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editorial

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Pathogenesis of polycythemia vera: do we have the right pieces to the puzzle?

Western scientific medicine in its process of rationalization is in search of causal models to sustain the nosography and classification of diseases, and to provide clues for therapy. The last 10 years of research have produced evidence that a genetic lesion, the resulting abnormal molecular product and the effects of this altered product on cell proliferation and differentiation are the components of a possible model of cancer development. The tenet of scientific theories, i.e. their falsifiability, also comes from evidence that any intervention which interrupts the model's chain of events will prevent cancer development. In the field of hematology, chronic myeloid leukemia and acute promyelocytic leukemia are the most fascinating examples of this paradigm.

In the search for such a model, the number of scientific papers on the pathogenesis of polycythemia vera (PV) has impressively increased in the last 5 years. There are three times as many articles about this disease as there are for essential thrombocythemia or myelofibrosis with myeloid metaplasia, the other chronic myeloproliferative disorders awaiting an explanation for the altered cell proliferation. This is due to the easy availability of affected patients (PV has a disease incidence of 1 in 100,000), a quasi-specific *in vitro* biologic marker such as growth factor-independent erythroid colonies, biotechnological material such as cloned erythropoietin receptor (Epo-R), and animal models.

An article reviewing disease mechanisms appears in this issue of the Journal.[1] Different targets have been addressed, spanning all the steps of receptor-mediated growth factor cell proliferation. Due to prominent erythroid proliferation and to the original description that *in vitro* erythroid colonies had appeared to be hypersensitive to Epo,[2] the Epo-R and the post-receptor signal transduction pathways were the subjects of a significant number of studies published in major hematologic and nonhematologic journals.[3-8] Number, binding affinity, expression levels, gene rearrangement, amplification, insertions or point mutations have all been examined for the Epo-R. As for transduction pathway defects, the SHP-1 gene was an especially attractive candidate since it binds to and negatively regulates signalling from the Epo-R. These studies failed to detect any genetic or structural anomaly on the Epo-R, or any alteration on specific erythroid post-receptor molecules. In particular, the gene encoding SHP-1 was found to be structurally and transcriptionally intact.[9] In retrospect, these results are not surprising. PV is a clonal disorder of hemopoiesis in which the defect is located at a differentiation level that encompasses erythroid, megakaryocyte and leukocyte stem cells, and in which polycythemia is associated with thrombocytosis and leukocytosis in a high proportion of patients. Since Epo-R is normally barely detectable on multipotent progenitors,[10] if the Epo-R was the primary defect of PV, the full picture of the disease could be justified only by hypothesizing that the result must be an aberrantly expressed and constitutively active molecule capable of stimulating myeloid and megakaryocyte as well as erythroid progenitors, thus transducing a growth signal in nonerythroid hematopoietic cells. This has been demonstrated to be possible in transfected adult mice, in which a phenotype resembling PV was generated when a recombinant retrovirus (SFFVcEpoR) carrying a constitutively activated form of Epo-R was injected.[11-13] In humans, this model for PV is inconsistent with the fact that the number of Epo-R, their expression and their affinity for Epo are identical to normal values,[7] and with *in vitro* data showing that erythroid progenitors are not in fact hypersensitive to Epo[14,15] but they are hypersensitive to several other growth factors,[16-18] and that myeloid and megakaryocytic progenitors are hypersensitive to growth factors other than Epo.[18-19] In conclusion, it can be reasonably stated that the Epo-R is an unlikely candidate for the proto-oncogene involved in PV. In humans, when Epo-R mutation ensues it allows isolated polycythemia to develop, as occurs in congenital or sporadic idiopathic erythrocytosis, without leukocyte or platelet abnormalities and with no propensity to leukemic transformation.[20] In these disorders the hypothesis that an altered Epo-R could be responsible for the pathogenesis is reasonable and there is now good evidence to support this.

Reported mechanisms possibly related to the pathogenesis of PV that could justify the full clinical picture and the biological markers of the disease are numerous. Activation of insulin-like growth factor-I signalling has been studied by Axelrod *et al*. and extensively discussed in the above mentioned review.[1] A defective homeobox B9 gene encoding transcription factors involved in the control of normal hemopoiesis was described in abstract form in 1996 at the ASH meeting.[21] The production of a

defective tyrosine phosphatase due to a gene mutation that leads to up-regulation of the function of several receptor kinase complexes in hemopoietic stem cells was reported in Blood a few months ago.[22] Mutations of the gene for *hbc*, a shared signalling subunit of various cytokine receptors that cause constitutive activation of a molecule normally expressed in multipotent progenitors have also been reported as an unpublished observation by Gonda and D'Andrea in a review article in Blood last year.[23] In spite of the enthusiasm of researchers who discover new pieces of the puzzle, we are far from a simple, linear and consistent model for the pathogenesis of PV (comparable to those of chronic myeloid leukemia[24] or acute promyelocytic leukemia[25]) but at least we are now playing with the right pieces.

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