Tumor-associated high endothelial venules (TA-HEVs): specialized blood vessels for lymphocyte entry into tumors

Mechanisms controlling lymphocyte entry into tumor during cancer immunity and immunotherapy?

The Cancer Immunity cycle (Chen and Mellman, Immunity 2013)

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High Endothelial Venules (HEVs): specialized blood vessels for lymphocyte entry into lymphoid organs


A long standing interest for HEVs (30 years of expertise !)

1st Isolation of HEV endothelial cells
Girard and Springer, Immunity, 1995

Regulation of HEVs by dendritic cells

Discovery of interleukin-33 (IL-33/NF-HEV)
Baekkevold… and Girard, Am J Path 2003
Carriere… and Girard, PNAS 2007
Tumor-associated HEVs (TA-HEVs) in human cancer

(Martinet*, Garrido* ...and Girard, Cancer Res 2011)

Human Solid Tumors Contain High Endothelial Venules: Association with T- and B-Lymphocyte Infiltration and Favorable Prognosis in Breast Cancer

Ludovic Martinet1,2, Ignacio Garrido1,2,4, Thomas Fillion4, Sophie Le Guellec4, Elisabeth Bellard1,2, Jean-Jacques Foumie3, Philippe Rochaix4, and Jean-Philippe Girard1,2

Cancer Res; 71(17) September 1, 2011

Breast Cancer

MECA-79

Human primary melanomas n = 225  (TA-HEVs in 60-70 % of tumor samples)

Human primary breast tumors n = 273

Melanoma

Ovarian Cancer

Lung Cancer

Colon Cancer
Tumor-associated HEVs (TA-HEVs) in human cancer
(Blanchard and Girard, Angiogenesis, 2021)

a) TA-HEVs in a CD20⁺ B cell-rich TLS (breast cancer)

b) TA-HEVs in a CD3⁺ T cell-rich area (melanoma)
TA-HEVs are located in the stroma and invasive margin

High endothelial venules (HEVs) in human melanoma lesions
Major gateways for tumor-infiltrating lymphocytes

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TA-HEVs are enriched at the invasive margin of melanoma lesions (not in the tumor core)

TA-HEVs are located in the tumor stroma
TA-HEVs are the main sites of lymphocyte entry into tumors treated with anti-PD-1/anti-CTLA-4 immunotherapy

*(Asrir*, Tardiveau*, Coudert*, Laffont*, Blanchard*, ...and Girard, Cancer Cell 2022)*

*In vivo* imaging of TA-HEVs with fluorescent mAb MECA-79

Wide field intravital microscopy (real time)

**MECA-79**

Blood vessel

**MECA-79**

TA-HEVs

Intravital microscopy (real time) - lymphocyte rolling and sticking in a MECA-79+ TA-HEV

*(Combined immunotherapy with anti-CTLA-4 and anti-PD-1 mAbs)*

Jean-Philippe GIRARD

SITC

18/09/23
TA-HEVs are the main sites of lymphocyte entry into tumors treated with anti-PD-1/anti-CTLA-4 immunotherapy (Asrir*, Tardiveau*, Coudert*, Laffont*, Blanchard*, ...and Girard, Cancer Cell 2022)

Multiphoton *in vivo* imaging (time lapse) - lymphocyte extravasation in MECA-79+ TA-HEVs

PyMT mammary carcinoma and CT26 colon carcinoma tumor-bearing mice treated with combined ICB

Fluorescent lymphocytes from tumor-bearing mice treated with combined ICB (anti-CTLA-4 + anti-PD-1 mAbs)
TA-HEVs predict response and survival of metastatic melanoma patients treated with combined immunotherapy

(Asrir*, Tardiveau*, Coudert*, Laffont*, Blanchard*, ...and Girard, Cancer Cell 2022)

Large cohort of patients with unresectable stage III or IV metastatic melanoma (n=93) treated with anti-PD-1 (n=65) or anti-CTLA-4/anti-PD-1 (n=28)

Collaborative study with Pr Caroline Robert (GR Villejuif)
Increasing TA-HEVs with an agonist of the lymphotoxin beta receptor (LTβR) ameliorates the efficacy of combined immunotherapy (Asrir*, Tardiveau*, Coudert*, Laffont*, Blanchard*, ... and Girard, Cancer Cell 2022)

DCs regulate HEV phenotype and function through the LTβR signaling pathway

Anti-CTLA-4/anti-PD-1 induce regression of non-regressing tumors when the function of TA-HEVs is increased by treatment with an agonist of LTβR (T, Triple therapy)