Follicular lymphoma microenvironment as a therapeutic target

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FL: a niche-centered disease

From a B-cell autonomous disease...

- Genetic hallmark: t(14;18)
- Recurrent secondary genetic hits
- Hierarchical models of successive genetic events

...to a niche-centered disease

- No true FL cell line
- Failure to establish FL xenografts in immunocompromised mice
- Tg mice with B-cell restricted Bcl2 overexpression do not develop FL
- Induction of ectopic LN-like microenvironment in invaded BM
- Some frequent genetic hits are not oncogenic per se
- Numerous microenvironment-related biomarkers
What are the characteristics of FL-specific cell niche?

What are their functional consequences?

How FL-microenvironment modifications are induced (inducer mechanisms, precursors)?

Is there a link between B-cell genetic alterations and microenvironment features?

Is it possible to identify circulating biomarkers?

Do FL cell niche provide suitable therapeutic targets?
Biological resource collection

Extension to 5 new French expert centers (CALYM CeVi program)

Transcriptomic/NGS approaches including single-cell

Purification/Generation of Relevant cell subsets

Functional analyses

Whole tissue

Blood

LN, Tonsils

Lymphoma patients
Matched healthy donors

> 3 M People

St Brieuc
St Malo
Laval
Rennes
Lorient
Vannes

St Malo
Laval

Transcriptomic/NGS
approaches

IHC/IF

FC
Microenvironment in FL

Quantitative and qualitative approaches

FL TAM

FL B cells

FL stromal cells

FL Tfh
FL Tfr

Quantification in BM plasma

CCL2 (pg/ml)

HD   FL

***

TNF/LT signature

PD-1

CXCR5

CFSE

FL-MSC ← HD-MSC

Quantitative and qualitative approaches

CXCL13
TNFRSF13 b
CCL19
CXCL12
IL7
PDPN
Tellier, Ménard Blood 2014, 123:3462

**Anti-tumor activity**

- **NK**
  - CD16
  - SIRPα
- **FL cells**
  - CD16
  - Anti-CD20
  - CD20
  - CD16
  - CD32
- **CD8**
  - TIM-3
  - CD16
- **CD16**
  - PD-1
  - ULBP
  - NKG2D
  - TCR
- **BTLA**
  - TIM-3
  - PD-1

**T**

- **BCL2**
- **CD20**
- **CD10**
- **merge**

**CCL2**

**Notch**

**IL-15**

**DC-SIGN**

**IL-4**

**CXCL12**

**CD40L**

- **TNF**
- **IL-4**

**Epron Leukemia 2012; 26:139; Grégoire Oncotarget 2015; 6:16471**

**Amin Blood 2015; 126:911; Pangault Leukemia 2010; 24:2080**

**Amé-Thomas Leukemia 2012, 26:1053; Ame-Thomas Blood 2015; 125:2381**

**Guilloton Blood 2012; 119:2556**
Blood signature of FL niche?

- Fully validated CMF panels
  - T/NK IC: CD3, CD4, CD45RA, CD8, CD56+CD16, HLA-DR, Tim-3, CD31, LAG-3, PD-1, CCR7, CD137, viability dye
  - M-MDSC: CD14, CD16, CD64, HLADR, CD141, CD1c, CD123, CD86, PD-L1
  - Tfh, Treg…

- Data bank from FL/DLBCL patients at diagnosis and relapse, matched HD, patients with inflammatory diseases (GVHD, AID, sepsis…)
Blood signature of FL niche?

**In vivo**

- CD4
  - % Ki67+
  - ***
  - C1J1, C1J8, C2J1

- CD8
  - % Ki67+
  - ***
  - C1J1, C1J8, C2J1

**In vitro**

- CD4
  - Proliferation index
  - **
  - C1J1, C1J8, C2J1

- CD8
  - Proliferation index
  - **
  - C1J1, C1J8, C2J1

**HD**
Loss of HVEM favors FL pathogenesis through B-cell intrinsic mechanisms.

Collab. HG Wendel (MSKCC, NY)
Enginnered CAR-T in FL

HVEM loss triggers modifications of FL microenvironment

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Human GC-Tfh

HVEM inhibit TNF/LT production by Tfh

Collab. HG Wendel (MSKCC, NY)
HVEM loss is associated with an activation of FL CAF

Proof of Concept of the Link between Genetic Alterations and Selection/Polarization of the Tumor Microenvironment

Boice, Salloun, Mourcin Cell 2016
CAR-T cells

Modified CART cells

CAR-T cells

*CAR-T = MICRO-PHARMACY*
R&D strategies

- In vitro evaluation of new drugs
  - Primary malignant cells
  - ADCC, ADCP (macro, PN), T cells…
  - Role of stromal cells (unique lymphoid stroma cell lines, lymphoma versus HD stromal cells)

- Immunomonitoring of lymphoma patients looking for biomarkers of drug activity
  - Large multicentric trials (French, European)
  - Multicolor FCM, banking & functional assays (Treg, DC, ADCC, MDSC…)
  - Blood + BM
R&D strategies

Mouse xenograft model

- B-cell line with indolent growth restricted to BM and SLO
- B-cell line + stromal cells under the kidney capsule
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Institut Carnot Calym
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