Vascular E-Selectin Mediates Chemo-Resistance in Acute Myeloid Leukemia Initiating Cells Via Canonical Receptors PSGL-1 (CD162) and Hcell (CD44) and AKT Signaling

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Abstract 793, ASH 2017, Atlanta, Georgia
How niches regulate this switch?
Signalling pathways between HSC and niche

Cancer stem cells share the majority of these – but outcomes may differ

Iwasaki and Suda, 2010, HSC niche chapter, Stem Cell Biology, Humana press
Selectins - classical role as leukocyte homing molecules

family of vascular Adhesion Molecules - involved in leukocyte homing

Injury / inflammation

i) Selectins,  
ii) Integrin ligands (ICAM1, PECAM1, VCAM)

3 – 12 hrs post injury / inflammation
Selectins - new role as stem cell regulators

Vascular niche E-selectin regulates hematopoietic stem cell dormancy, self renewal and chemoresistance

Ingrid G Winkler¹, Valérie Barbier¹, Bianca Nowlan², Rebecca N Jacobsen²,³, Catherine E Forri John T Patton⁴, John L Magnani⁵ & Jean-Pierre Lèvesque²,³

BrdU+ % of HSC

HSC proliferation

8-fold less HSC turnover in E⁻/⁻
E-selectin expression at the BM vascular niche increases following stress

Bone Marrow endothelial cells (flow cytometry)

Endothelial cells in:
- control mice
- Post-irradiation

14 days post irradiation

Winkler et al., Nat Med 2012
Vascular E-selectin is upregulated in Acute Myeloid Leukaemia

**AML MODEL.**

MLL- (11q23) driven monomyelocytic leukaemia

Q. How to AML cells respond to E-selectin?

![Diagram showing bone marrow with labels: HSC, LSC, osteoblasts, endothelial cells, macrophage, and nerve.]

![Graph showing % E-selectin +, endothelial cells (CD31+ Lin- CD45-GFP) in mice with no leukaemia and MLL-AF9 leukaemia.]

Winkler & V Barbier, Unpublished
Vascular E-selectin promotes AML survival to chemotherapy

Q. If we block E-selectin does it chemo-sensitise in vivo?

D Pattabiraman, J Erbani, unpublished
Absence of E-selectin sensitises AML LSC to chemotherapy

Perivascular AML cell after cytarabine (xenograft mouse)

Ninomiya et al., Leukemia 2007

V Barbier & I Winkler, unpublished
Perivascular AML cell after cytarabine (xenograft mouse)

Ninomiya et al., Leukemia 2007

Therapeutic E-selectin blockade Sensitises LSC to chemotherapy

GMI-1271. GlycoMimetics, Inc.
small synthetic mimetic antagonist

V Barbier & I Winkler, unpublished
Increase mouse survival

GMI-1271. small synthetic mimetic antagonist

prelim data Phase I/II trial - Abstract #894. Session 616 (7:30pm)

V Barbier & I Winkler, unpublished
Remaining questions

What are the....

• Ligands mediating these interactions
• Signalling pathways involved.
Two canonical receptors

- PSGL1 (CD162)
- CD44 (HCAM1)
Absence of canonical receptors appears to reverse E-selectin mediated chemo-resistance

In vitro
Pro-survival Signalling pathway

Western Blot for AKT phosphorylation.

Reporter cells for NF-kB mediated signalling

p-AKT Ser473

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Does blocking AKT / NF-kB pathway reverse E-selectin mediated chemo-resistance?
SUMMARY

Malignant cells survive therapy

Cell intrinsic factors

Environmental factors (niche)
Malignant cells survive therapy
Collaborators

Haematologists - PAH & Mater, Australia
Andrew Perkins
Paula Marlton

GlycoMimetics – MA, USA
John Magnani – Glycobiologist

University of Queensland
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Centenary Institute, Sydney
John Rasko

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