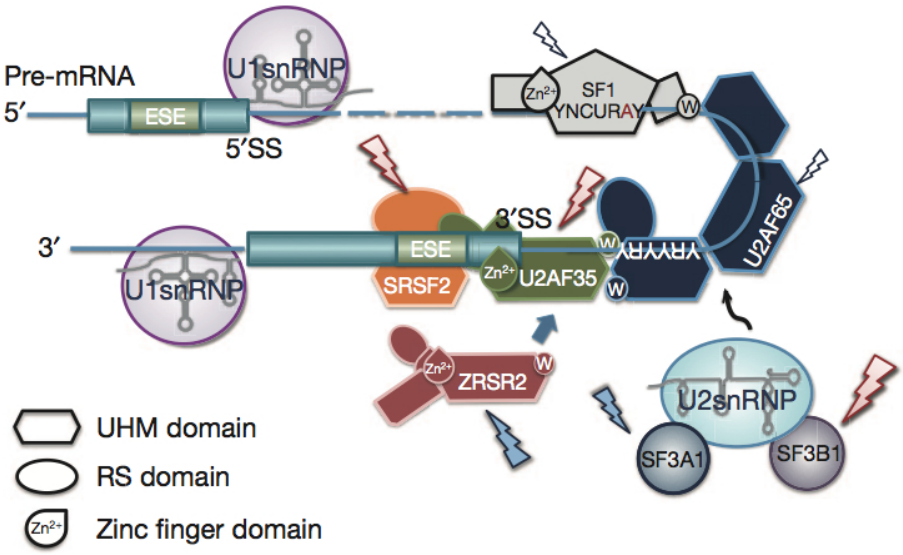
Spliceosome Mutations

Mutations in the splicing machinery have initially been described in myelodysplastic syndromes (MDS) by Yoshida *et al.*[1] These mutations affect especially the factors SRSF2, U2F1, SF3B1 and ZRSR2. They have also been identified in chronic myelomonocytic leukemias (CMML) and in acute myeloid leukemias (AML) with dysplastic features or secondary to treatments.[1,2]

Overall, these mutations are infrequent in the chronic phase of myeloproliferative neoplasms (MPN), in which they are detected in 9.4% of cases.[1] However, they seem more frequent in primary myelofibrosis (PMF), with 34% cases showing mutation of the spliceosome.[3] Also, their frequency depends on the factor considered.



Yoshida et al. Nature 2011

SF3B1 mutations are infrequent in classical MPN (polycythaemia vera (PV), essential thrombocytemia (TE), PMF) and CMML, showing frequencies < 7%.[2,4,5] On the other hand, they are very frequent (about 85% of cases) in refractory anemia with ring sideroblasts and thrombocytosis (RARS-T).[6] These mutations are strongly associated with the presence of ring sideroblasts in MDS, and also in MPN.[4,7,8] They do not modify the clinico-biological presentation nor the prognosis in MPN, but they are associated with a favorable prognosis in RARS-T.[6]

SRSF2 mutations seem to be more frequent in CMML[1] (28%) and in PMF (2.6-17%).[5,9] In contrast to Lasho *et al.*, Zhang *et al.* suggest that they are associated with blast crisis (18.9% of cases) more frequently than with the chronic phase (2.6% of cases).[5] The two studies are in agreement with the negative impact of these mutations on patient survival.

U2AF1 mutations also seem to be more frequent in PMF, with a frequency estimated between 2.6 and 16%.[3,5] They are associated with high risk diseases (with cytopenia) and thus, with a shorter survival.[3]

Spliceosome mutations are mutually exclusive,[1] although one PMF patient has been described as carrying mutations in *SRSF2*, *SF3B1* and *U2AF1*.[3] *SF3B1* and *U2AF1* mutations are frequently associated with *JAK2*V617F and *MPL*W515 mutations.[2,3] *SRSF2* mutations are frequently associated with *IDH1/2* mutations.[9]

References

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