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Human Clonal Hematopoiesis Cancer: A Perspective

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Perspective

People's tissues accumulate an increasing number of somatic mutations as they age. Although the majority of these mutations have little or no functional impact, a mutation that confers a fitness advantage on a cell may occur. When this occurs in the hematopoietic system, a significant proportion of circulating blood cells may be derived from a single mutated stem cell. This type of outgrowth, known as "clonal hematopoiesis," is very common in the elderly. We will discuss recent advances in our understanding of clonal hematopoiesis, its relationship to cancer, its link to nonmalignant ageing diseases, and its potential impact on immune function. Clonal hematopoiesis offers insight into the process of mutation and selection that occurs in all somatic tissues. Traditional risk factors are only partially predictive of the development of cardiovascular disease, which is the leading cause of death in the elderly. Recent epidemiological studies have found that human ageing is associated with an increased frequency of somatic mutations in the hematopoietic system, which give a mutant cell a competitive advantage, allowing for clonal expansion, a phenomenon known as clonal hematopoiesis. Surprisingly, these mutations have been linked to an increased risk of cardiovascular disease, implying a previously unknown link between somatic mutations in hematopoietic cells and cardiovascular disease. We present an up-to-date review of clonal hematopoiesis and its relationship to ageing and cardiovascular disease in this article. We also provide a detailed report on the experimental studies that have helped us understand the relationship between clonal hematopoiesis and cardiovascular disease, as well as the mechanisms by which hematopoietic somatic mutations contribute to disease pathology. Clonal expansions of mutated hematopoietic cells, known as clonal hematopoiesis, are common in the elderly. One expected consequence of mutation-associated clonal hematopoiesis is an increased risk of hematologic cancers, as demonstrated by several studies. The hematopoietic stem cells that acquire these somatic mutations, however, also give rise to mutated immune effector cells such as monocytes, granulocytes, and lymphocytes. These effector cells have the potential to influence a wide range of disease states, particularly those with a chronic inflammatory component. Indeed, several studies have now found a link between clonal hematopoiesis and an increased risk of atherosclerotic cardiovascular disease. Emerging evidence links clonal hematopoiesis to other nonhematologic diseases. In this section, we will look at recent research that has linked clonal hematopoiesis to altered immune function, inflammation, and nonmalignant ageing diseases. Clonal hematopoiesis is a common premalignant condition characterised by the abnormal expansion of clonally derived hematopoietic stem cells harbouring somatic mutations in leukemia-related genes. Aside from increasing age, this phenomenon is more common in people with lymphoid or solid tumours and is linked to genotoxic stress exposure. In this context, clonal hematopoiesis increases the risk of developing therapy-related myeloid neoplasms and appears to contribute to poor cancer-related survival via a variety of potential mechanisms. These include changes in the bone marrow microenvironment, inflammatory changes in clonal effector cells, and immune response modulation. Understanding how clonal hematopoiesis promotes the initiation of therapy-related myeloid neoplasms and their interactions with non-myeloid malignancies will help to inform screening and surveillance strategies, as well as suggest targeted therapies in this vulnerable population. In this paper, we look at the clinical implications of clonal hematopoiesis in cancer patients and discuss potential strategies for mitigating the negative effects of clonal expansion. Inherited bone marrow failure syndromes (IBMFSs) are defined by ineffective hematopoiesis and an increased risk of developing myeloid cancer. The pathophysiologies of various IBMFSs vary and can be linked to defects in a variety of biological processes, such as DNA damage repair (Fanconi anaemia), telomere maintenance (dyskeratosis congenita), and ribosome biogenesis (Diamond-Blackfan anemia, Shwachman-Diamond syndrome). Somatic mutations that lead to clonal hematopoiesis have been described in IBMFSs, but the distinct mechanisms by which mutations drive clonal advantage in each disease, as well as their associations with leukaemia risk, remain unknown. Clinical observations and laboratory models of IBMFSs indicate that germline deficiencies result in a qualitatively impaired functional state at birth. Somatic alterations can promote clonal hematopoiesis in this context by increasing the competitive fitness of specific hematopoietic stem cell clones. Some somatic alterations alleviate baseline fitness constraints by normalising the underlying germline deficit via direct reversion or indirect compensation, whereas others alleviate them by disrupting senescence or tumor-suppressor pathways. Clones with normalising somatic mutations may have limited transformation potential due to the preservation of functionally intact fitness-sensing and tumor-suppressor pathways, whereas those with mutations that impair cellular elimination may have an increased risk of malignant transformation due to tumor-suppressor pathway subversion. Because clonal hematopoiesis is not a determinant of malignant transformation, rational surveillance strategies will rely on the ability to identify specific clones with increased leukemic potential in advance. We present a framework for understanding the processes that promote clonal hematopoiesis in IBMFSs in order to inform clinical surveillance strategies [1-5].

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