CHAPTER 13

Immunogenetics of Aging

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Abstract

Deterioration of the immune system with aging is associated with an increased susceptibility to infectious diseases, cancer and autoimmune disorders. It has been demonstrated that immunosenescence is associated with chronic, low-grade inflammatory activity. The aging process is very complex and longevity is a multifactorial trait, which is determined by genetic and environmental factors and the interaction of "disease" processes with "intrinsic" aging processes. It is hypothesized that the level of immune response as well as possibly longevity could be associated with genes regulating immune functions. It is further hypothesized that the diversity of these genes might influence successful aging and longevity by modulating an individual's response to life-threatening disorders. Several studies have focused on the role of genes encoding molecules with immune functions. In this chapter we will review the data on the role of HLA and cytokine gene polymorphisms in human longevity and comment on the future directions in this field.

Aging is a complex process and longevity is a biological phenomenon which shows a large inter-species as well as inter-individual variability that could be determined by the interaction of many factors: genetic background, environment, lifestyle and nutrition. The somatic theory explains aging in terms of accumulation of mutations in the genome of somatic cells leading to cell senescence, cell death or transformation, as well as loss of function. A variety of models in different species demonstrate that mutations in different genes are able to induce a consistent and marked increase of the lifespan. Most of these genetic variations which significantly impact upon longevity address a limited number of pathways highly conserved in evolution. Assuming that Homo sapiens is not an exception to this order, many studies over the last few years have been focused on these evolutionarily conserved pathways in order understand the genetics of human aging and longevity. Furthermore, genetic heritability of human lifespan was confirmed by investigations in different populations showing heritability estimates between 0.10 and 0.33 and therefore that genes account for about 25% of longevity determination.

Different approaches have been applied in order to search for genetic determinants of human longevity. One of these approaches, utilized by the Leiden research program on aging, is a population approach that focuses on determinants of age-associated diseases, to explain the majority of disabilities and impaired well-being at old age. Recently, approaches that identify longevity genes in model organisms were combined with approaches in man focusing on genes evolved for somatic maintenance and repair mechanisms aimed to clarify determinants assuring human longevity. Another approach to discover genomic regions associated with longevity is based on methods that allow for an extensive sampling of the genome, without making any a priori assumptions about "candidate" loci. The advantage of such a strategy is that the search for longevity-associated loci is not restricted to the small number of already-known candidate genes, but is potentially extended to the whole genome. Several studies have also focused on polymorphic microsatellite

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loki and indicated an association between increased microsatellite instability and aging. One of the possible causes for this could be age-associated impaired mismatch repair capacity, leading to the accumulation of DNA damage, resulting in alterations of cellular functions and increased incidence of diseases in elderly. Another investigation was based on screening of Alu sequences, repetitive elements interspersed on all chromosomes and constituting more than 10% of the human genome. Genomic regions enriched in Alu sequences are potentially unstable and mutations may cause the exonization of intronic Alu sequences, with important effects on gene expression and functionality. Interestingly, Alu elements are not randomly scattered throughout the genome. On the contrary, as many as 45% of Alu elements are contained within genes; and they are found to be highly clustered in genes that are involved in metabolism, transport and signaling processes. Thus, Alu sequences may be seen as good markers of highly variable and potentially unstable loci in functionally important genomic regions.

In order to identify genes responsible for human longevity, some recent studies were based on the model of centenarians, as these individuals represent the best example of successful aging. These studies have shown that centenarians largely escape most of the major age-related diseases and that they are characterized by a complex remodeling of immune responses, and particularly by largely conserved or even upregulated innate immunity. Chronic low-grade inflammation appears to be a major component of the most common age-related diseases, such as diabetes, osteoporosis and osteoarthritis, dementia, cardiovascular diseases and cancer. Moreover, there is evidence that glucose utilization is remarkably well-conserved and insulin resistance remarkably absent or is very low in centenarians, suggesting that they are also characterized by a well-conserved IGF1/insulin pathway. Data in animal models and evidence in centenarians suggest that longevity is associated with the capability of cells to cope with a variety of stressors, including oxidative stress.

Using these approaches, different investigations have shown that human longevity might be associated with several functionally different genes such as genes involved in DNA repair, cell proliferation and apoptosis (p 53 p 66); insulin/IGF1 signaling pathway; genes that counteract oxidative stress (e.g., Paraoxonase1); polymorphic genes related to immune responses and inflammation. However, the data on genes involved in the regulation of immune response are still limited and here we focus on the impact of such genetic factors.

**Immunity and Aging**

The ageing process seems to be directly correlated with immune deterioration, resulting from the combination of different genes and environmental factors. Several studies showed that senescence of the immune system is related to a decrease of cellular and humoral responses and an increased frequency of infectious, autoimmune and malignant diseases. The T-cell-mediated immune responses are more strongly affected in comparison with humoral immune responses. T-cell proliferation to antigens and mitogens, as well as cell-mediated cytotoxicity, decrease with age. Senescence negatively influences the membrane structures participating in the early stages of T-cell activation, as well as the transcription factors regulating gene expression. These age-associated changes also affect the distribution of the T-cell subpopulations. A decrease in absolute number of CD4+ and CD8+ subpopulations was found with age. An increase in the relative proportion of CD8 lymphocytes not expressing CD28 is commonly found in the elderly. "An immune risk phenotype" (a low number of CD4, a high number of CD8, decreased production of IL-2 and poor proliferative responses to mitogens, less CD28+ and CD57+ cells) which is predictive of a shorter remaining lifespan in the very elderly has been described. Decreased antibody responses to exogenous antigens result from both suppressed T-cell function and B cell functional activity. Although there is an increased absolute number of NK cells in the peripheral blood, their functional capacity is reduced with age, which contributes to a higher susceptibility to malignant and viral diseases. Nowadays, it is accepted that many aspects of senescence are characterized by inflammatory status and that senescence is associated with a chronic low-level inflammatory activity leading to tissue damage. The established "immune risk phenotypes" are likely to be related to an inability to control the systemic inflammation. However, the extent to which these changes depend on the