Somatic \textit{JAK2} mutations and their tumor phenotypes

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In this issue of \textit{Blood}, Grisouard et al use transgenic mice to describe the phenotype associated with the human polycythemia vera (PV)-associated \textit{JAK2} exon 12 mutation (\textit{JAK2}-N542-E543del) and demonstrate Stat1-independent erythroid-only proliferation.\textsuperscript{1}

Activating \textit{JAK2} mutations can arise from chromosomal translocations or point mutations/deletions/insertions. The former result in \textit{JAK2} fusion proteins that always involve the \textit{JAK2} kinase domain (JH1), in association with an oligomerization domain from one of several partner proteins, which promotes constitutive \textit{JAK2} phosphorylation and signal activation. Tumor phenotypes associated with \textit{JAK2} fusion proteins include both myeloid and lymphoid neoplasms with a certain degree of phenotypic specificity (see figure).\textsuperscript{2} \textit{ETV6-JAK2} [t(9;12)(p24p13)] has been associated with T or B acute lymphoblastic leukemia (T-ALL or B-ALL, respectively); \textit{PCML-JAK2} [t(8;9)(p22; p24)] with chronic eosinophilic leukemia and atypical chronic myeloid leukemia (aCML); \textit{BCR-JAK2} [t(9;22)(p24q11.2)] with aCML and B-ALL; \textit{PAX5-JAK2} [inv(9)(p13p24); t(9;9)(p13p24); del(9p13p24)] with B-ALL; \textit{SSBP2-JAK2} [t(5;9)(q14.1p24.1)] with B-ALL; \textit{STRN3-JAK2} [t(9;14)(p24q12)] with B-ALL; and \textit{SECI3A-JAK2} [t(4;9)(q21p24)] with HL. B-ALL has also been associated with \textit{JAK2} point mutations/deletions/insertions, involving the JH2 pseudokinase domain; these include a \textit{JAK2} exon 14 mutation (L611S) reported in a single case of B-ALL,\textsuperscript{3} and recurrent \textit{JAK2} exon 16 mutations seen in \textlesssim18\% of patients with DS-associated B-ALL.\textsuperscript{4} The latter always affect the arginine 683 residue (eg, R683G, R683S, and D1R8ED), and some of these mutations have been shown to induce JAK-Stat activation and cytokine-independent growth. Interestingly, \textit{JAK2}D1R8ED bone marrow transplant assays in mice displayed a phenotype similar to that seen with \textit{JAK2}V617F, suggesting a crucial role for the DS-associated trisomy 21 in directing the oncogenic activity to B-lymphoid rather than myeloid cells.\textsuperscript{5}

The myeloproliferative neoplasm–associated \textit{JAK2}V617F is the prototype \textit{JAK2} point mutation and involves the JH2 pseudokinase domain (exon 14).\textsuperscript{6} \textit{JAK2}V617F is closely associated with PV, essential thrombocytosis, primary myelofibrosis, and refractory anemia with ring sideroblasts and thrombocytosis, with respective mutational frequencies of \textlesssim98\%, 50\%, 60\%, and 40\%, respectively. The phenotypic diversity seen with \textit{JAK2}V617F has been attributed to differences in mutant allele burden, presence of other coexisting mutations, and the order and stem cell level of mutation acquisition.\textsuperscript{7} Conversely, the PV phenotype has infrequently been associated with other mutations, including \textit{JAK2} exon 12 mutations.\textsuperscript{8}

\textit{JAK2} exon 12 mutations were first described by Scott et al in 2007 and shown to account for the majority of patients with \textit{JAK2}V617F-negative PV.\textsuperscript{8} Unlike the case with \textit{JAK2}V617F, which is a single nucleotide alteration, multiple \textit{JAK2} exon 12 mutations, often heterozygote, have been described and include nucleotide substitutions, deletions, or duplications; the most frequent were N542-E543del, E543-D544del, F537-K539delinsL, K539L, and R541-E543delinsK.\textsuperscript{9} These mutations also involve the JH2 pseudokinase domain adjacent to its border with the JH3 domain, spanning residues 536 to 547. Compared with PV patients with \textit{JAK2}V617F, those with \textit{JAK2} exon 12 mutations were younger and displayed higher hemoglobin levels, primarily erythroid proliferation, absence of bone marrow tri-lineage hyperplasia, and lower incidence of leukocytosis or thrombocytosis; however, survival and rate of disease complications were reported to be similarly affected by the 2 mutation variants.\textsuperscript{9}

The abovementioned specificity of \textit{JAK2} exon 12 mutations to PV and, in particular, to the erythroidysis phenotype, has been recapitulated in animal models. In their original description,\textsuperscript{8} Scott et al used \textit{JAK2}K539L retroviral mouse models and induced marked erythroidysis, which was more pronounced than was seen in \textit{JAK2}V617F mice; in contrast, although leukocytosis accompanied the erythroidysis phenotype in both instances, its degree was significantly higher in \textit{JAK2}V617F mice. The approach taken by Grisouard et al used \textit{JAK2}-N542-E543del transgenic mice and generated an even more erythroid-specific phenotype, without leukocytosis, thrombocytosis, or myelofibrosis. Multiple factors might have contributed to the overlapping but apparently distinct phenotypes observed between the \textit{JAK2}K539L and \textit{JAK2}-N542-E543del mice, including the different strategies of genetic engineering applied in constructing the animal


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models and potential differences in phenotype associated with specific JAK2 exon 12 mutations; the latter might be consequential to disease natural history and specific treatment response. Additional observations from the transgenic mouse model of Grisouard et al included a Stat1- and allele burden–independent mechanism of action for JAK2-N542-E543del and altered expression of iron regulating proteins, including increased expression of transferrin receptor-1, which binds circulating transferrin-bound iron.

The remarkable phenotypic similarity between JAK2 exon 12 mutated human disease and the corresponding phenotype in mice suggests a disease-initiating pathogenetic role for the mutation; this is also consistent with its almost exclusive association with PV, making it more amenable to molecularly targeted therapy compared with JAK2 exon 12 mutated PV is relatively rare and characterized by an indolent clinical course, this will require a concerted collaborative effort with access to retrospective data.

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REFERENCES

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