Type I Diabetes

Tuesday, February 19, 2008
9:00 AM

- Diabetes Mellitus: systemic disease with multiple metabolic abnormalities, mainly elevation in plasma glucose (lipid metabolism, ketones)
- Classification
  - Type I
    - Immune Mediated - 85%
    - Idiopathic - 15%
  - Type II
  - Other types (MODY, secondary DM)
- Signs of Type I: Polyuria; Polydipsia (thirst); Polyphagia (hunger); weight loss; fatigue; increased frequency of infections; rapid onset (type II is much slower progressing); insulin dependent; early onset
- Differences between type I and II: type I has islet cell antibodies and patients are typically thin
- Polygenic: HLA linkage, non-MHC genes
- Autoimmune etiology: antibodies to islet autoantigens, autoreactive T cells
- Immune modulation alters course: antigen vaccination, general immunosuppression
- Type I is chronic autoimmune disease but can also develop in adults/elderly
- Loss of first phase insulin response (pre-diabetes)
- Diabetes full blown once mass is below 10%
- Genetic Links
  - Elevated cytokines (IFNγ, IL-1β, TNFα, etc.)
  - Increased apoptosis/necrosis, decreased neogenesis
  - Hyperglycemia --> glucose toxicity
  - Environmental Factors
  - All combine to lead to β cell death
- Multiple factors
  - Autoreactive T cells --> islet autoantibodies (not shown to directly kill β cells)
    - Father has greater effect than mother --> imprinting
    - HLA class II genes have highest incidence
  - HLA complex: (DQ2, DQ8), DR3, DR4 are most associated w/ Type I
  - Sibling sharing 2 HLA haplotypes w/ type I affected sibling at much higher risk of developing
- Environmental factors
  - Congenital rubella syndrome - similar antigens to those in Type I DM --> immune response
  - Cocksakie B virus?
  - Enterovirus?
  - Streptozotocine (low doses)?
- Loss of self tolerance to self-antigens
• Insulin - main antigen in T1DM
  • GAD65
  • ICA512/IA-2
  • Znt8 - 60% of Type I
  • Can be one or multiple antigens
    ▪ Starts w/ insulin --> epitope spreading to GAD, Znt8, IA2
  • Theory is that not enough insulin enters thymus during T cell development --> recognition as non-self
• T Cells
  • Cell-mediated immunity
    ▪ CD4
    ▪ CD8
    ▪ NK cells?
    ▪ M'phages?
    ▪ Dendritic cells?
  • Normal individuals have balance btwn pathogenic and regulatory T cells
    ▪ T1D prone express too much pathogenic/too little regulatory
    ▪ T1D protected are reverse
  • XLAAD
    ▪ FOXP3 stop codon
    ▪ Genetic defect can lead to type 1 diabetes in presence of other autoimmune disorders for abnormalities in regulatory T cell maturation
    ▪ Tregs may play role in suppressing possible autoimmune disorders
• Cytokines: CD4 T cells
  • IL-12 --> Th1 --> IFN-γ, IL-2 --> cell-mediated immunity, autoimmunity, pro-inflammation, allograft rejection
  • IL-10 + IFN-α --> Tr1 --> IL-10 + TGF-b --> suppression/regulation
  • IL-4 --> Th2 --> IL-4/5 --> humoral immunity/anti-inflammatory
  • IL-β, IFN-γ, TNF-α --> oxidative stress --> NO production --> β cell death
• Role of Autoantibodies
  • Markers of disease
    • GAD65, IA-2, Insulin, Islet cell
  • Assays
    ▪ Immunoprecipitation for GAD-65, IA-2 antibodies
    ▪ Radioimmunoassay for insulin antibodies
    ▪ Immunoperoxidase staining for islet cell antibodies
  • More antibodies --> increases probability of developing type II
• Conclusions
  • Type I DM is a polygenic disease w/ HLA DR3, DR4 having the strongest effect
  • CD4 and 8 T cell responses to islet autoantigens are pathogenic
  • Defect of Reg T cells in suppressing pathogenic autoimmune responses is assoc w/ Type I DM
  • Proinflammatory cytokines IL-β, IFN-γ, TNF-α can cause β cell death
  • Gene defects in FOXP3 and AIRE cause multiple autoimmune diseases incl. T1DM
  • Presence of antibodies to insulin, GAD-65, IA-2 are high risk markers of T1D progression