**Article:**
Grey, William George (2022) WT1 β'ing catenin into shape:a new interaction driving epigenetic plasticity in AML? Haematologica-The hematology journal. ISSN: 1592-8721

https://doi.org/10.3324/haematol.2022.281119

haematologica
Journal of The Ferrata Storti Foundation

# WT1 β'ing catenin into shape: a new interaction driving epigenetic plasticity in AML?

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*Received: April 5, 2022.*
*Accepted: April 12, 2022.*

*Citation: William Grey. WT1 β'ing catenin into shape: a new interaction driving epigenetic plasticity in AML?*
*Haematologica. 2022 Apr 21. doi: 10.3324/haematol.2022.281119. [Epub ahead of print]*

# WT1 β'ing catenin into shape: a new interaction driving epigenetic plasticity in AML?

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Acute myeloid leukaemia (AML) is a heterogeneous disease of the haematopoietic system with a dismal prognosis. Indeed, two-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 leukaemic stem cells (LSCs), the cancer stem cells of haematopoietic disorders – has underpinned drug resistance and relapse, with β-catenin and Wnt signalling regularly reported as a key hub for this plasticity[2,3].

In this issue, 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 signalling alterations, a critical pathway for balancing healthy haematopoietic stem cell function[5] and drug resistance in AML LSCs[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 this interaction can occur in the cytoplasm of AML, demonstrating 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 hypothesise it is through an intermediate DNA or RNA molecule.

The majority of β-catenin-WT1 interaction is Wnt-responsive and nuclear localised in cell lines, suggesting that it only occurs in the presence of stabilised and nuclear translocation β-catenin. On the contrary, in primary patient AML samples, this interaction is both nuclear and cytoplasmic, potentially suggesting the *stabilisation* 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 localisation. In agreement with this, induction of clinically relevant WT1 mutations in cell line models induced Wnt signalling in the absence of Wnt stimulation, demonstrating that the WT1 mutations present in patients may be driving β-catenin activity.

Whilst perturbing WT1 clearly alters β-catenin activity, this appears to be reciprocal, whereby the absence of β-catenin results in hyper-degradation of WT1, for which the authors hypothesise 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 LSC drug resistance conferred by β-catenin can be overcome by targeting WT1, and whether WT1 mutant AML has specific β-catenin-dependent vulnerabilities.

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