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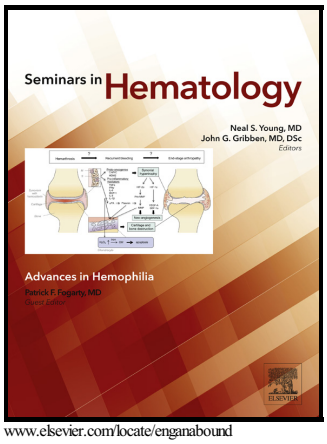

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Clonal Hematopoiesis

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Abstract

Cancer results from multistep pathogenesis, yet the pre-malignant states that precede the development of many hematologic malignancies have been difficult to identify. Recent genomic studies of blood DNA from tens of thousands of people have revealed the presence of remarkably common, age-associated somatic mutations in genes associated with hematologic malignancies. These somatic mutations drive the expansion from a single founding cell to a detectable hematopoietic clone. Owing to the admixed nature of blood that provides a sampling of blood cell production throughout the body, clonal hematopoiesis is a rare view into the biology of pre-malignancy and the direct effects of pre-cancerous lesions on organ dysfunction. Indeed, clonal hematopoiesis is associated not only with increased risk of hematologic malignancy, but also with cardiovascular disease and overall mortality. Here we review rapid advances in the genetic understanding of clonal hematopoiesis and nascent evidence implicating clonal hematopoiesis in malignant and non-malignant age-related disease.

Introduction

The identification of pre-malignant states, such as cervical dysplasia and colonic tubular adenomas, and early interventions to prevent malignancy are major achievements in public health and cancer biology. However, pre-cancerous states for some hematologic malignancies, especially those of myeloid lineages, have proved elusive. In the 1990s, experimental evidence for blood clonality among healthy women raised the possibility that clonal hematopoiesis is an early step in the multistep pathogenesis of hematologic malignancy[1]. More recently, large-scale studies enumerating the common mutations in hematologic malignancies have enabled the targeted search for the cellular and molecular basis of pre-cancerous lesions in hematopoiesis. Finally, over the past few years, a number of researchers using a diversity of genomic technologies have converged on the finding that clonal hematopoiesis is indeed common, age-related, and pre-malignant.