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A progenitor cell origin of myeloid malignancies

All cancers rely on cells that have properties of long-term self-renewal or stemness to maintain and propagate the tumor, but the cell of origin of most cancers is still unknown. Here, we design a stochastic mathematical model of hematopoietic stem and progenitor cells to study the evolutionary dynamics of cancer initiation. We consider different evolutionary pathways leading to cancer-initiating cells in JAK2V617F-positive myeloproliferative neoplasms (MPN): (i) the JAK2V617F mutation may arise in a stem cell; (ii) a progenitor cell may first acquire a mutation conferring self-renewal, followed by acquisition of the JAK2V617F mutation; (iii) the JAK2V617F mutation may first emerge in a progenitor cell, followed by a mutation conferring self-renewal; and (iv) a mutation conferring self-renewal to progenitors may arise in the stem cell population without causing a change in the stem cell's phenotype, followed by the JAK2V617F mutation emerging in a progenitor cell. We find mathematical evidence that a progenitor is the most likely cell of origin of JAK2V617F-mutant MPN. These results may also have relevance to other tumor types arising in tissues that are organized as a differentiation hierarchy.