Stemness and Relapse: “Chicken or the Egg” Question

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Disease recurrence upon chemotherapy is a major clinical challenge in acute myeloid leukemia (AML) treatment. In the classical stem cells model, relapse originates from leukemic stem cells (LSCs) that are already present at diagnosis and are able to withstand chemotherapy due to dormant features. Whereas high leukemic stem cells signature scores accurately predict therapy resistance in AML patients, dormancy has not been formally proven in AML. This concept, based on initial observations whereby quiescent AML LSCs escaped the action of cytotoxic drugs, has been recently challenged. Opposing the dogma linking relapse to LSCs, preclinical models demonstrated that cytarabine-resistant cells are not enriched in LSCs frequencies nor in quiescent LSCs. Subsequent studies confirmed these findings, showing that LSCs were effectively depleted during chemotherapy both in xenografts and patient samples. Yet, disease reemergence was preceded by the postchemotherapy reappearance of leukemic cells with self-renewal potential, thus suggesting a model whereby relapse originates from a transient population of self-renewing leukemic-regenerating cells, molecularly distinct from therapy-naive LSCs. Moving toward this direction, Duy et al now demonstrate that relapse originates from transient senescent-like cells able to repopulate leukemia.

Performing ex vivo cultures, the authors first demonstrated that AraC induces a senescent-like phenotype in primary AML cells, which was associated with a higher clonogenic potential and a higher leukemic repopulation capacity in vivo. However, as evidenced from single cells RNA sequencing, senescent-like cells were not enriched for LSCs signatures or LSCs markers, arguing against an enrichment of LSCs in senescent-like cells.

Where do these cells arise from? AraC induced senescence regardless of the mutational status of p53 and p16 or their expression levels, thus excluding these pathways in senescence occurrence. This phenomenon, moreover, was not restricted to a specific cell population given that both immature and mature AML cells were able to undergo senescence. As evidenced from an ex vivo clonal recurrence model, senescence in AML cells does not reflect an intrinsic chemoresistance either. When AML clones were allowed to grow from single cells isolated before multiple cycles of chemotherapy and from the fraction of cells surviving each of them (nadir phase), no major shift in the half maximal effective concentration was observed after each drug-recovery cycle. Upon each cycle, instead, the authors observed a gradual increase in fraction of cells surviving AraC, thus suggesting that senescence might represent a cellular resilience mechanism enabling leukemic cells to persist after the exposure to cytotoxic drugs. Consistent with this, senescence signatures were enriched in residual AML cells collected in three patients at nadir postinduction therapy as compared to their matched diagnostic specimens. This paralleled a depletion of leukemia stem cell signatures at nadir as compared to diagnosis. Interestingly, however, leukemic stem cells signatures were again enriched when relapsed samples were compared to those collected at nadir.

These data are intriguing and are reminiscent of previous murine models showing that senescence epigenetically reprograms bulk leukemia cells into leukemia-initiating cells. Taken collectively, these results suggest that AraC induces a transient senescent-like phenotype which enables AML cells to survive cytotoxic drugs and might contribute to epigenetically shape their stemness properties (Figure). In this model, relapse-related stemness is the consequence of the leukemic cell survival, and not its cause, as proposed instead by the classical model. This has profound clinical implications as it argues that therapies preventing senescence occurrence would be more effective to achieve a stable remission that strategies targeting LSCs. Emphasizing the importance of including patient samples at nadir postinduction chemotherapy when analyzing disease evolution over time, the study by Duy reconciles some controversies in our understanding of AML relapse. Moreover, it arises several interesting issues. Among them, what is the exact nature of senescent-like AML cells? In addition to being enriched in senescent signatures, these cells showed a diapause-like dormancy signature, thus interrogating the relationship between senescence and dormancy in AML. A deeper
understanding of this aspect will further clarify the molecular mechanisms underlying the acquisition of the senescent-like phenotype described in this study. Since altered metabolic states characterize senescent cells, previous data linking AraC resistance with a high oxidative metabolism are intriguing in this context as they suggest exploring whether senescence induction in AML cells is linked to specific targetable metabolic pathways. Last, how does leukemia recover from senescent cells? As suggested by the transcriptional profile, which is characterized by an enrichment in proinflammatory cytokines, senescent-like AML cells might possess the ability to remodel the microenvironment and/or its immune milieu. Thus, in addition to possibly restoring stem cells functions via an epigenetic reprogramming, senescent AML cells might contribute to leukemia relapse by remodeling the bone marrow microenvironment and/or mediating a senescent phenotype in BM niche components in a paracrine manner.

To conclude, even though it remains unclear whether senescence induction occurs in all AML subtypes, the work by Duy et al is interesting and important as it provides a novel model challenging the current therapeutic paradigm to achieve a stable remission in AML.

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