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SCHWERPUNKT

ARBEITSVORHABEN

Somatische Mutationen und deren Rolle in der Evolution des Immunsystems

Lymphocytes are circulating cells expressing a repertoire of antigen-binding receptors directed against potential pathogens. The human genome carries 25,000 genes, but there can be almost as many different receptors as there are lymphocytes in the body (1,000,000,000,000). This vast diversity, the basis of vertebrate adaptive immunity, is created by somatic mechanisms that involve

DNA lesions. The lesions instigate DNA changes and recombination between different gene components. In the antibody-producing B cell, the genes are subjected to V(D)J gene rearrangement during differentiation and, after activation

by antigens, heavy chain switch recombination and somatic hypermutation. The first creates the diverse receptors, and the second secures a functional change in the non-ligand-binding part of the antibody (for example, signaling phagocytosis instead of initiating bacterial cell lysis). The third, hypermutation, causes nucleotide substitutions in the DNA sequence, which results in altered antibody protein sequence; this process produces improved antibody binding to ligand and therefore more efficient removal of the pathogen.

All the DNA changes, whether mutation or recombination, start with DNA breakage. The right results improve survival of the organism, but the wrong results decrease viability. We would like to explore what factors in the history of

host-parasite interactions and what environmental/pathogenic pressures might have given rise to mechanisms involving systematically induced DNA lesions that, however regulated, include risks for chromosomal damage and oncogenesis.

Recommended Reading

Lee, S. S., D. Fitch, M. F. Flajnik, and E. Hsu. "Rearrangement of immunoglobulin genes in shark germ cells." J. Exp. Med. 191 (2000): 1637-1648.

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The evolution of multiple isotypic IgM heavy chain genes in the shark

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