The article by Ng and colleagues in this issue of Blood opens a new window on the identification of molecular mechanisms that regulate the fate of mesenchymal stem cells in vitro. In the early 1970s, Friedenstein and colleagues were the first to report the presence of fibroblastoid cells that could be flushed out from adult bone marrow, form colonies on plastic, and, when transplanted subcutaneously with appropriate carriers, give origin to ossicles in which the hematopoietic component had originated from the host. In other words, Friedenstein provided the first evidence of the existence in the bone marrow of what later on would have been called mesenchymal stem cells (MSCs). Over the years, it has become progressively clear that such cells, which can differentiate into a variety of mesenchymal lineages such as osteoblasts, chondrocytes, and adipocytes, are not an exclusive feature of the bone marrow, but can also be isolated from other adult organs and tissues including fat. A large number of studies have provided evidence in support of MSC plasticity, their potential use for tissue engineering purposes, their extraordinary immunomodulatory properties, and their ability to be recruited at sites of injury, where they would contribute a natural in vivo system for tissue repair through cell fusion, production of specific cytokines, or even differentiation into the appropriate cell phenotype. A characterization of both their cell surface–specific antigens and their anatomical location in vivo has been pursued as well.

However, despite this impressive body of work, numerous questions related to the developmental origin of these cells, their proposed pluripotency, and their participation in the physiological processes of bone modeling and remodeling in vivo remain largely unanswered. More importantly, a detailed and systematic analysis of the complex network of signaling pathways, which very likely regulate MSC ability to self-renew, proliferate, and eventually differentiate, has just begun. The identification of this network is critically important in reaching a deeper understanding of the rules that govern the size of the MCS pool both in vivo and in vitro, which would then ultimately allow for appropriate pharmacologic or genetic intervention.

Ng and colleagues use a global gene-expression profiling approach and compare the transcriptomes of bone marrow MSCs...
Endothelial cells are not all alike

Hau C. Kwaan  NORTHWESTERN UNIVERSITY MEDICAL SCHOOL

In this issue of Blood, Stefanescu et al discover the characteristics that distinguish sensitive versus nonsensitive endothelial cells to injury by TTP plasma.

An important factor in the pathogenesis of thrombotic thrombocytopenic purpura (TTP) is injury to microvascular endothelial cells (MVECs). Such injury was demonstrated in earlier work by Mitra et al, who found that apoptosis of MVECs can be induced in vitro by plasma obtained from TTP patients. They further observed that MVECs derived from the brain, kidneys, and skin are most sensitive to TTP plasma, whereas those derived from lung and liver are not.1 Macrovascular endothelial cells derived from major vessels do not share this behavior. In this issue of Blood, Stefanescu and coauthors, part of the same research group as Mitra et al, reveal the distinguishing features of sensitive versus nonsensitive MVECs.

In a series of experiments, Stefanescu and colleagues used MVECs derived from the skin as representative of the sensitive group and MVECs derived from the lung as representative of the nonsensitive group. They also studied large-vessel endothelial cells. TTP plasma–induced apoptosis in these endothelial cells was studied in the presence of tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) and IFN-γ. They clarify the mechanism of apoptosis by observing that, in the sensitive MVECs, ubiquitination of the caspase 8 regulator c-FLIP led to degradation of its proteasome. Likewise, c-FLIP silencing with anti-FLIP siRNA in the nonsensitive MVECs rendered them sensitive to apoptosis. Such differences in sensitivity in the various lineages of MVECs are consistent with the clinical manifestations of TTP, being common in the central nervous system and kidneys and rare in the lungs and liver.2

It would, perhaps, have been more exciting if the authors had shown similar findings with the other known sensitive MVECs (those derived from the brain and kidney) and with the other known nonsensitive MVECs (those derived from the liver). Nevertheless, their discovery of the role of c-FLIP in regulation of MVEC apoptosis may have important therapeutic implications for TTP. What is still an enigma is the link between endothelial injury and the development of autoantibodies against ADAMTS13. The presence of the antibodies results in a drastic lowering of blood levels of ADAMTS13, and leads to platelet aggregation and microvascular platelet thrombi formation. Such investigative challenges are not abating, but the present findings represent yet another step toward solving this riddle.

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES

Comment on Stefanescu et al, page 340

Endothelial cells are not all alike
A new window on MSCs

Ernestina Schipani