Human AML stem cell: evolution of concept

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The history of human acute myeloid leukemia stem cells (AMLSCs) began from the seminal study performed by Dick JE group proving that only CD34+CD38- human primary acute myeloid leukemia (AML) cells can repopulate in severe combined immunodeficient mice. The concept of leukemic stem cell (LSC) impeded a huge change of the treatment strategy against AML from killing proliferating leukemic cells to eradicating quiescent/dormant LSCs. As next-generation sequencing technologies developed, multiple and recurrent genetic mutations were discovered in large cohorts of AML patients, updated understanding about leukemogenesis improved the old concept of LSC to a revised version of a serial developmental model of LSC, that is, pre-LSCs are generated as seeds by the first hit on epigenetic regulators and then leukemia-initiating LSCs emerged from seeds by the second hits on genes involved in transcription, signaling, etc. Dreams for a universal and targetable AMLSC biomarker sparing healthy HSCs becomes to be weakened after the confrontation of significant heterogeneity of AMLSCs in genomic and immunophenotypic viewpoints. However, there is still hope for effective targets for AMLSCs since evidence that grouped gene signatures like 17-gene LSC score and common epigenetic signature like HOXA clusters independent of various gene mutations exists. Recently, LSC niche in the bone marrow has been actively investigated and expands our knowledge about the physiology and vulnerability of AMLSCs. We have no applicable weapon that always works in AMLSCs for now. However, we will find a way in the end. We always have.