Immunoglobulin diversity

Introduction

- An immunoglobulin (Ig) consists of 2 identical light chains (L) and 2 identical heavy chains (H) (for example IgG-type); at the three-dimensional level, an Ig chain consists of one N-terminal variable domain, V, and one (for an L chain) or several (for an H chain) C-terminal constant domain(s), C.
- The cells of the B line synthesize immunoglobulins. They are either produced at a membrane (on the surface of the B-lymphocytes) or are secreted (by the plasmocytes).
- B cells can generate antibodies to a large variety of chemical structures. The number of B cells in an individual is limited.

Theories to explain the diversity of antibodies

Before it was possible to examine the immunoglobulin genes directly, there were two main hypotheses for the origin of this diversity.

- The germline theory held that there is a separate gene for each different immunoglobulin chain and that the antibody repertoire is largely inherited.
- By contrast, **somatic diversification theories** proposed that the observed repertoire is generated from a limited number of inherited V-region sequences that undergo alteration within B cells during the individual's lifetime.
- Cloning of the immunoglobulin genes revealed that the antibody repertoire is, in fact, generated by DNA rearrangements during B-cell development.

How a large number of antibodies produced?

- generation of diversity……
- The exons encoding the antigen binding portions of the receptor (the so-called variable regions) are assembled by chromosomal breakage and rejoining in developing lymphocytes
- The exons encoding the antigen binding domains are assembled from so-called V (variable), D (diversity), and J (joining) gene segments by “cut and paste” DNA rearrangements.
- This process, termed V(D)J recombination, chooses a pair of segments, introduces double-strand breaks adjacent to each segment, deletes (or, in selected cases, inverts) the intervening DNA, and ligates the segments together.
- Diversity is tremendously amplified by the characteristic variability at the junctions (loss or gain of small numbers of nucleotides) between the various segments.

Antigen receptor variable exons are assembled by V(D)J recombination Assembly of a complete variable exon occurs in two steps (in the case of an Ig heavy chain gene or a TCR beta or delta gene), as shown. First, a D and a J segment are chosen from among several possibilities, and are brought together to form a D-J rearrangement. Then a V region is selected and joined with the D-J rearrangement to form a complete VDJ exon. Immunoglobulin light chain genes and TCR alpha and gamma genes rearrange in a single step, involving V-J recombination, as D segments are absent from these loci.