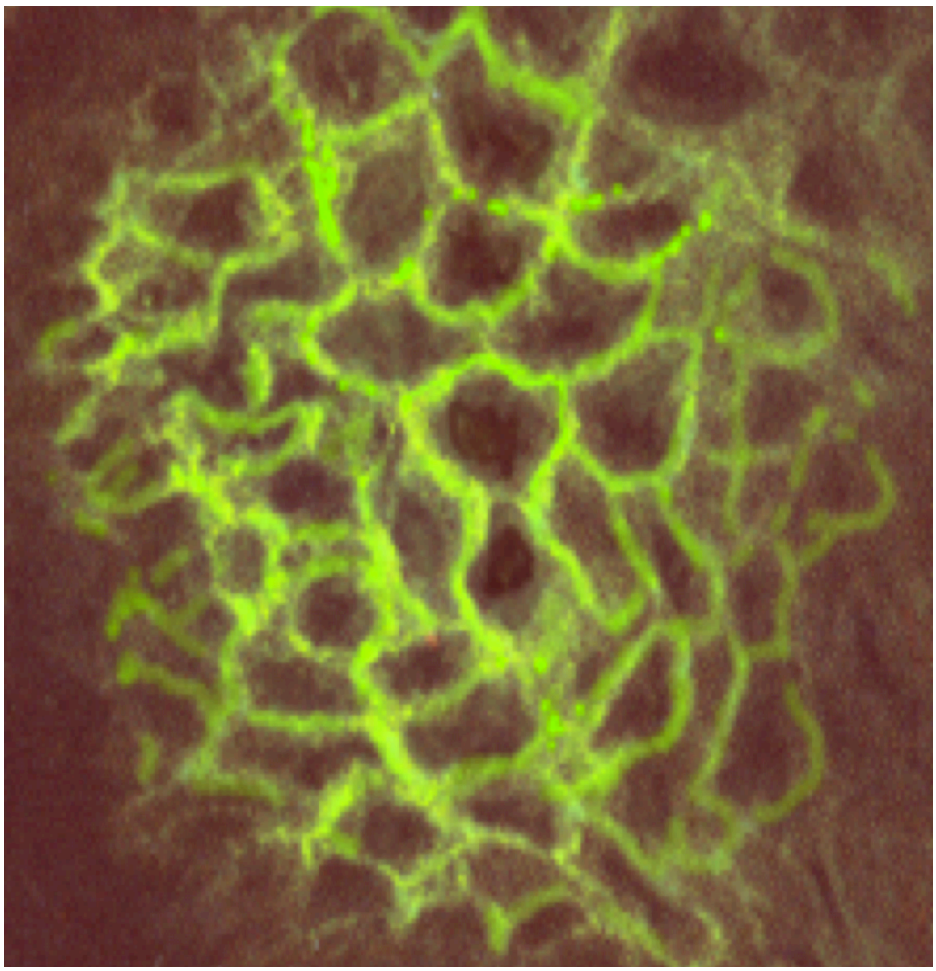
Lecture 21. The Genetics of Autoimmunity

Learning Objectives and Summary



Immunfluorescence micrograph of skin biopsy incubated with serum obtained from a patient with Pemphigus vulgaris. Disease susceptibility is conferred by the HLA DRB1*0402 allele. Using this allele, investigators were able to identify HLA DRB1*0402-binding peptides. Seven of these peptides were contained within desmoglein, which is present in intercellular junctions in the epidermis

21. Genetics of Autoimmunity

Learning objectives:

1. Understand the immunologic features of autoimmune disease and how autoimmunity is an extension of the way in which the T cell repertoire of the adaptive immune system is selected on self peptide-MHC.
2. Appreciate how different autoimmune diseases are driven by the recognition of different autoantigens and have different effector mechanisms that result in injury.
3. Understand the role MHC genes play in autoimmunity through selection of the T cell repertoire and how autoimmunity evolves to autoimmune disease.

SUMMARY

1. The fundamental abnormality in autoimmune diseases is that the adaptive immune system is triggered by self-peptides to initiate an immune response against self-molecules that results in tissue injury. This reflects the fact that T cell repertoire of the adaptive immune system is generated by selection of T cells on self-peptides presented by self-MHC molecules.

2. The identification of autoantibodies led to the concept of autoimmunity; however, the fundamental defect in autoimmunity is inappropriate and sustained activation of T cells.

3. Effector processes mediating tissue injury in autoimmune diseases are like those found in many other immune responses and can be grouped as Types II, III and IV (corresponding to the Gell-Coombs classification of hypersensitivity).

4. There is a strong genetic predisposition to develop autoimmune diseases. Evidence for this includes familial aggregation in blood relatives and high identical twin concordance for these diseases, although most modes of inheritance suggests several genes are responsible.

5. Among the genes identified that confer susceptibility, particular MHC alleles confer the greatest relative risk, implying that T cell recognition of peptide-MHC is a central event. However, most evidence suggests that self-peptide is not strongly bound by the MHC molecule (low peptide-MHC affinity), thus allowing for positive selection in the thymus. However, this might allow the survival of T cells with even very high affinity for the self-peptide (high affinity of TCR with peptide-MHC), and the potential for autoimmunity.

6. Autoimmune diseases develop in previously healthy individuals many years after birth and the disease “appears” to be acquired because critical stochastic and/or environmental factors act on the adaptive immune system to convert genetic susceptibility to actual disease.

7. The events underlying the pro-autoimmune T cell repertoire generation include those that affect central or peripheral repertoire generation, tolerization, as well as pathways that intensify immune responsiveness or reduce its regulation.

8. Rheumatoid arthritis is distinctive because susceptibility is associated with a structural motif shared by a group of MHC alleles.

9. MHC haplotypes are central to the genetic basis of autoimmune disease because a T cell positively selected by one MHC molecule may be eliminated by another MHC allotype during negative selection. Therefore all the MHC alleles on a haplotype may influence disease susceptibility, either positively or negatively. This is as illustrated by the strong susceptibility to develop T1 DM or to be resistant to the disease as specified by combinations particular HLA-DR and HLA-DQ alleles. (NB the numerical allele details of this are not important to remember but the overall concept is central to understanding how MHC molecules influence the T cell repertoire).

10. MHC haplotypes are highly ethnic in their distribution and account for the varying frequencies of autoimmune diseases in different populations. The haplotypes reflect both biologic selection and founder effects. They provide an interesting perspective on history