Mesenchymal stromal cells and leukemia therapy in mice and man

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Mesenchymal stromal cells (MSCs) and macrophages are normal components of the bone marrow micro-environment and important regulators of normal hematopoiesis.[1] Consequently, MSC and macrophage dysfunctions are associated with an abnormal bone marrow micro-environment and abnormal hematopoiesis. In some circumstances, these abnormalities support the growth of leukemia cells but how this occurs is unknown. Also unknown is whether there is an important interaction between these cell types.

Xia and co-workers studied these questions are in a leukemia model.[2] Using RNA-Seq analyses they showed MSCs lose functionality as leukemia progresses. This process could be reversed by injecting MSCs from a normal donor into the femur of leukaemia-bearing mice. Interestingly, the action of donor MSC was indirect, operating by improving the function of recipient MSCs. Results were partial normalization of the bone marrow micro-environment, partial restoration of normal bone-marrow function, slowed leukemia growth and prolonged survival of mice with leukemia. Similar effects could be obtained by giving leukemia-bearing mice host macrophages re-programmed by normal donor MSCs.

The question is how are these effects mediated? As indicated, macrophages are important in maintaining a normal bone marrow micro-environment, mostly by regulating the function of normal hematopoietic stem and progenitor cells. Abnormal macrophage function, although not causing leukemia, promotes growth of leukemia cells over normal hematopoietic cells. Functions of macrophages are plastic and can be re-shaped by soluble factors and express arginase 1 (Arg1). Co-culture of macrophages with MSCs can polarize them from pro- (M1) to anti-inflammation (M2) phenotype. These data make it possible to understand why and how injection of normal MSCs into leukemia-bearing mice might improve normal hematopoiesis and impede leukemia. It also makes sense that giving abnormal macrophages re-programmed by co-culture with normal MSCs might operate transitioning to an anti-inflammatory phenotype.

Lastly, what are the implications of these data for leukemia therapy in humans? We are a long way off from a practical application of these data. Men are not mice and there are many unanswered questions and obstacles to overcome. Whose MSCs to use, how to give them, how many to give, how often, can we achieve the same effects with soluble factors rather than cells and many others. MSCs from an allogeneic donor might causegraft-versus-host disease (G*v*HD) which, if controlled, might not be entirely bad because of its association with an anti-leukemia effect.[3] Clearly, much remains to be done to translating these interesting observations to the clinical but the authors have given us a nice start.

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