WT1 β'ing catenin into shape: a new interaction driving epigenetic plasticity in acute myeloid leukemia?

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Acute myeloid leukemia (AML) is a heterogeneous disease of the hematopoietic system with a dismal prognosis. Indeed, 2-year survival rates are as low as 5-15% in poor-risk older patients,[1] highlighting the critical need to better understand disease biology and drive new therapeutic approaches. Epigenetic plasticity – especially in leukemic stem cells, the cancer stem cells of hematopoietic disorders – has underpinned drug resistance and relapse, with β-catenin and Wnt signaling regularly reported as a key hub for this plasticity.[2,3]

In this issue of *Haematologica*, Wagstaff *et al.* report a crosstalk between β-catenin and another poor prognostic factor in AML, WT1, with reciprocal regulation of their respective gene transcription functions and converging cellular phenotypes.[4] Indeed, modulation of either protein can result in Wnt signaling alterations, a critical pathway for balancing healthy hematopoietic stem cell function[5] and drug resistance in AML leukemic stem cells.[2,6–8] In 2019, Morgan *et al.* reported the first nuclear and cytoplasmic interactomes of β-catenin in AML,[9] showing that β-catenin-LEF1 interactions were relevant to DNA binding. The present study moves beyond β-catenin-DNA dynamics, finding that β-catenin interacts with a protein that has RNA binding capacity.[10] Surprisingly, Wagstaff *et al.* report that this interaction can occur in the cytoplasm of AML cells, demonstrating that different nucleic acid targets depend on the sub-cellular location. This is critically important as the interaction between β-catenin and WT1 does not appear to be direct, and the authors hypothesize that it is through an intermediate DNA or RNA molecule.

The majority of the β-catenin-WT1 interaction is Wnt-responsive and nuclear-localized in cell lines, suggesting that it only occurs in the presence of stabilized and nuclear translocated β-catenin. In contrast, in primary patient AML samples, this interaction is both nuclear and cytoplasmic, potentially suggesting that the stabilization of β-catenin is more important than its nuclear translocation. Despite the discrepancy between cell line models and primary patient material, WT1 appears to be necessary for β-catenin nuclear translocation, as in its absence there is minimal β-catenin nuclear localization. In agreement with this, induction of clinically relevant WT1 mutations in cell line models induced Wnt signaling in the absence of Wnt stimulation, demonstrating that the WT1 mutations present in patients may be driving β-catenin activity.

While perturbing WT1 clearly alters β-catenin activity, this appears to be reciprocal, in that the absence of β-catenin results in hyper-degradation of WT1, for which the authors hypothesize that β-catenin is actively protecting WT1 from degradation. To further complicate matters, proteosome inhibition downregulates WT1, presumably through feedback at the epigenetic level.[11] This makes unpicking the relationship between β-catenin and WT1 even more difficult and it would be interesting to find the intermediate partners required for β-catenin and WT1 interactions and how they vary in AML.

In a therapeutic context, there is potential for redundancy between β-catenin and WT1 targeting, as inhibition of a single target or pathway may be insufficient if the other molecule can compensate.[12,13] Therefore, it will be interesting to see in future work if leukemic stem cell drug resistance conferred by β-catenin can be overcome by targeting WT1, and whether WT1-mutant AML has specific β-catenin-dependent vulnerabilities.

Disclosures

No conflicts of interest to disclose.

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