Ingrid Winkler

Title. Vascular bone marrow niches protect AML leukaemia stem cells from chemotherapy.

Disclosure. Co-author John Magnani is an employee of GlycoMimetics. GlycoMimetics funded the parts of this work involving their mimetics.
blood

Bone marrow

Active

Dormant

myeloid

lymphoid

Active

Dormant

myeloid

lymphoid

Australia
HSC

Iwasaki and Suda, 2010,
HSC niche chapter, Stem Cell Biology, Humana press
E-selectin

Iwasaki and Suda, 2010,
HSC niche chapter, Stem Cell Biology, Humana press
Vascular niche E-selectin regulates hematopoietic stem cell dormancy, self renewal and chemoresistance

Ingrid G Winkler¹, Valerie Barbier¹, Bianca Nowlan², Rebecca N Jacobsen²,³, Catherine E Forristal², John T Patlon¹, John L Magnani¹ & Jean-Pierre Lévesque²,³
Vascular niche E-selectin regulates hematopoietic stem cell dormancy, self renewal and chemoresistance

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*8-fold less HSC turnover in E-/-*

BrdU+, % of HSC

\[ \begin{align*}
\text{WT} & \quad 0 \\
\text{E-/-} & \quad 8
\end{align*} \]

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

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Vascular E-selectin expression low in steady-state

BM endothelial cells

Endothelial cells in:
control mice
Post-irradiation

3% positive in steady-state

E-selectin
Vascular E-selectin increases following stress

BM endothelial cells

Endothelial cells in:
- control mice
- Post-irradiation

E-selectin
Vascular E-selectin is upregulated in Acute Myeloid Leukaemia

**AML MODEL.**

MLL- (11q23) driven monomyelocytic leukaemia

How to AML cells respond to E-selectin?
Vascular E-selectin is upregulated in Acute Myeloid Leukaemia

AML MODEL.

MLL- (11q23) driven monomyelocytic leukaemia

How to AML cells respond to E-selectin?
Vascular E-selectin is upregulated in Acute Myeloid Leukaemia

.... promotes survival to chemotherapy
Absence of E-selectin sensitises LSC to chemotherapy
MLL-AF9 Leukaemia

Absence of E-selectin sensitises LSC to chemotherapy
Absence of E-selectin sensitises LSC to chemotherapy.
Absence of E-selectin sensitises LSC to chemotherapy
Perivascular AML cell after cytarabine (xenograft in mouse)

Ninomiya et al., Leukemia 2007
Therapeutic E-selectin blockade Sensitises LSC to chemotherapy

GMI-1271.
synthetic E-selectin GlycoMimetic antagonist.
Specifically blocks E-selectin binding site
Therapeutic E-selectin blockade Sensitises LSC to chemotherapy

GMI-1271.
synthetic E-selectin GlycoMimetic antagonist.
Specifically blocks E-selectin binding site
Identify E-selectin as a novel therapeutic target

Key Findings

• E-selectin expression on BM vasculature increases during AML

• Adhesion to E-selectin protects LSC from chemotherapy

• Adjunct GMI-1271 together with chemotherapy

= 95% reduction in LSC survival.
Thankyou for listening...

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