ONWUEGBUNAM CHIAMAKA LAURA

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1. ANTIBODY DIVERSITY: SUMMARY

a) About 50 Vκ-genes exist in the human genome. This is a fairly large number, much higher than somatic theories predicted, although smaller than predicted by most germ- line theorists.

b) Five different Jκ-segments exist in the human genome. Thus, if every V-region can be used with any J-segment, a total of about 250 (50 x 5) different combinations can be made. (In the case of heavy chains, the existence of several D-segments increases this number even more.) This process is referred to as COMBINATORIAL JOINING.

c)DNA rearrangement is imprecise. The joining of V and J (and the joining of D segments to V and J) is a deliberately error-prone process, resulting in random nucleotide substitutions and deletion/insertions at the site of rearrangement. Therefore, the joining of a particular V-region and a particular J-segment can yield different results in different cells in which it occurs. If this increases the number of potential V-regions by about ten-fold, we now have about 2500 possible kappa chain V-regions (250 x 10).

d) Somatic mutation occurs in rearranged V-regions. Expressed kappa chain genes have been cloned and sequenced from many antibody secreting cells, and in most cases

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they have been found to differ from any existing germ-line V-region in sequence positions other than the site of joining of V and J. These somatic mutations tend to be localized to the hypervariable regions, and occur by a local relaxation of the normal processes of error-correction in newly synthesized DNA. The presence of these mutations may increase the number of possible V-regions by another ten-fold or more, resulting in at least 25,000 different kappa V-region sequences (2500 x 10).

e) Heavy and light chains associate in random combinations. If a comparable number of different H-chain V-regions can be produced (which is an underestimate), then there are potentially some 6x108 different antibody combining sites (25,000 X 25,000), a number considerably larger than the one million we initially set out to explain. This random association of H- and L-chains is referred to as COMBINATORIAL ASSOCIATION.

2. IMMUNE RESPONSE TO TUMOURS.

The immune response to tumors is complex. Cells of the immune system can inhibit tumor growth and progression through the recognition and rejection of malignant cells, a process referred to as immunoediting. Yet, immune responses can also promote tumor cell growth, survival, and angiogenesis through the induction of oncogenic inflammation. Immunodeficiency can predispose to the development of spontaneous and virally induced cancer, and established tumors often generate immunosuppressive microenvironments that can block productive antitumor immunity, serving as a substantial barrier to effective immune therapy. Through a deeper understanding of the complicated relationship between tumors and the immune system, tumor immunology strives to harness the immune system to generate protective antitumor responses in patients.

IMMUNE RESPONSE TO ORGAN TRANSPLANTATION

Immunosenescence is the process of progressive dysfunction of the immune system that increases the susceptibility of the elderly to infection, autoimmune disease, and cancer, contributing significantly to morbidity and mortality of the elderly.

The aging process causes important anatomical and functional changes in a number of systems that result in reduction of the functional reserve and inability to cope with stress. As the functional reserve decreases, organs are exposed to overload during stress conditions, resulting in a vicious cycle activating the immune system while contributing to tissue injury and reduction of function.

The immune system undergoes a complex and continuous remodeling with aging. Immunosenescence changes result into both quantitative and qualitative modifications of specific cellular subpopulations rather than a global deterioration of the immune system, as previously thought. Even stem cells, despite their extensive proliferative and regenerative capacity, how signs of aging.

The most striking alterations are found in phenotypes and functions of T-cell components and less frequently in components of the natural (innate) immune system. Consequently, chemotaxis, phagocytosis, natural cytotoxicity, and complement activity are relatively well preserved in elderly individuals. Most alterations of B cells seem secondary to T-cell dysfunction.