
Selective elimination of leukemia stem cells: Hitting a moving target.

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Authors:	Leslie A Crews, Catriona H M Jamieson
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Public Summary:

Despite the widespread use of chemotherapeutic cytotoxic agents that eradicate proliferating cell populations, patients suffering from a wide variety of malignancies continue to relapse as a consequence of resistance to standard therapies. In hematologic malignancies, leukemia stem cells (LSCs) represent a malignant reservoir of disease that is believed to drive relapse and resistance to chemotherapy and tyrosine kinase inhibitor (TKIs). Major research efforts in recent years have been aimed at identifying and characterizing the LSC population in leukemias, such as chronic myeloid leukemia (CML), which represents an important paradigm for understanding the molecular evolution of cancer. However, the precise molecular mechanisms that promote LSC-mediated therapeutic recalcitrance have remained elusive. It has become clear that the LSC population evolves during disease progression, thus presenting a serious challenge for development of effective therapeutic strategies. Multiple reports have demonstrated that LSC initiation and propagation occurs as a result of aberrant activation of pro-survival and self-renewal pathways regulated by stem-cell related signaling molecules including beta-catenin and Sonic Hedgehog (Shh). Enhanced survival in LSC protective microenvironments, such as the bone marrow niche, as well as acquired dormancy of cells in these niches, also contributes to LSC persistence. Key components of these cell-intrinsic and cell-extrinsic pathways provide novel potential targets for therapies aimed at eradicating this dynamic and therapeutically recalcitrant LSC population. Furthermore, combination strategies that exploit LSC have the potential to dramatically improve the quality and quantity of life for patients that are resistant to current therapies.

Scientific Abstract:

Despite the widespread use of chemotherapeutic cytotoxic agents that eradicate proliferating cell populations, patients suffering from a wide variety of malignancies continue to relapse as a consequence of resistance to standard therapies. In hematologic malignancies, leukemia stem cells (LSCs) represent a malignant reservoir of disease that is believed to drive relapse and resistance to chemotherapy and tyrosine kinase inhibitor (TKIs). Major research efforts in recent years have been aimed at identifying and characterizing the LSC population in leukemias, such as chronic myeloid leukemia (CML), which represents an important paradigm for understanding the molecular evolution of cancer. However, the precise molecular mechanisms that promote LSC-mediated therapeutic recalcitrance have remained elusive. It has become clear that the LSC population evolves during disease progression, thus presenting a serious challenge for development of effective therapeutic strategies. Multiple reports have demonstrated that LSC initiation and propagation occurs as a result of aberrant activation of pro-survival and self-renewal pathways regulated by stem-cell related signaling molecules including beta-catenin and Sonic Hedgehog (Shh). Enhanced survival in LSC protective microenvironments, such as the bone marrow niche, as well as acquired dormancy of cells in these niches, also contributes to LSC persistence. Key components of these cell-intrinsic and cell-extrinsic pathways provide novel potential targets for therapies aimed at eradicating this dynamic and therapeutically recalcitrant LSC population. Furthermore, combination strategies that exploit LSC have the potential to dramatically improve the quality and quantity of life for patients that are resistant to current therapies.