Blocking Vascular Niche E-Selectin Dampens AML Stem Cell Regeneration/Survival Potential In Vivo By Inhibiting MAPK/ERK and PI3K/AKT Signalling Pathways

Ingrid G Winkler1, Valerie Barbier2, Joshua Tay1, Jean-Pierre Levesque2, John L. Magnani3, Corrine E Fiveash2 and Johanna M Erbani2
1Mater Research Institute - University of Queensland, Brisbane, QLD, Australia; 2Mater Research Institute - University of Queensland, Brisbane, Australia; 3GlycoMimetics Inc., Rockville, MD

Poster 2657

Rationale

We have previously shown vascular E (endothelial)-selectin to play a key role in niche-mediated chemoresistance in Acute Myeloid Leukemia (AML). Now we report that the cell surface glycosylation of AML blasts - and thus their E-selectin-binding potential - alters during therapy and queried whether these variations influence treatment outcome.

Introduction

The vascular adhesion molecule E-selectin has been shown to be a key component of the Bone Marrow (BM) Haematopoietic Stem Cell (HSC) niche with a role in facilitating HSC activation at the expense of self-renewal (Winkler et al., 2012).

How do AML cells respond to E-selectin at the vascular niche?

1a. AML blasts with highest E-selectin binding survive chemotherapy

1b. FACs sorted AML blasts show E-selectin blockade dampens AML regenration potential

2a. In vitro adhesion to E-selectin directly mediates cytoarabine resistance in AML

2b. Therapeutic blockade of E-selectin at the same time as chemotherapy doubles treatment efficacy

Conclusion and significance

Here we show that [1] vascular niche E-selectin blockade by Gmi-1271 dampsen malignant AML reconstituation/survival potential in vivo when administered as sole agent alone.

[2] E-selectin blockade mediates these effects via dampening a range of intracellular survival/algrediation signalling pathways in the malignant cell, and finally

[3] these data suggest E-selectin blockade may synergise with other specific pathway inhibitors to improve treatment outcomes - but only for malignant cells that are significantly glycosylated to interact with E-selectin. A Phase II Clinical Trial to study efficacy of Gmi-1271 in combination with chemotherapy in AML patients (NCT03616470) is currently in progress.