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HEMOSTASIS

Comment on Martıñez et al, page 3012

Microvesicles: from “dust to crown”

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In this issue of Blood, Martıñez and colleagues report that Hedgehog (Hh) membrane–anchored morphogens that are associated with microvesicles (MVs) shed from activated T lymphocytes induce megakaryocytic differentiation of K562 cells, as well as stimulating megakaryocytic development from primary human CD34+ progenitors. Thus, the authors provide further evidence that MV–related mechanisms operate in normal hematopoiesis.

Generally, cells communicate by secreted growth factors, cytokines, chemokines, small molecular mediators, and cell-to-cell adhesion contacts. However, attention is now being focused on circular membrane fragments called microvesicles (MVs), which for many years have been largely overlooked. This MV–mediated cell-cell communication system probably emerged very early during evolution and was a kind of template for the development of cell-cell interaction mechanisms involving soluble bioactive mediators and fine-tuned ligand-receptor interactions. 1-3

MVs are shed from the surface membranes of normal and malignant cells, as well as secreted from the endosomal compartment as circular membrane fragments. MVs contain numerous proteins and lipids similar to those present in the membranes of the cells from which MVs originate. Furthermore, since they engulf some cytoplasm during membrane blebbing, they may also contain proteins and mRNA derived from it. Moreover, MVs may “hijack” infectious particles (eg, HIV or prions) from the cytoplasm or possibly even whole intact organelles (eg, mitochondria).

Shedding of membrane–derived MVs is a physiological phenomenon that accompanies cell activation and growth, and the number of MVs shed from cells increases upon (1) cell activation, (2) hypoxia or irradiation, (3) oxidative injury, (4) shearing stress, and (5) exposure to proteins from an activated complement cascade. 2 Growing experimental evidence indicates that the enrichment of MVs in various bioactive molecules plays an important pleiotropic role in many biologic processes, including cancerogenesis, coagulation, immune responses, and modulation of susceptibility/infectability of cells to retroviruses or prions (see figure). 2-3

MVs are released by various cell types and differ in composition depending on their cell of origin and status. Their level is elevated in the peripheral blood (PB) of patients suffering from infection, cancer, or cardiovascular disorders. The number of MVs circulating in PB increases during injury, inflammation, thrombosis, and cell activation.

In this issue of Blood, Martıñez and colleagues describe that MVs derived from T lymphocytes (1) circulate in peripheral blood, (2) express Hh morphogens on the surface, and (3) stimulate megakaryopoiesis. Thus, a novel MV–related mechanism for transferring/spreading morphogens has been described, similar to that observed during early embryogenesis. 1 Furthermore, the Hh signaling pathway had been proposed to regulate Meg differentiation. Interestingly, the number of Hh+ MVs increases in diabetic patients,

Different mechanisms by which MVs may interact with target cells. MVs may (1) stimulate target cells directly by surface-expressed ligands acting as a kind of “signaling complex”; (2) transfer surface receptors from one cell to another; (3) deliver proteins, mRNA, bioactive lipids, and even whole organelles (eg, mitochondria) into target cells; and, finally, (4) serve as a vehicle (“Trojan horse” mechanism) to transfer infectious particles between cells (eg, HIV or prions). In this issue of Blood, Martıñez and colleagues describe that MVs derived from T lymphocytes express Hh morphogens that may induce megakaryopoietic differentiation in hematopoietic progenitors.
which triggers thrombopoiesis and may contribute to thrombotic complications. Further work, however, requires the identification of other biologic compounds that are expressed by T-cell–derived MVs and their additional potential targets (eg, perhaps the endothelium).

Since all cells present in the hematopoietic microenvironment secrete MVs, the MV–related network modulates hematopoietic development. Thus, MVs should no longer be considered cell debris or biologically irrelevant cell dust. Augmenting evidence demonstrates that they are important mediators of intercellular communication and underappreciated components of the hematopoietic niche.

Comment on Brunet de la Grange et al, page 2998

Another piece for the SCL/TAL1 puzzle

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Roles for the SCL/Tal1 gene in primitive hematopoiesis and adult erythropoiesis have been revealed using various murine knockout models. In this issue, a broader lineage effect for SCL in adult human erythropoiesis was revealed using lentiviral vectors expressing lentiviral vectors that lowered rather than obliterated SCL expression in human CD34⁺ progenitor cells.

In this issue, Brunet de la Grange and colleagues add provocative new data to the ongoing controversy over the role of the stem cell leukemia (SCL; aka TAL1) gene during adult hematopoiesis. SCL was first identified as a translocation partner in a leukemia with both myeloid and lymphoid lineage markers. Murine knock-out studies have clearly revealed that SCL is essential for primitive hematopoiesis, but its exact function in regulating lineage commitment and self-renewal in postnatal stem and progenitor cells is still in dispute. The embryonic lethality of the SCL knock-out model has meant that the study of how SCL functions during definitive (or adult) hematopoiesis has required experimental ingenuity, and the resulting models have produced conflicting results. However, all models have found that SCL is essential for adult erythropoiesis and megakaryopoiesis. Two main points of contention remain: first, whether SCL has any role in regulating the repopulating ability of stem cells, and second, whether SCL affects lineage commitment decisions unrelated to the erythroid pathway.

The paper by Brunet de la Grange et al suggests that SCL acts not only at the level of erythroid commitment, but also at both multipotent and myeloid committed stages of adult hematopoiesis. Lentiviral vectors were used to express SCL-directed shRNA in human CD34⁺ cells. The resulting decrease in SCL expression caused both a significant loss of lymphomyeloid repopulating potential as well as a block to both erythroid and myeloid production. With the intrinsic limitations of the in vitro and in vivo models that are available to measure human stem cells, it is not possible to make direct comparisons of these data with that from classic murine transplantation assays used to measure murine short- and long-term repopulating stem cells. Nevertheless, the data suggest that, in the case of multipotent (lymphomyeloid) stem cells, SCL regulates the most primitive (long-term repopulating) subset of human cells (revealed in vitro only after 10 weeks in culture and in vivo at 12 weeks after transplantation). In short-term assays, reduction in SCL expression caused a loss of committed myeloid and erythroid progenitors. Lymphopoiesis was not affected in short-term assays, consistent with the rapid down-regulation of SCL upon lymphoid commitment. Why then were the effects of manipulating SCL expression more wide ranging than in some previous reports? Species differences do not seem to explain the differences, as similar data were obtained when the authors used the shRNA strategy with murine stem/progenitor cells. One key difference is that with the shRNA strategy, although SCL expression was significantly decreased, it was still detectable at low levels. One might expect that partial inhibition would produce less rather than more of a derangement in hematopoiesis compared with the conditional knock-out models where SCL expression is completely absent. This may represent another example of how the exquisite regulation of hematopoiesis is accomplished by a network of relative levels of multiple transcription factors rather than by individual genes turned on or off in a sequential manner.

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