Chronic myeloid leukemia stem cells.

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Public Summary:
Scientific Abstract:
Chronic myeloid leukemia (CML) is typified by robust marrow and extramedullary myeloid cell production. In the absence of therapy or sometimes despite it, CML has a propensity to progress from a relatively well tolerated chronic phase to an almost uniformly fatal blast crisis phase. The discovery of the Philadelphia chromosome followed by identification of its BCR-ABL fusion gene product and the resultant constitutively active P210 BCR-ABL tyrosine kinase, prompted the unraveling of the molecular pathogenesis of CML. Ground-breaking research demonstrating that BCR-ABL was necessary and sufficient to initiate chronic phase CML provided the rationale for targeted therapy. However, regardless of greatly reduced mortality rates with BCR-ABL targeted therapy, most patients harbor quiescent CML stem cells that may be a reservoir for disease progression to blast crisis. While the hematopoietic stem cell (HSC) origin of CML was first suggested over 30 years ago, only recently have the HSC and progenitor cell-specific effects of the molecular mutations that drive CML been investigated. This has provided the impetus for investigating the genetic and epigenetic events governing HSC and progenitor cell resistance to therapy and their role in disease progression. Accumulating evidence suggests that the acquired BCR-ABL mutation initiates chronic phase CML and results in aberrant stem cell differentiation and survival. This eventually leads to the production of an expanded progenitor population that aberrantly acquires self-renewal capacity resulting in leukemia stem cell (LSC) generation and blast crisis transformation. Therapeutic recalcitrance of blast crisis CML provides the rationale for targeting the molecular pathways that drive aberrant progenitor differentiation, survival and self-renewal earlier in disease before LSC predominate.

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