# Myelodysplasia and Acute Leukemia as Late Complications of Marrow Failure: Future Prospects for Leukemia Prevention

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• Clonal evolution • Myelodysplasia • Aplastic anemia
• Natural selection • Fanconi's anemia
• Apoptosis • Leukemogenesis

Patients with bone marrow failure syndromes are at risk for the development of clonal neoplasms including acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and paroxysmal nocturnal hemoglobinuria (reviewed elsewhere in this issue and in).[1,2] From 10% to 20% of survivors of acquired aplastic anemia develop a clonal disease within the decade following their diagnosis,[3–6] and the relative risk of clonal neoplasms is even more significantly increased in children and adults with inherited bone marrow failure syndromes.[7] Informed by advances in studies on evolutionary adaptation,[8–10] recent studies testing the adaptive nature of clonal evolution in mammalian hematopoietic stem cells are clearly positive.

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## THE INFLAMMATION AND CANCER CANON

Inflammatory disorders, infectious and noninfectious, are known to predispose patients to neoplastic diseases. Although the type of inflammatory disorder can be variable, one constant is that the tissue at risk is the inflamed tissue itself. For example, inflammatory bowel disease is a risk factor for colon cancer, hepatitis C infection is a risk factor for hepatocellular carcinoma, and so forth. A recent wave of interest in the linkage between inflammation and cancer has resulted in a canonical view that the neoplastic cells grow because they respond to the proliferative, antiapoptotic, and proangiogenic effects of the cytokines released in the inflamed tissue. Given that a large population of stem cells is under the influence of these proproliferative cytokines, if this feed-forward model is sufficient to account for subsequent neoplasia the neoplasms themselves ought to be polyclonal; yet, they are not. Because neoplasms are usually clonal (arising from one mutant stem cell) the model fails to explain a key step in this process: the emergence and domination of the niche by the progeny of a single mutant stem cell. An alternative model, one that applies the rules of natural selection, better reconciles the clinical course of disease in humans and mice. To compare this model with the more canonical one requires a thorough understanding of the concept of ''selection coefficients.''

## SELECTION COEFFICIENTS AND DETERMINANTS OF CLONAL EVOLUTION

Principles of natural selection were developed in reference to studies on species but are legitimately applicable to asexual populations.[9] When these principles are tested in the laboratory using hematopoietic stem cells of mice with marrow failure, they have informed clinicians about the importance of the microenvironment in processes of clonal evolution.[11,12] In selection of species and subspecies, emergence and fixation of adaptive mutations depends first on an environmentally induced stress on a population that makes that population less fit. An apt example is found in studies on selection of dark and light colored rock pocket mice[13] that differ in only one allele that influences coat color. In a neutral environment, both strains survive equally well but in the real world (in this case an environment with owls in it), the dark colored mice are easier for the predators to spot if they are running about on sand. Conversely, the light colored ones are easy pickings sitting on lava-beds. In effect, the environment does its work to select the fit population not by influencing directly that population but by purging its unfit competitors. There is evidence that this is true not only for bacteria in which adaptation to antibiotic challenge results in resistance,[14,15] but also for mammalian cells.[16] This unabashedly Darwinian model is a perfectly applicable model to apply to populations of stressed hematopoietic stem cells.

To develop a clear picture of clonal evolution that occurs in the setting of bone marrow failure requires clarification of the relationships that exist between the target cells and the selective forces in the environment that determine fitness.[17] Some mathematical models have even suggested that selective pressure is a more important determinant in initiation of a tumor than is an increased baseline mutation rate,[18] but it is intuitively more appealing to accept that variations in fitness in stem cell populations increase not only as a function of the relative fitness differences between two competing populations (a notation of which is known as the ''coefficient of selection'') but in proportion to the population size and mutation rate.[9]

The likelihood of clonal evolution depends on the relative fitness differences between normal stem cells and mutant (potentially adapted) stem cells. This relative difference is expressed as the selection coefficient. A high selection coefficient exists when a somatic mutation accords to cells a uniquely strong advantage. Two models of