Immunophenotyping of myelodysplasia

Cell maturation anomalies in bone marrow samples have long been recognized by the patient scrutiny of morphologists, have led to detailed descriptions of possible abnormalities and later to clinically relevant classifications of myelodysplasia (MDS). That the diagnosis and fine description of MDS belong to the realm of morphologists has long been considered a prerogative although, since the early 1980s the development of monoclonal antibodies, progressively allowed maturation-associated immunophenotypic patterns to be defined. The new technology was mostly applied, first in UV microscopy then in flow cytometry, to the definition of acute leukemias with large numbers of identical cells. However, flow cytometrists progressively tried to retrieve the putative maturation stages defined on diseased blasts within normal bone marrow samples. They were thus confronted with the great complexity of the variety of bone marrow cells at various maturation stages physiologically populating our bones, and the need to perfect their skills. As time went by, multicolor labeling and complex gating strategies became perfect their skills. As time went by, multicolor microscopy then in flow cytometry, to the definition of acute leukemias with large numbers of identical cells. However, flow cytometrists progressively tried to retrieve the putative maturation stages defined on diseased blasts within normal bone marrow samples. They were thus confronted with the great complexity of the variety of bone marrow cells at various maturation stages physiologically populating our bones, and the need to perfect their skills. As time went by, multicolor labeling and complex gating strategies became increasingly available until, at the dawn of the 21st century, it now seems feasible to add immunophenotypic information to the definition of MDS. Such approaches have indeed been recently described and one such description is published in this issue of Haematologica. Flow cytometry for MDS does, however, jingle some of our well-established routines. Gone are the straightforward evaluations of positive cell percentages. As increasingly suspected with the development of multiparametric labeling, we are here typically in the realm of immunophenotypic patterns, i.e. partly subjective interpretation of the images provided by cytograms built from immunolabeling with lineage and maturity markers. Impressive progress has been made rapidly, but a lot remains to be done, be it only on the proper and pertinent definition of clinically relevant marker associations that can help physicians in decision making. A new field to watch closely is opening up!

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References


Inherited protein S deficiency: from genotype to phenotype

The protein C (PC) anticoagulant pathway is essential for inhibiting thrombosis in the microcirculation. The pathway is triggered by thrombin, which promotes coagulation at sites of exposed subendothelium but adopts anticoagulant properties when it binds to thrombomodulin on intact endothelium and activates circulating PC. The endothelial protein C receptor (EPCR) binds to both the inactive and active forms of PC and augments PC activation. However, dissociation of activated protein C (APC) from EPCR is required for APC to exert its anticoagulant effects, which it does by forming a complex with protein S (PS) and proteolytically inactivating factors Va and VIIa. Inactivation of factor VIIa is enhanced by intact factor V (Figure 1). In addition to its APC co-factor activity, PS may also exert APC-independent anticoagulant effects by inhibiting prothrombin activation and formation of the prothrombinase complex. The importance of this anticoagulant pathway is emphasized by the predisposition to venous thromboembolic disease experienced by individuals with inherited abnormalities in components of the pathway. Deficiencies of PC and PS each account for about 6% of families with inherited thrombophilia, while factor V Leiden, a mutation in the factor V gene which reduces the efficiency of factor Va inactivation by APC, can be demonstrated in about 45% of families with venous thrombosis. It has also been suggested that defects in the genes encoding thrombomodulin and EPCR may contribute to the risk of venous thrombosis.

Synthesized by hepatocytes, megakaryocytes and endothelial cells, PS is a 69kDa, vitamin K-dependent glycoprotein that circulates in plasma in two forms. Approximately 60% circulates bound to the complement component C4b-binding protein (C4bBP) while the remainder exists as free PS. Only free PS possesses APC co-factor activity. PS is syn-