The “Sweet” crosstalk between refractory leukemia cells and vascular niche

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In this issue of *Haematologica*, Feng *et al*. report that decitabine-refractory leukemia breaches the bone-marrow vascular barrier through fucosylated small extracellular vesicles (sEV), increasing endothelial permeability and facilitating leukemic transendothelial migration and early homing.[1] This study links hypomethylating agents (HMA) refractoriness to a specific microenvironmental change: disruption of endothelial tight junctions and increased vascular permeability.

Primary resistance to HMA such as decitabine remains a major cause of treatment failure in elderly patients with myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML), where refractory clones rapidly expand and drive poor outcomes.[2,3] Clonal selection under drug pressure, epigenetic plasticity, and therapy-associated transcriptional programs shape residual disease and influence relapse kinetics. Increasing evidence, however, indicates that refractoriness is not explained by intrinsic drug tolerance alone; resistant cells also remodel the bone-marrow niche, including the vascular endothelium, to create a more permissive and protective microenvironment.[4] The vascular niche has, therefore, come into focus as a functional gatekeeper in leukemia, capable of shaping proliferation, stem cell-like programs, and treatment response.[5,6] Endothelial barrier programs regulate the passage of circulating cells into marrow space and determine exposure to perivascular survival cues. Tight-junction proteins such as ZO-1, occludin, and claudin-5 provide a direct molecular handle on barrier integrity, and permeability assays translate this into function.[7] When junction integrity is reduced, leukemic cells cross more efficiently, gain earlier access to perivascular support, and reseed the marrow faster after cytoreduction. This perspective aligns with evidence that homing, adhesion, and trafficking pathways shape disease kinetics and therapeutic response in myeloid malignancies.[8]

Feng *et al*. position sEV as a transferable unit that links refractory leukemia to endothelial barrier failure. Refractory cells show preferential detection in bone marrow and spleen early after injection, and plasma from refractory patients or leukemia-derived material reduces tight-junction proteins and increases permeability in endothelial monolayers. Purified sEV reproduce this endothelial phenotype, with vesicles from refractory cells showing stronger effects than those from parental counterparts, thereby sharpening attention on vesicle-mediated communication at the vascular barrier. This interpretation is consistent with prior reports, including earlier work from the same group, showing that leukemia-derived exosomes can reprogram bone-marrow stromal compartments toward leukemia support.[9]

What sets this study apart is that glycosylation is treated as a driver of the vesicle phenotype. The authors show that sEV from refractory cells carry higher terminal fucosylation, link this shift to increased FUT4, and associate it with enrichment of non-sialylated Lewis^{x} (Le^{x}) structure. Modulating FUT4 shifts this surface signature and correspondingly alters endothelial readouts: FUT4 knockdown in leukemia cells weakens tight-junction loss and permeability changes, whereas FUT4 overexpression strengthens them. Upstream, TWIST1 is shown to drive FUT4 transcription, connecting a therapy-associated cell state to this glycosylation output. Downstream, ICAM3 is identified as a Le^{x}-modified vesicle protein enriched in refractory sEV, with evidence consistent with increased abundance and stability. Together, the data support a TWIST1–FUT4–Le^{x} axis on sEV that converges on endothelial junction disruption and vascular leakiness, facilitating transmigration and early niche access.

Clinically, primary HMA failure is often followed by rapid marrow re-infiltration and early relapse. This course reflects more than persistence under drug exposure; it also reflects how quickly leukemic cells can re-enter supportive marrow space when the system is stressed and cell numbers are low. The vascular barrier is the first physical checkpoint in that process. When endothelial junction integrity is weakened, marrow entry becomes easier and perivascu-

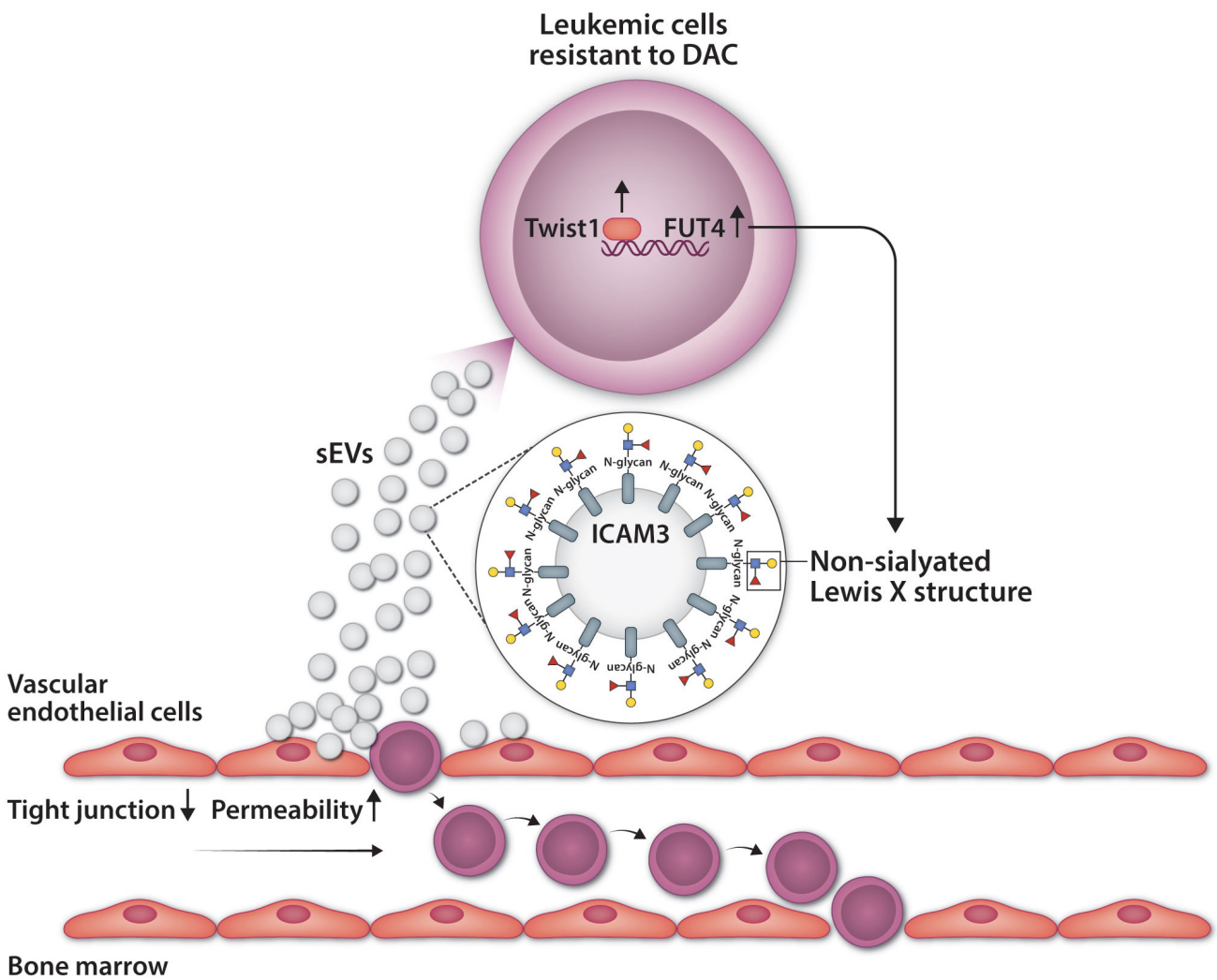

Figure 1. Decitabine-refractory leukemia remodels the vascular barrier through fucosylated exosomal intercellular adhesion molecule 3. Decitabine-refractory leukemic cells up-regulate TWIST1 and fucosyltransferase 4 (FUT4), enriching fucosylated, non-sialylated Lewis^{x} (Le^{x}) structures on exosomal intercellular adhesion molecule 3 (ICAM3) carried by small extracellular vesicles (sEV). These vesicles weaken endothelial tight-junction integrity, increase vascular permeability, and promote leukemic transendothelial migration and homing to the bone marrow.

lar support is reached earlier. This view is consistent with reports that bone-marrow vascular permeability is altered in AML and can influence disease course and treatment response.[4] It also provides a simple way to interpret vesicle programs in refractory disease. sEV circulate, reach endothelium early, and can shift barrier behavior before heavy leukemic infiltration, allowing a refractory state to manifest as a niche phenotype rather than remaining confined to the malignant clone.

This framing also strengthens the rationale for niche-directed strategies in refractory disease. It places vascular gatekeeping upstream of marrow reseeding and focuses attention on a tractable interface instead of a generic "microenvironment." Prior work showing benefit from targeting vascular adhesion signals supports the view that endothelium contributes to therapy response.[4] The present study adds a biochemical layer to that interface by linking FUT4-dependent fucosylation on circulating sEV to junction loss. The same vesicle features can, therefore, be pursued as plasma biomarkers during HMA therapy, while the same pathway highlights points of intervention to limit early niche access. A key step for specificity is to identify how endothelium recognizes and internalizes fucosylated vesicles, since blocking an endothelial decoding step is likely to be more selective than broadly altering glycosylation. This focus on the vascular interface provides a practical basis for translational testing in HMA-refractory disease.

Overall, this study links HMA refractoriness to endothelial barrier failure through FUT4-dependent glycosylation of sEV (Figure 1). It provides a rationale to develop plasma biomarkers and to evaluate vascular niche-directed combinations in refractory disease.

Disclosures

No conflicts of interest to disclose.

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