of patients with T1D obtained at autopsy indicate a mononuclear cell infiltrate in islets (termed insulitis) consisting mainly of macrophages, **B cells** and **T cells**. Both **CD4+** and **CD8+ T cells** are required for disease development, by destroying the insulin-producing β cells through the effector functions of **Th1 cells** and direct killing by **cytotoxic T lymphocytes** (**CTLs**) (Fig 2). CTLs initiate killing by various mechanisms including the production of inflammatory cytokines such as **TNF-α** and **IFN-γ**, which act synergistically with **IL-1** produced by macrophages in targeting the β-cells; they also directly kill β-cells through the secretion of **perforin** or by **apoptosis** by the activation of the **Fas-Fas-L pathway**.

The rate and extent of β-cell destruction can vary amongst patients, as can the age of onset and the number and type of autoantibodies present at diagnosis thus T1D is heterogenous in presentation.

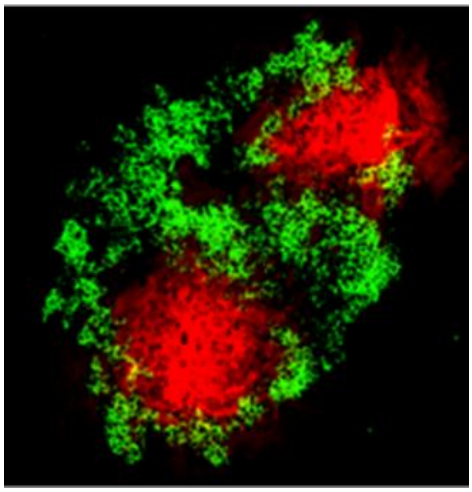

Figure 2. Insulitis. A pancreatic islet (insulin in red) being invaded by T lymphocytes (green).

Genetics

Type 1 diabetes is polygenic disease with a strong genetic component. The major susceptibility locus for T1D maps to the HLA region on chromosome 6p21 and this accounts for 30-50% of the genetic risk; specifically, these are the loci *HLA-DRB1 and HLA-DQB1*. The highest risk DR/DQ haplotypes for T1D are DR3-DQA1*0501-DQB1*0201 (DR3) and DR4-DQA1*0301-DQB1*0302 (DR4). In addition, more than 40 non-HLA, loci have been confirmed which impart a smaller effect on disease risk – these include the insulin gene, CTLA-4, PTNP22, and IL-2RA.