Broadening the differential diagnosis associated with germline *DDX41* mutations

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In this issue of *Haematologica*, the authors Korotev *et al*. highlight the unintuitive characteristics of inherited *DDX41* mutations and shed light on how these variants might contribute to oncogenesis, not just in myeloid malignancies, but in solid tumors as well.[1] In their work, they examine a large collection of 43 families with germline *DDX41* loss-of-function variants comprising over 90 affected individuals to better understand this truly atypical cancer predisposition gene.

Abnormalities of the *DDX41* gene are the most common inherited myeloid malignancy predisposition mutations, present in roughly 3% of patients with myelodysplastic neoplasms (MDS) and representing nearly 80% of the inherited risk in this disorder.[2,3] Mechanistically, DDX41 is quite pleiotropic as it is involved in small nuclear RNA processing, ribosome biogenesis, RNA splicing, and R-loop resolution.[4] However, how pathogenic germline *DDX41* mutations manifest and lead to malignant transformation remains unclear. Historically, inherited cancer predisposition mutations have been identified by studying pedigrees notable for disease onset at an early age, high penetrance in affected individuals, and unusual phenotypic features.[5] The *APC* gene, for example, named after its association with multiple adenomatous polyps of the colon, has a high rate of progression to colon cancer in mutation carriers that occurs before the median age of sporadic cases. Inherited gene mutations linked to myeloid disorders such as MDS and acute myeloid leukemia (AML) also are known such as those in the transcription factor RUNX1 responsible for familial platelet disorder with predisposition to AML.[6] Affected carriers can have prodromes with thrombocytopenia, platelet dysfunction, and bone marrow dysplasia that precedes malignant transformation which is often identified at a young age. When progression to MDS or AML does occur, it may be accompanied by additional somatic mutations involving the remaining *RUNX1* allele, consistent with Knudson's two-hit hypothesis for tumor suppressor genes.[6]

As the study by Korotev *et al*. confirms, germline *DDX41* mutations share some of these features, including the propensity to acquire secondary somatic mutations in the unaffected allele (frequently a missense variant at codon 525) and the presence of mild bone marrow dysplasia in the majority of carriers studied well before progression to MDS or AML.[1] This finding is important as mild dysplasia could be misinterpreted as disease progression before malignant transformation has occurred and lead to inappropriate therapy. But unlike more classical inherited cancer predisposition genes, *DDX41* has several unique features. First, its associated age of disease onset is close to 64.[3,7,8] This is near the median age at which sporadic cases of MDS are diagnosed, making it difficult to identify potential *DDX41* germline mutation carriers based on their age alone. Second, the penetrance of myeloid malignancies in *DDX41* mutation carriers is difficult to establish since there are more competing causes of morbidity and mortality at this older age of disease onset. An affected person who might have had a very high chance of developing MDS or AML had they lived into their 70s, but instead died at an early age, would be a less informative member of their pedigree leading to an underestimation of the true penetrance rate. On the other hand, *DDX41* mutations are often identified in families with a history of myeloid malignancy, like the families studied by Korotev *et al*. who report an estimated penetrance rate of 54% by age 90. Screening for *DDX41* mutations in a population unselected for myeloid malignancy may give a lower apparent penetrance rate, possibly due to distinct environmental exposures, the presence of less pathologic or hypomorphic mutations in some individuals, or differences in genetic background in others.[3,8] As always, the risk associated with a likely germline *DDX41* mutation must be considered in the context in which it was identified. After their initial discovery in a particular malignancy, cancer predisposing gene mutations often become associated with additional forms of cancer.[5] The BRCA genes initially

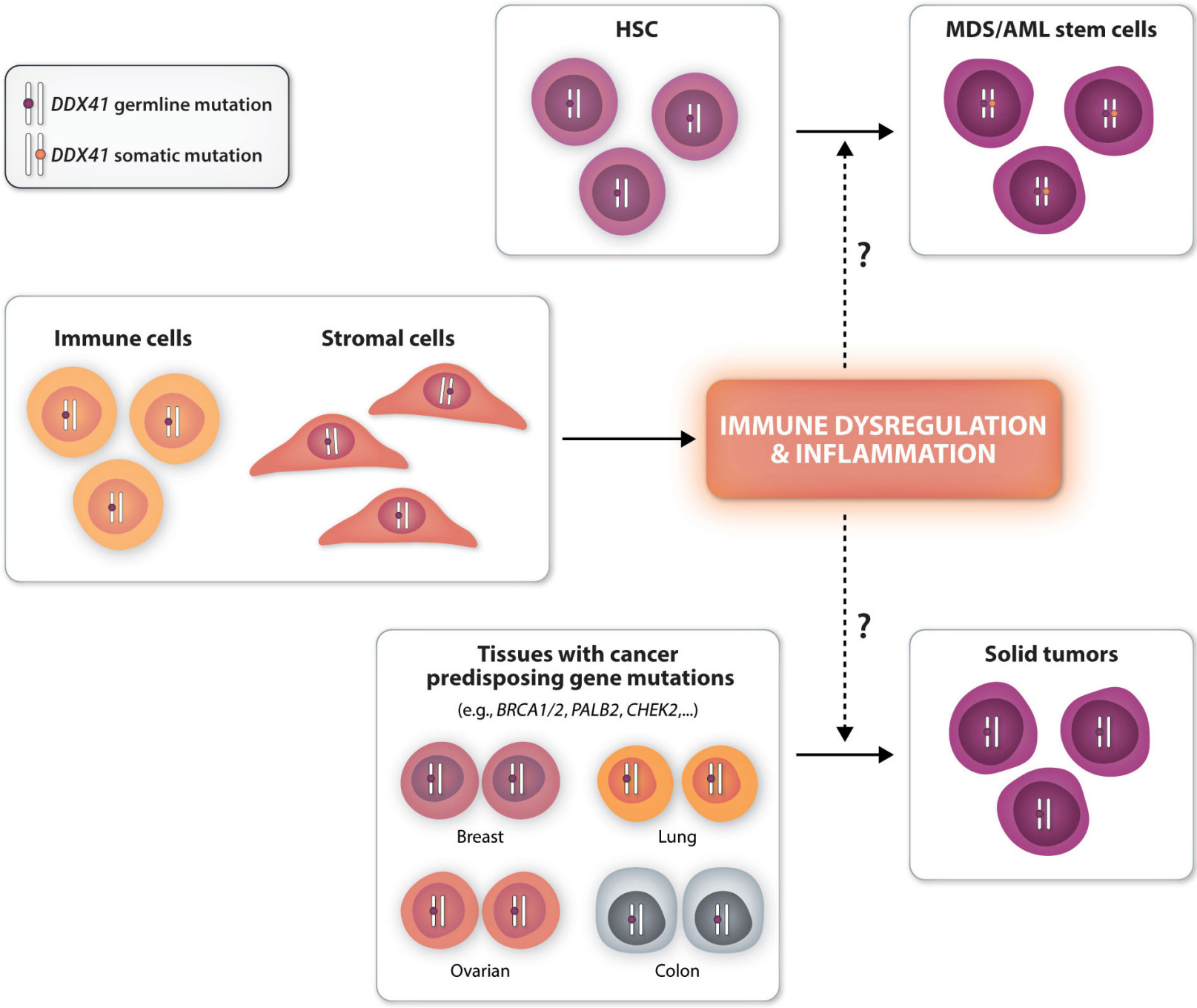

Figure 1. Tumor development in *DDX41* germline mutation carriers. In this issue, Korotev *et al*. examine 43 families with over 90 individuals harboring *DDX41* germline variants associated with predisposition to develop myeloid malignancies such as myelodysplastic neoplasms (MDS) and acute myeloid leukemia (AML). They note that somatic mutation of the remaining, intact *DDX41* allele often accompanies malignant myeloid transformation. However, this does not seem to occur in solid tumors which they find are often present in these families, particularly when probands also carry a corresponding solid tumor predisposition gene mutation. The authors demonstrate how patient-derived, *DDX41* mutant lymphoid cell lines in culture upregulate inflammatory cytokines and NF-kB levels, suggesting that immune dysregulation and aberrant inflammation may drive tumor development in *DDX41* germline mutation carriers. HSC: hematopoietic stem cell.

associated with breast and ovarian cancer predisposition, for example, are now known to clearly contribute to the risk of other cancers including prostate, pancreatic, and melanoma. As Korotev *et al*. show, this may be the case for *DDX41* variants as well. In their study, families had a significant rate of solid tumors identified in 24% of deleterious *DDX41* mutation carriers before age 75. No single type of malignancy predominated and many had concurrent solid tumor predisposition mutations in genes such as *APC*, *BRCA1*, *BRCA2*, and *PALB2* consistent with the solid tumors identified. Somatic *DDX41* mutations were not found in these solid tumors or in a TCGA dataset suggesting that the mechanism promoting solid tumor evolution in *DDX41* germline mutation carriers is distinct from that driving myeloid malignancies and may not be cell intrinsic at all. Instead, the authors speculate that germline *DDX41* mutations could promote certain forms of inflammation that increase solid tumor risk in a cooperative fashion. In support of this position, they demonstrate that patient-derived lymphoid cell lines with *DDX41* mutations upregulate inflammatory cytokines and NF-κB in culture. They also raise the possibility that patients with cancer predisposition gene mutations who are subsequently treated for their solid tumors may be at greater risk of evolving a myeloid malignancy if they also carry a *DDX41* mutation. This provocative study lends support to the idea that germline *DDX41* mutations may be indirect modifiers of

solid tumor risk while more directly promoting the development of myeloid neoplasms. Given the pleiotropic mechanisms ascribed to *DDX41*, how this occurs still leaves many open questions. But it is clear that we will need to broaden our conception about *DDX41*-related malignancy risk and surveillance in people harboring these variants.

Disclosures

RB reports employment and equity in Aptose Biosciences; DMC chair for Ipsen, Gilead, and Keros; consultancy to Geron, Servier, and BMS; and scientific advisory board for NeoGenomics.

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