blood advances

Better eat!

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Comment on Lineburg et al, page 2032

In this issue of *Blood Advances*, Lineburg et al describe the interplay between graft-versus-host disease (GVHD), hematopoietic stem cell (HSC) engraftment, and the inflammatory response specifically with respect to autophagy.[1] This observation opens the possibility of understanding engraftment in the setting of GVHD and whether manipulation of cytokines could improve clinical outcomes.

Our ability to live in this third rock from the sun is fully dependent on the air we breathe, being 21% oxygen and 78% nitrogen and with the rest being a long list of other gases. Because nitrogen in the air is neutral, all of our biological processes are dependent on oxygen which is continuously loaded onto red blood cells to be delivered to our tissues. Although oxygen is critical for our tissue function (oxidative phosphorylation and the Krebs cycle), it is also a highly reactive nonmetal, and reactive oxygen species (ROS) is a natural byproduct of our normal metabolism using oxygen. These ROS such as hydroxyl radicals, superoxide, hydrogen peroxide, and others must be tightly regulated and disposed of; otherwise they might cause DNA damage as well as damage to other cellular components.[2] Excessive production of ROS is a leading cause of inflammation and can lead to bone marrow failure syndromes.[3,4]

All this activity of using oxygen for respiration occurs in our mitochondria. These intracellular organelles are the powerhouse of our cells where adenosine triphosphate (ATP) is produced. ATP is the currency by which energy for any cellular activity occurs. Interference with oxidative phosphorylation can lead to senescence, block in cellular proliferation, or apoptosis.[5] Mitochondria can increase or decrease in numbers through the process of fusion or fission depending on what the acute energy needs are or whether there are pathological states. Given the importance of our "fuel cells," defective mitochondria are destroyed by a process called autophagy (in the case of mitochondria – mitophagy), which allows for an optimal number of functional working units. Autophagy, rather than just being a primordial degradation process, is in fact a carefully choreographed process designed to maintain homeostasis.[6] Perturbations of this process leads to multiple, different pathologies especially inflammation. In the case of inflammation, there is a 2-way communication where regulators of autophagy can control inflammation and vice versa.[7]

There are few medical procedures where this control of autophagy and inflammation is taxed more than in the case of an allogeneic hematopoietic cell transplantation (HCT). Within this procedure, there is the tension of inflammation/immunity needed for the graft-versus-leukemia (GVL) effect and too much inflammation in the setting of GVHD. In addition, inflammation is a negative regulator of hematopoiesis, which can be mediated by cytokines or direct T-cell–mediated destruction of hematopoietic niches.[8] Both components are critical for the success of this procedure. Excessive inflammation negatively affects HSCs, leading to poor or lack of engraftment. The authors of this elegant study clearly demonstrate that in the setting of an allogeneic HCT and in the presence of GVHD, inflammatory cytokines, specifically tumor necrosis factor and IL-1β, induce autophagy in HSCs, which is increased with the presence of allogeneic T cells. When autophagy was genetically ablated by knocking out 2 central proteins, *Atg*5 or *Atg*7, there was no impact on HSC numbers, but there was noted delayed engraftment and reduced competitive fitness; specifically, autophagy was required for engraftment and survival of mice in the setting of GVHD. In HSCs that were unable to undergo autophagy, there was primary graft failure leading to transplant-related mortality. These data suggest that, in addition to its role in stem-cell maintenance, there is an important role for autophagy in times of inflammatory stress brought on by GVHD. In addition, immune suppression in the early posttransplant phase would enhance recipient engraftment.

In summary, the data in this article support the role of autophagy in HSC and progenitors in the presence of GVHD after an allogeneic HCT, wherein, lack of autophagy leads to graft failure.

The release of inflammatory cytokines during GVHD leads to increased autophagy in HSC and progenitors during the engraftment time. These experiments were done in knockout mice, but potentially overtaxing this system in human HSCs when there is intense inflammation in the setting of GVHD, may ultimately lead to insufficient autophagy and poor graft function. These data lead to a testable hypothesis as to whether specific blockade of IL-1β or TNF during GVHD can enhance donor engraftment.

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