



Tumor Immune Microenvironment: A Holistic Approach Workshop

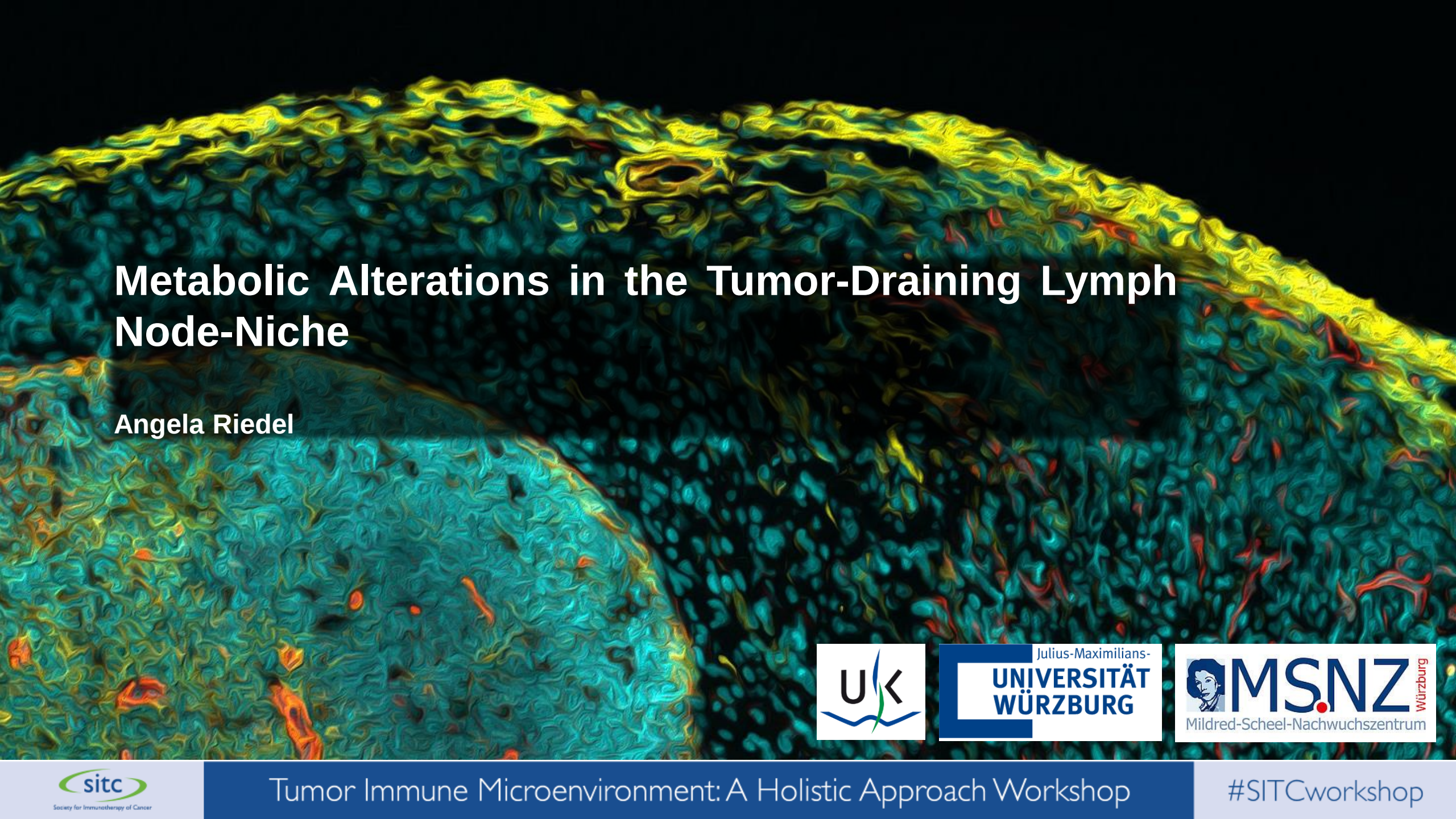
April 21-22, 2022 • San Diego and Virtually

#SITCworkshop



Society for Immunotherapy of Cancer

No financial interests or relationships to disclose

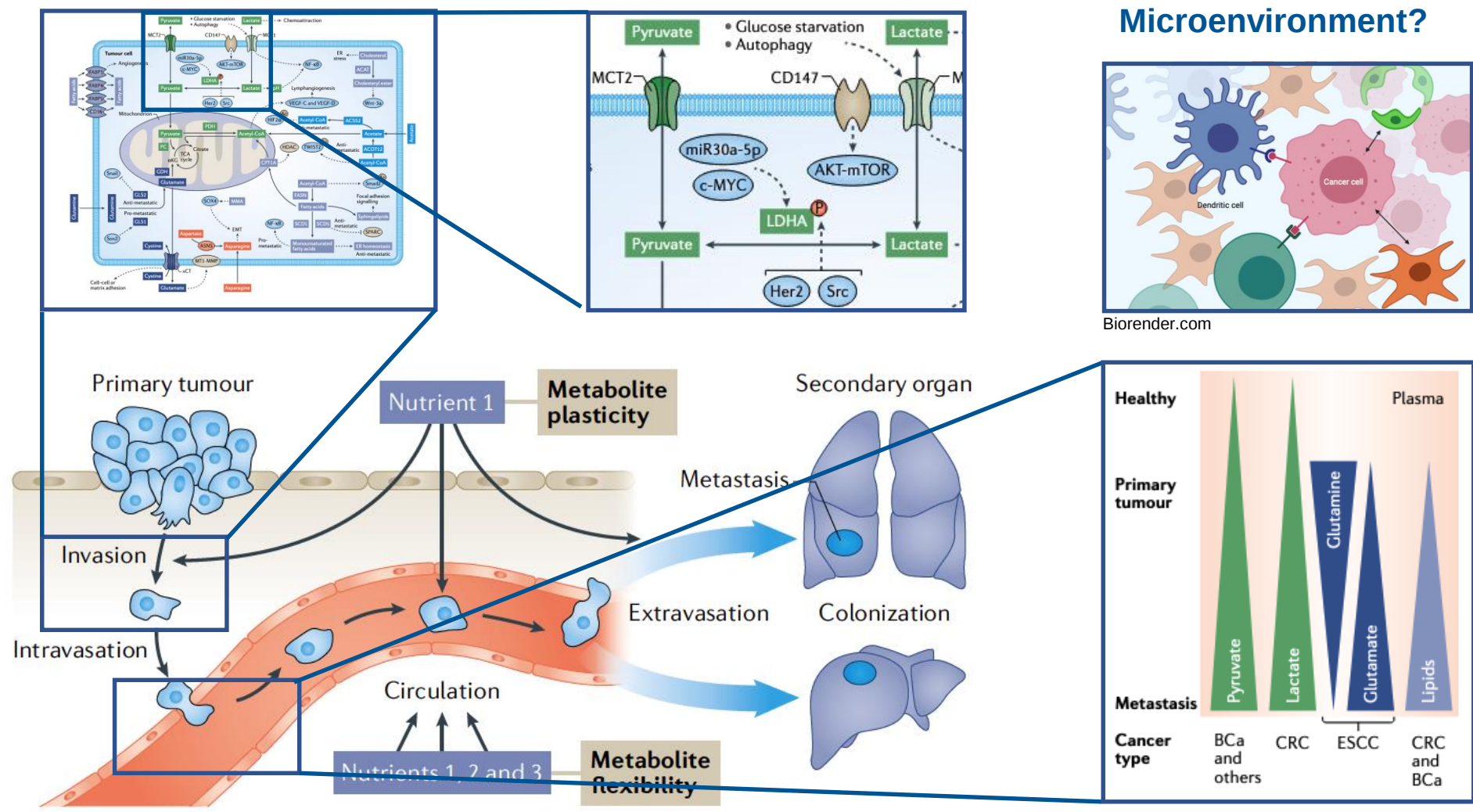


Metabolic Alterations in the Tumor-Draining Lymph Node-Niche

Angela Riedel



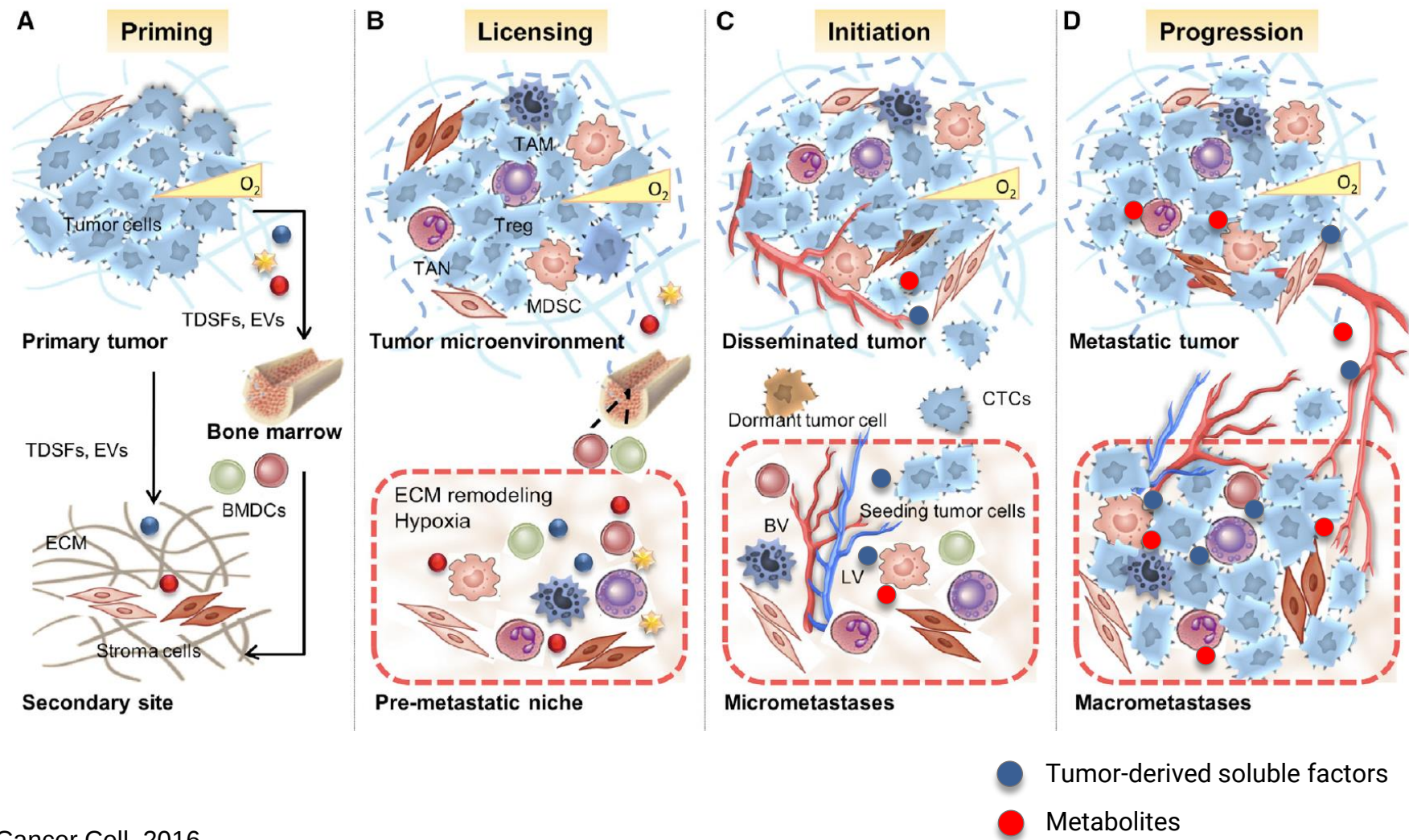
Metastasis and Metabolism: A story of cancer cells and their microenvironment



After Bergers and Fendt, Nat Rev Cancer, 2021

Angela Riedel 21-04-22

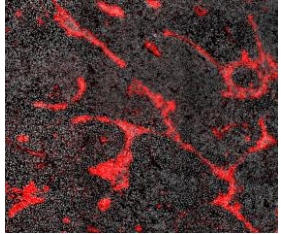
Metastasis: A story of cancer cells and their microenvironment



After Cao et al, Cancer Cell, 2016

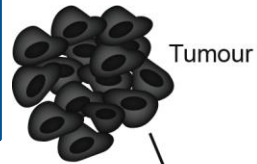
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Tumor-draining lymph nodes (TDLNs) – metastasis and immunity

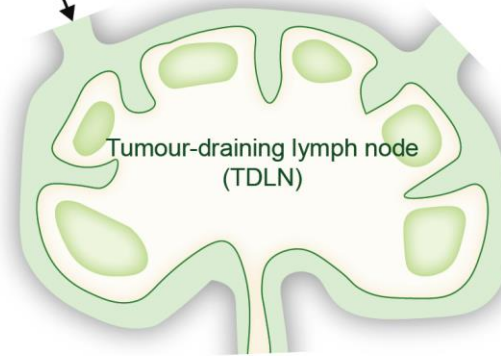


Tumour - Lymphatics

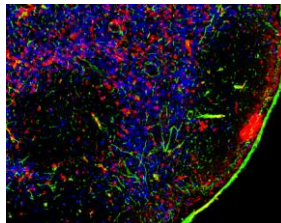
- Lymphatic vascular invasion is linked to poor prognosis



Tumour



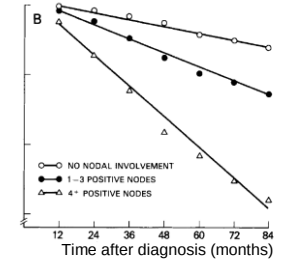
Tumour-draining lymph node (TDLN)



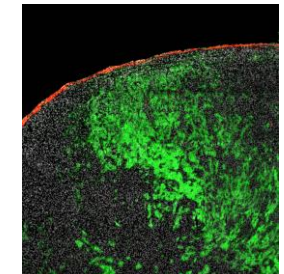
LN – T cells

- LNs are immunological hubs and key to immunity

- LN involvement - disease free survival
- Tumor staging



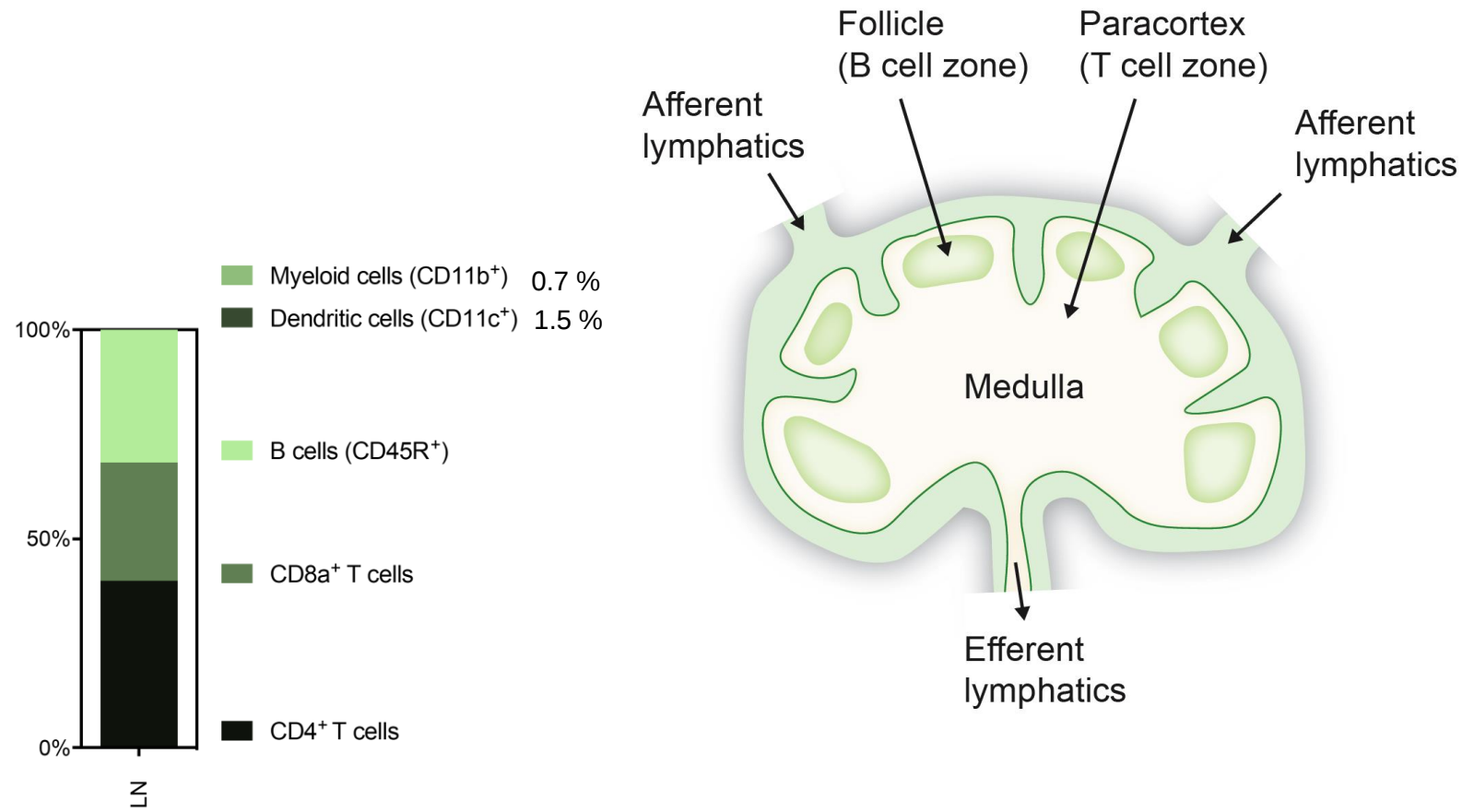
- LN metastasis are detected first
- Are an indicator for distant metastasis



LN – Cancer cells

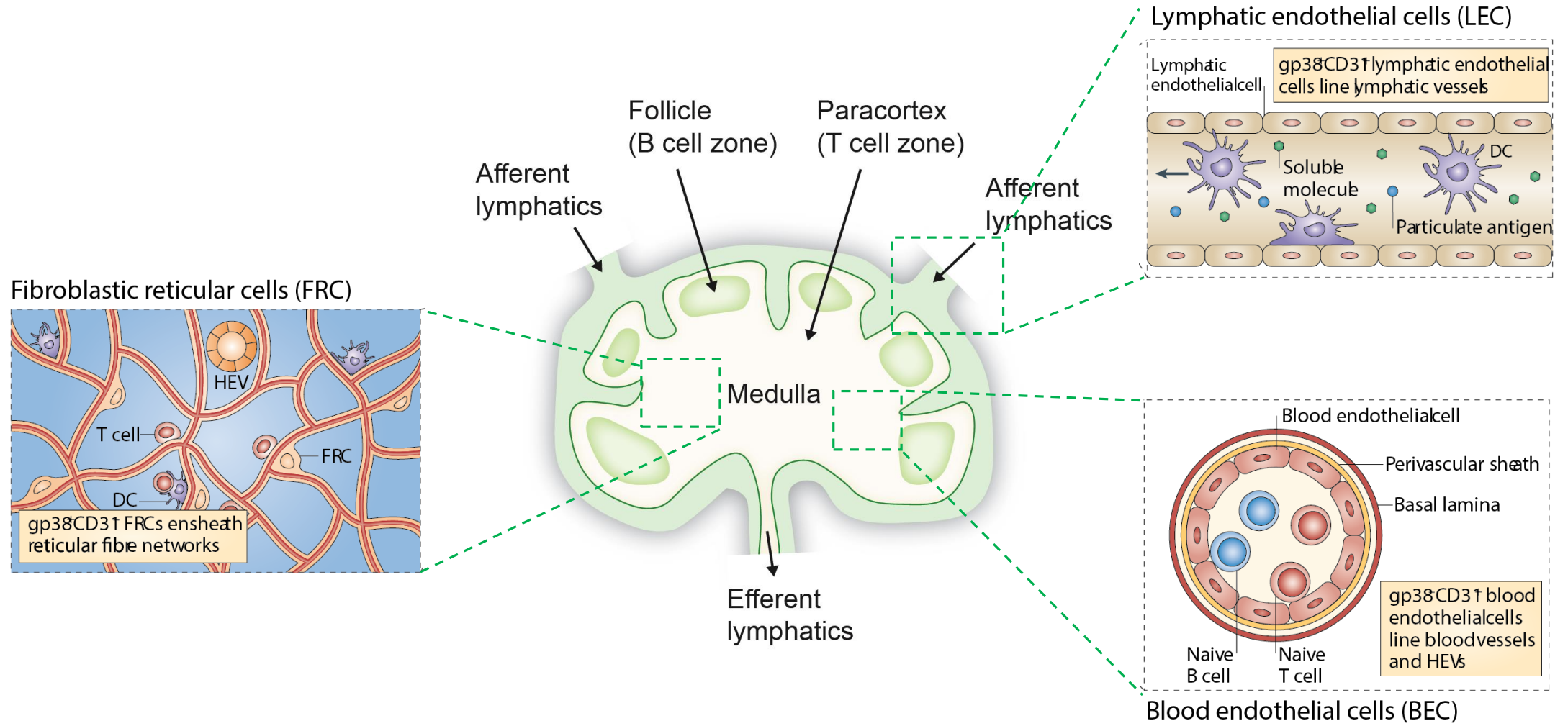
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Lymph node (LN) – Immune cells



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Lymph node (LN) – Stromal cells

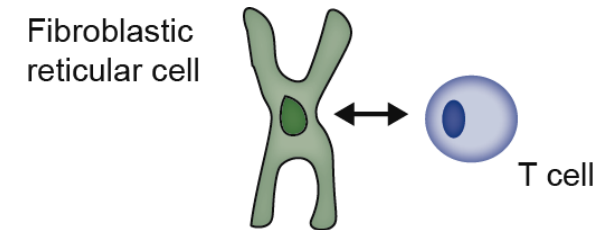


After Turley et al., Nat Rev Immunology, 2010

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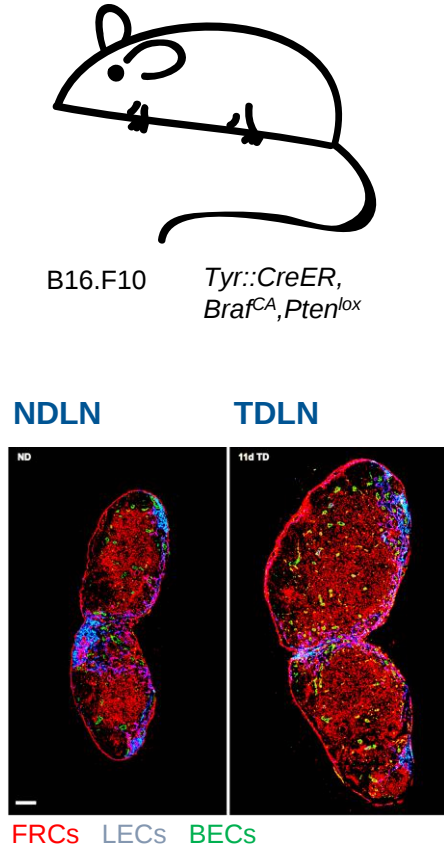
Fibroblastic reticular cells (FRCs) are essential for LN function

- **FRCs support effective immune responses in LNs:**
- Structure and conduit network (LN architecture)
- Chemokine signalling – immune cell guidance, interaction, recruitment, migration (**CCL21**) and survival (**IL7**)
- **... but can also mediate tolerogenic responses:**
- Can restrict T cell activation (via e.g. NO, COX, PGE etc)
- Restrict T cell responses by presenting peripheral tissue-restricted antigens
- Support T_{reg} cells (via e.g. IL33)
- Effective immune response damage ↔ Autoimmunity and stromal

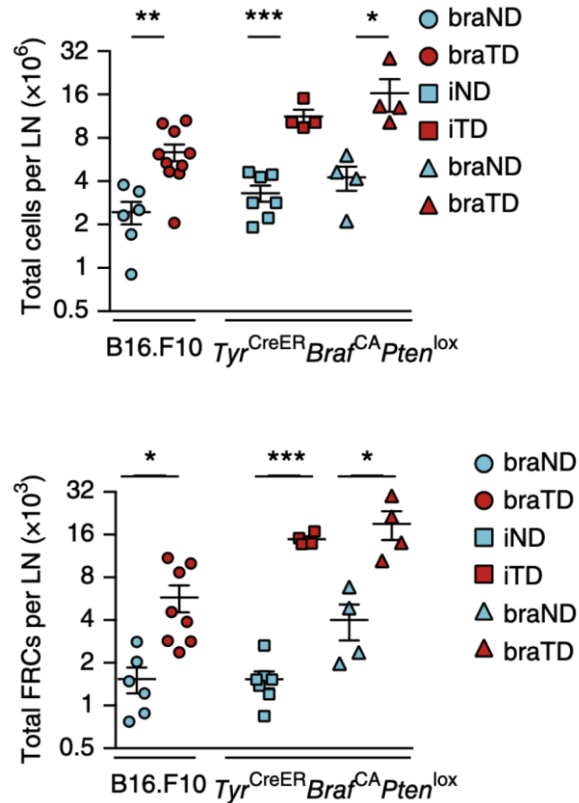


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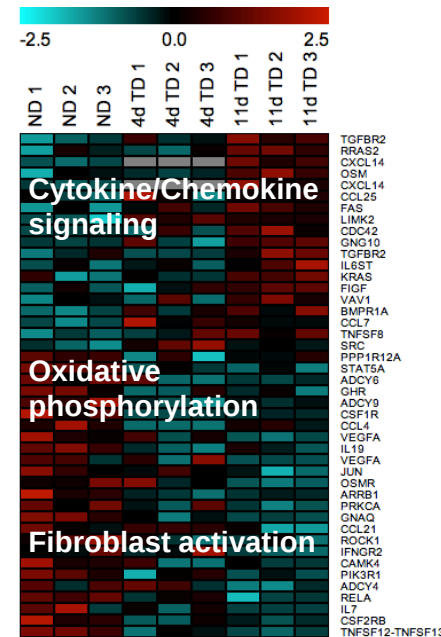
FRCs of pre-metastatic TDLNs are transformed



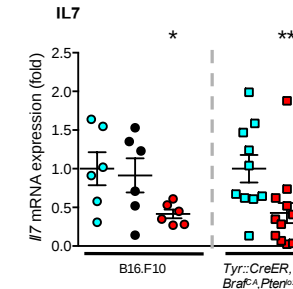
TDLNs enlarge and remodel



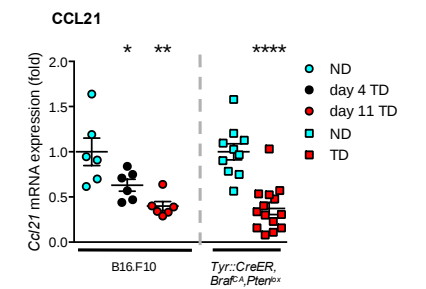
FRC deregulated pathways



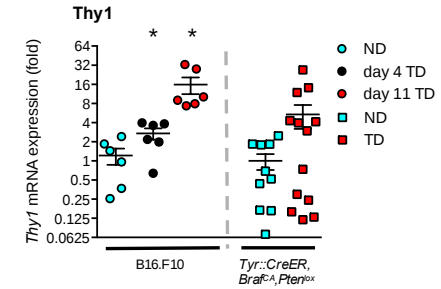
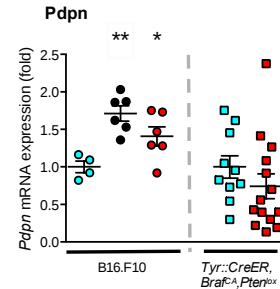
Survival



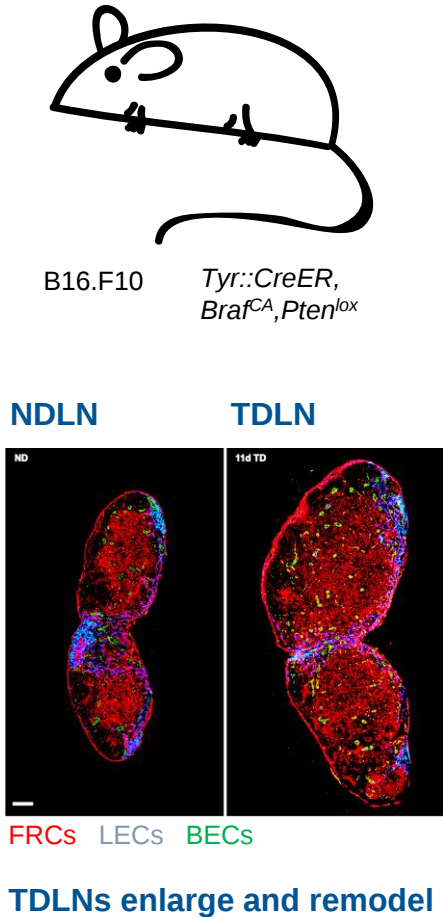
Homing + location



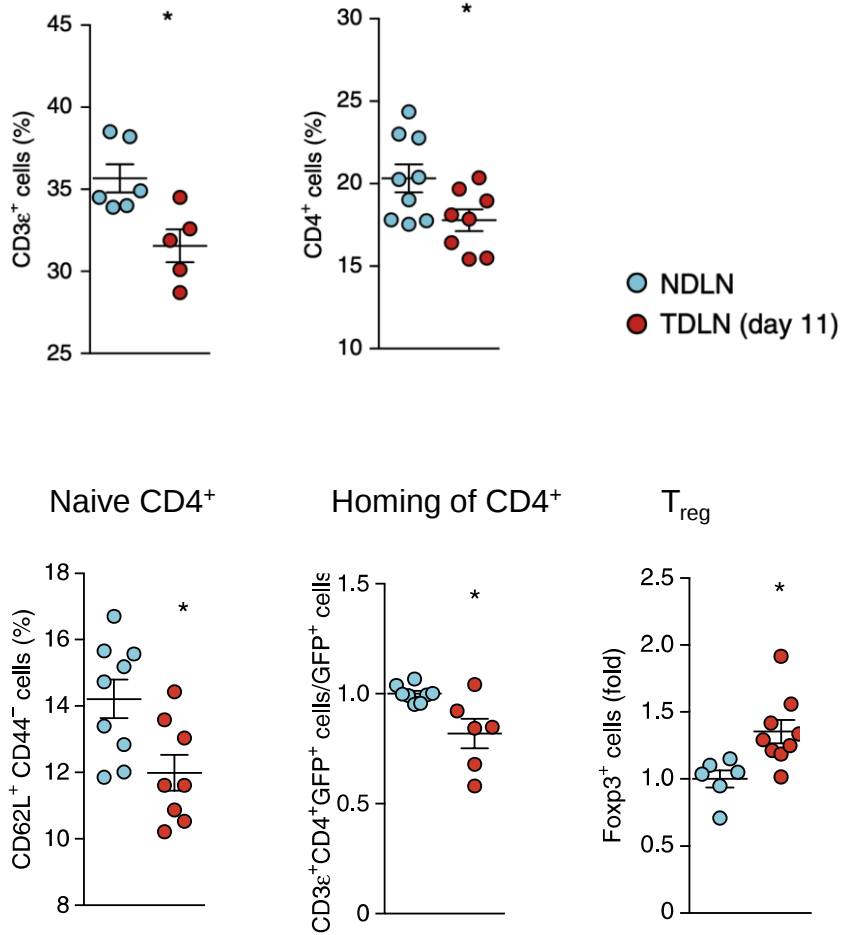
Activation



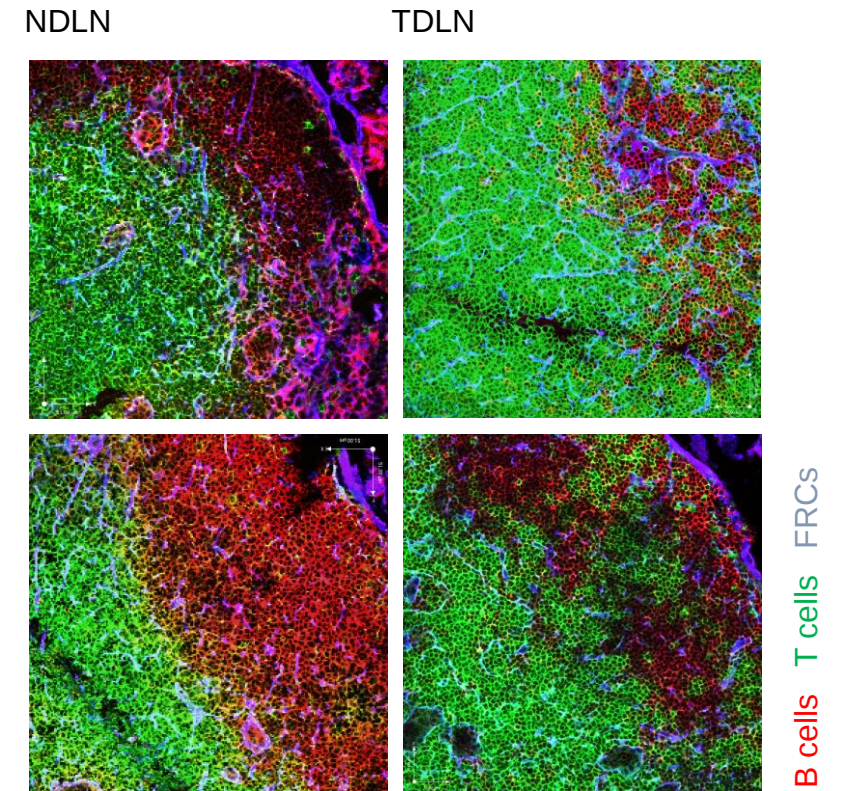
Immune cell compartments of pre-metastatic TDLNs are altered



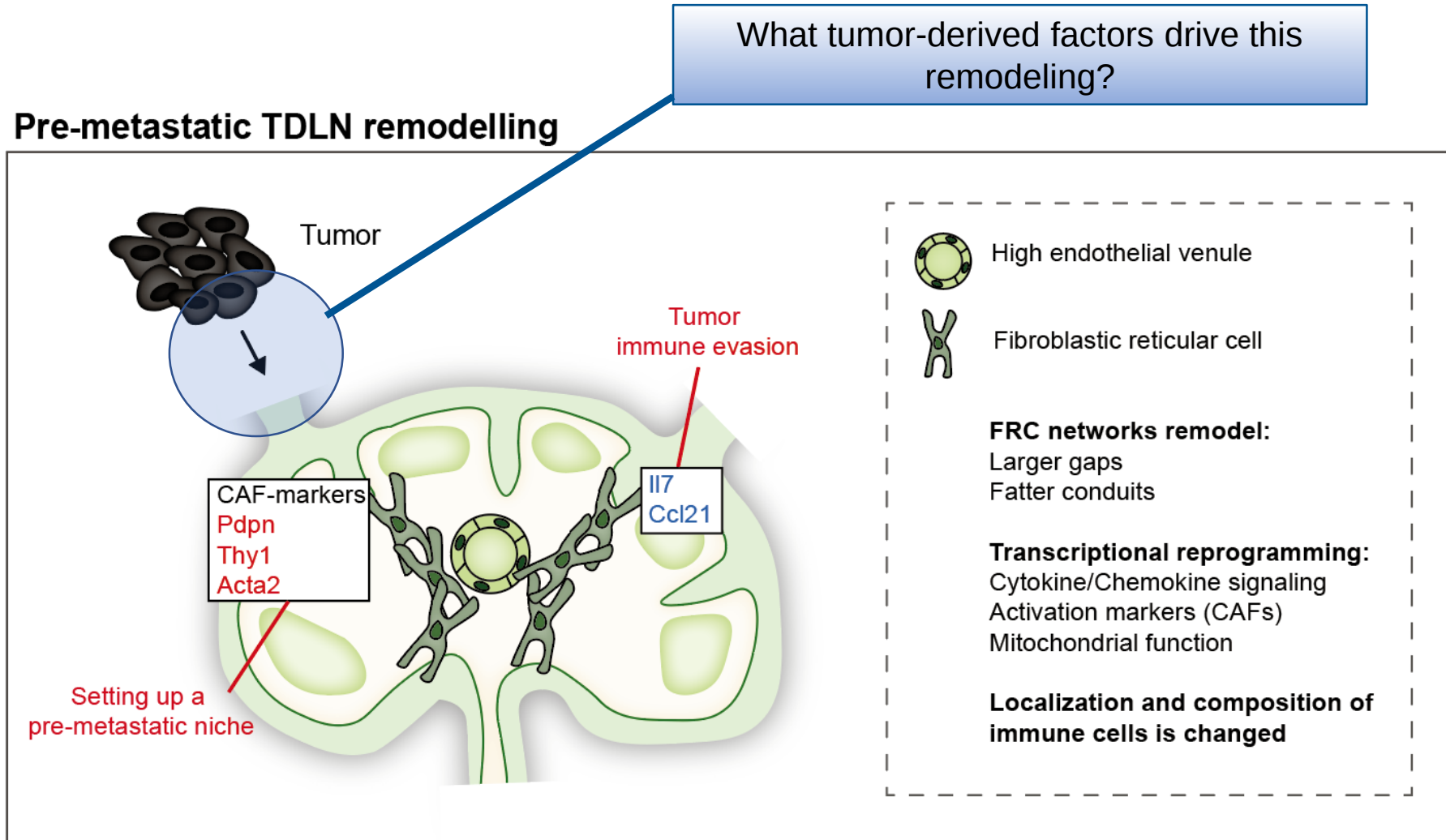
Changed immune cell composition and...



...localization



Tumor factors that drive pre-metastatic TDLN remodelling



Riedel et al., Nature Immunology 2016

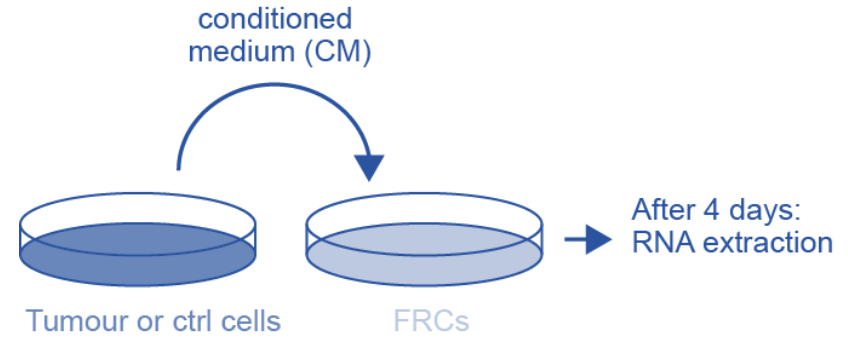
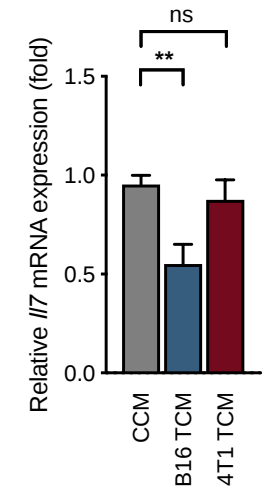
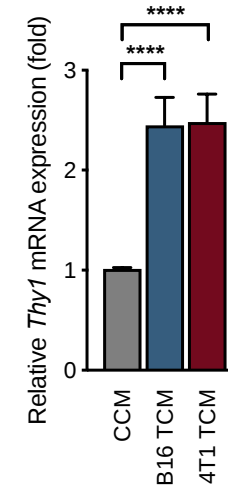
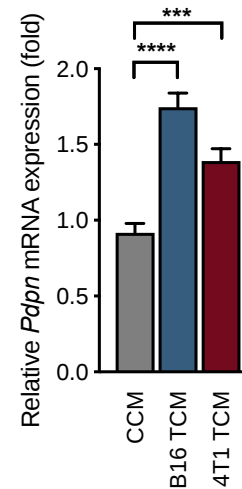
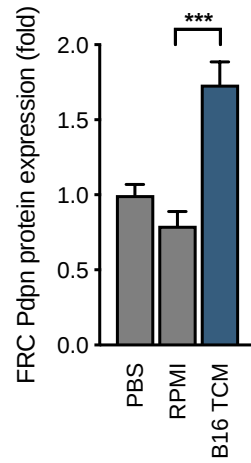
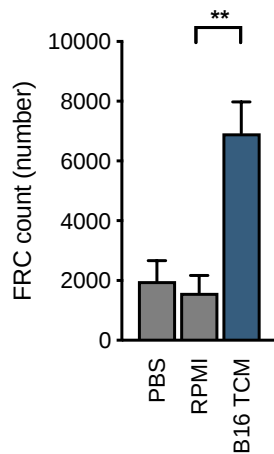
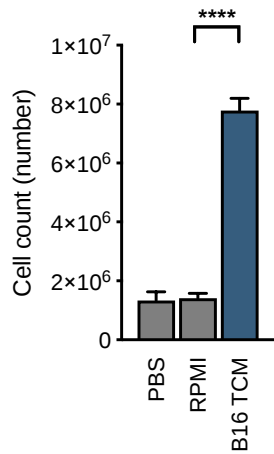
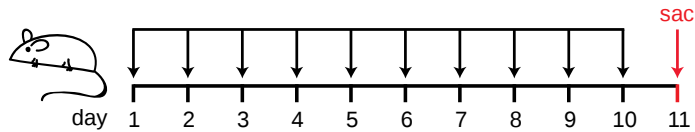
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Soluble factors mediate FRC activation

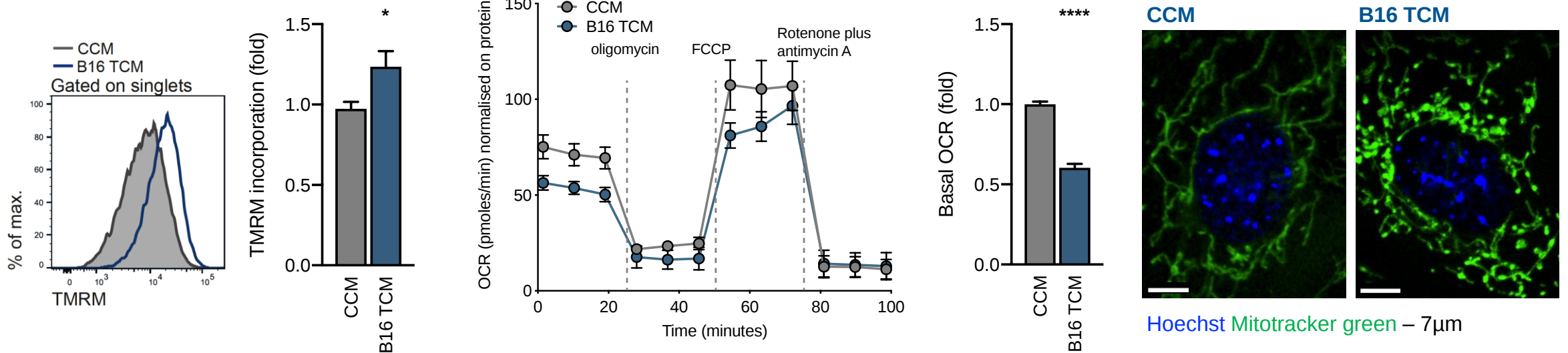
B16.F10 Melanoma model
4T1 Breast cancer model

TCM Tumor-conditioned medium
CCM Control-conditioned medium

B16.F10 conditioned medium (TCM) injections

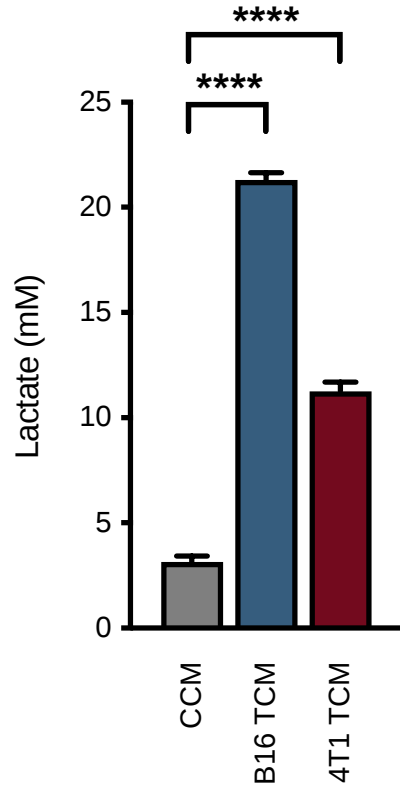


Tumor-derived soluble factors mediate FRC mitochondrial imbalance

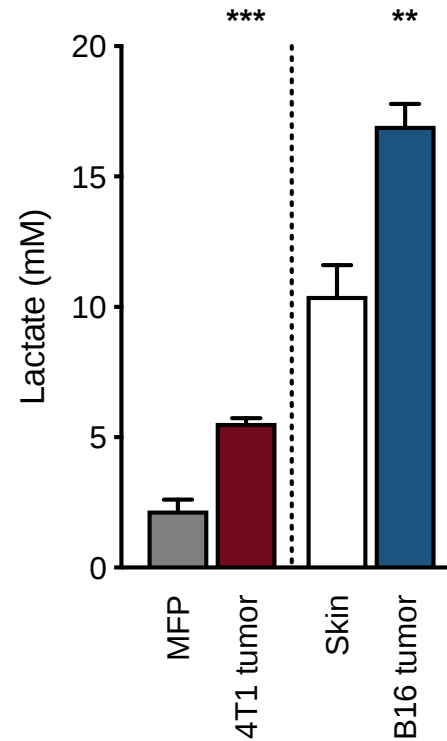


Lactate levels are increased in tumors and TDLNs

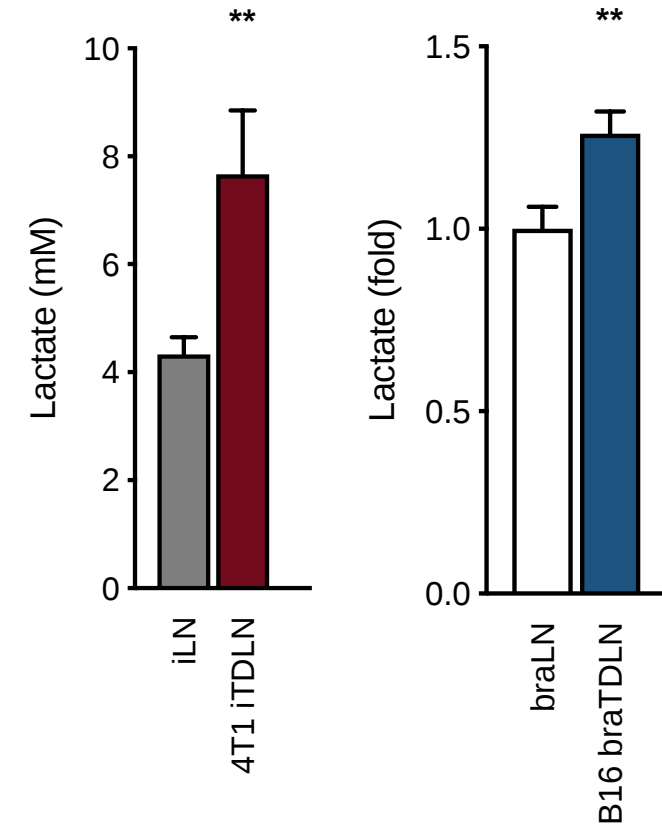
In vitro, metabolomics



In vivo, tumors express Ldha and secret lactate

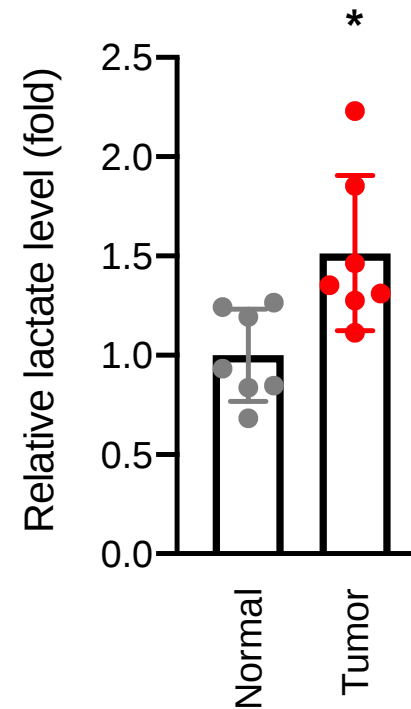


In vivo, lactate is increased in TDLNs

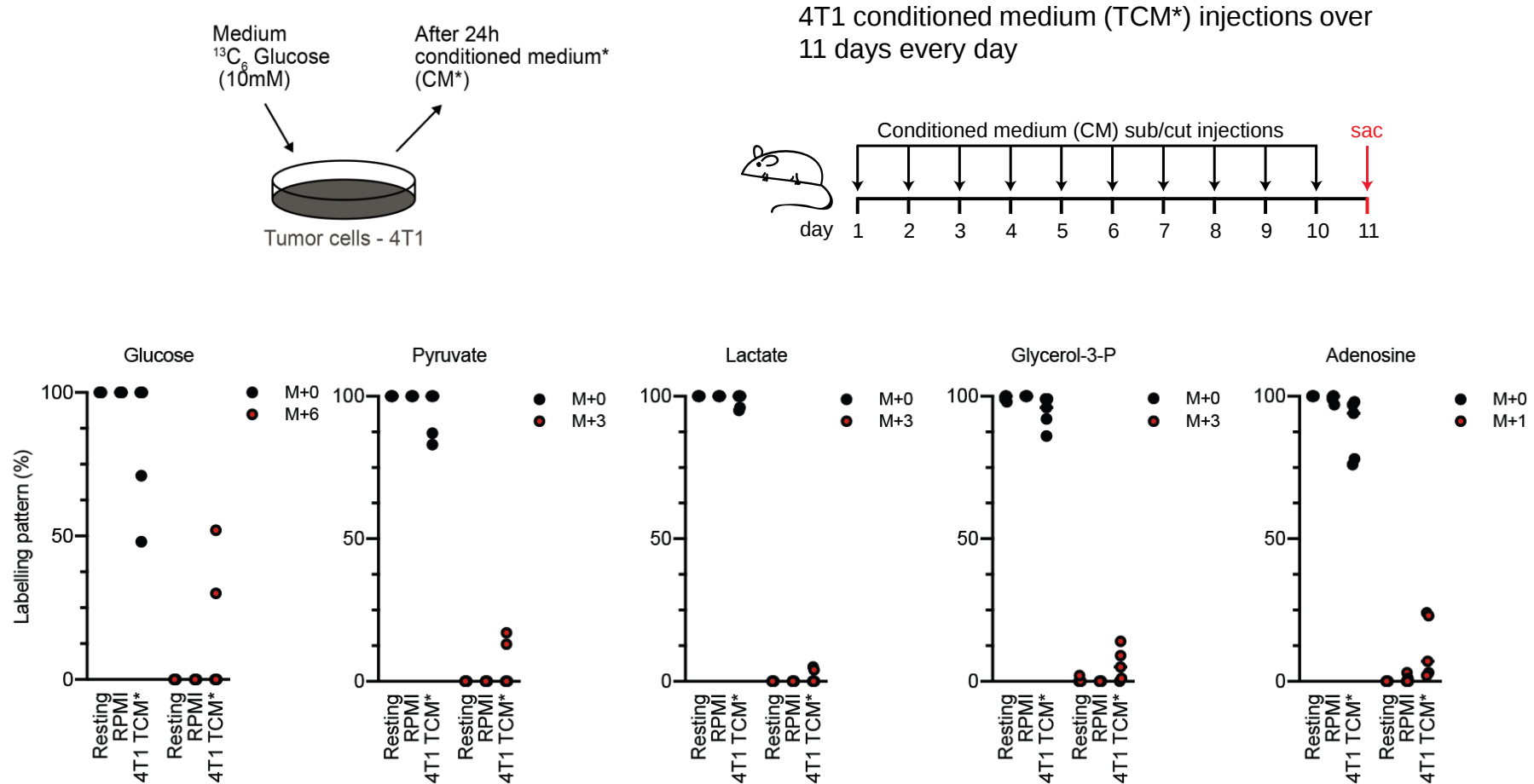


Lactate levels are increased in human breast cancer samples

Human breast cancer patient samples (interstitial fluid)



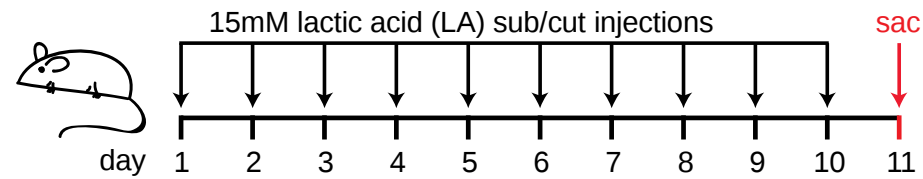
Tumor-derived metabolites can reach the LN



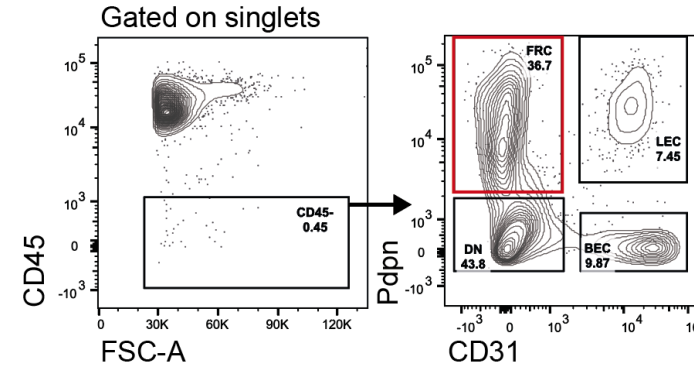
Riedel et al., Cancer Immunology Research 2022

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Tumor-derived lactic acid (LA) drives FRC remodeling

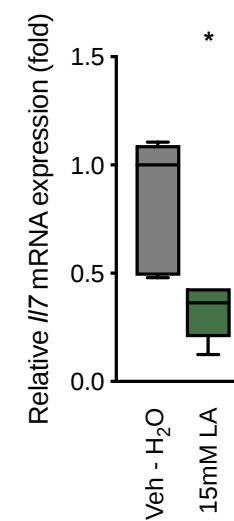
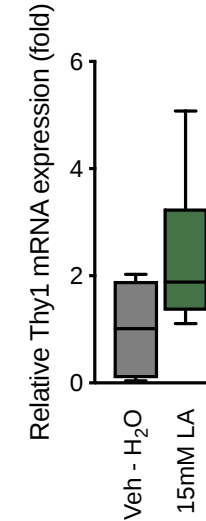
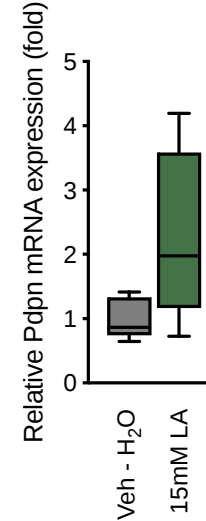
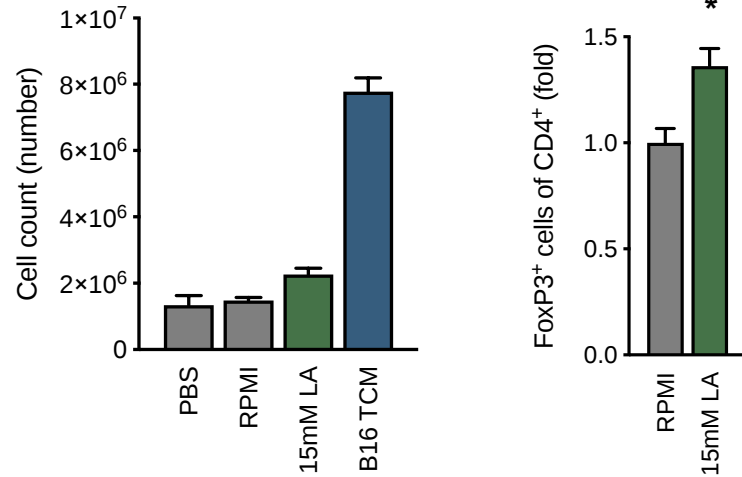


Ex vivo, sorted FRCs



2-tailed ttest: $p=0.0564$

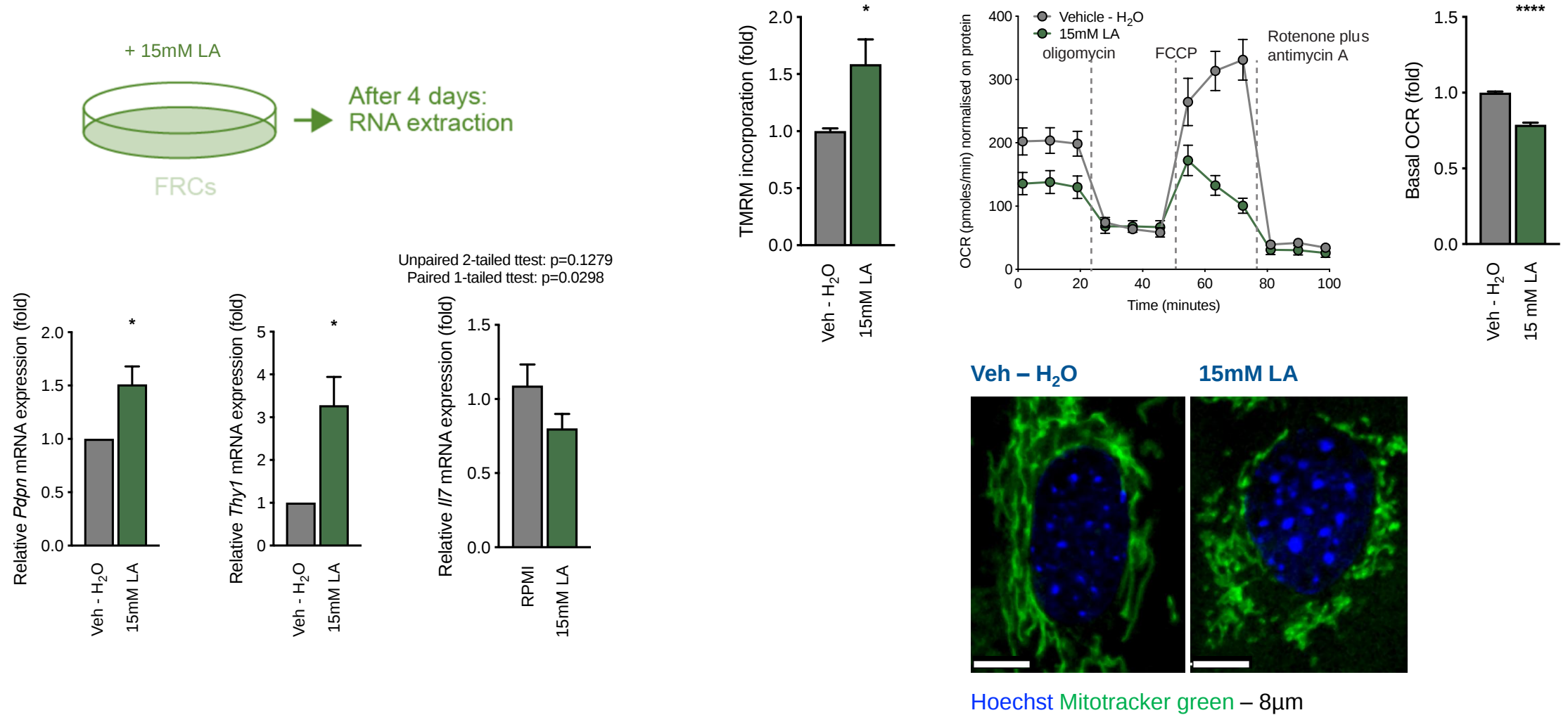
2-tailed ttest: $p=0.0700$



Riedel et al., Cancer Immunology Research 2022

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Tumor-derived lactic acid (LA) drives FRC remodeling

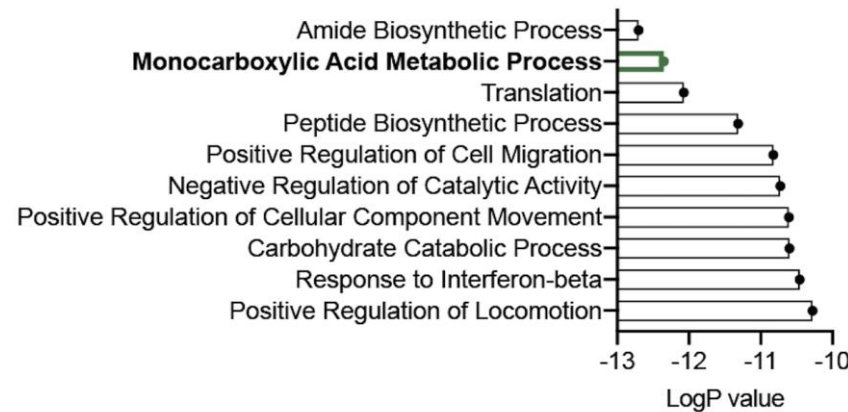
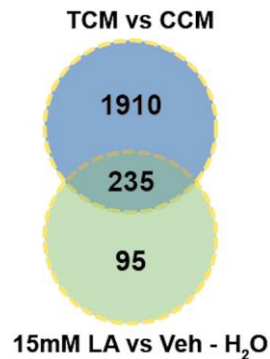
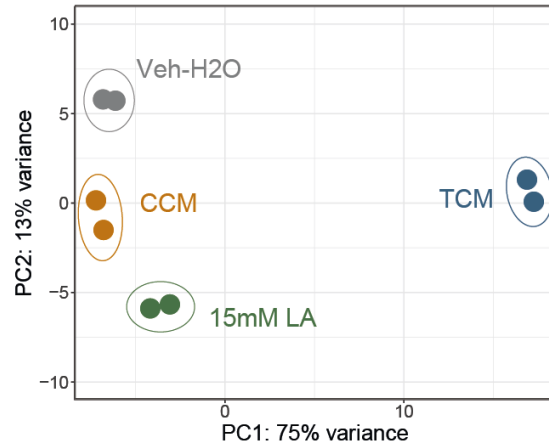


Riedel et al., Cancer Immunology Research 2022

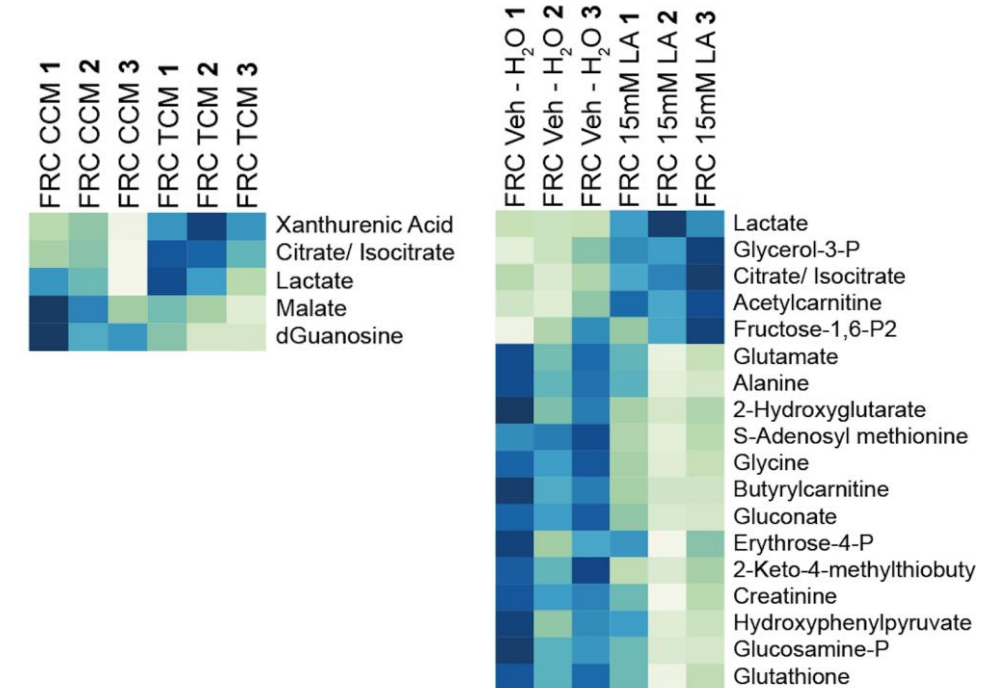
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Tumor-derived lactic acid (LA) drives FRC metabolic changes

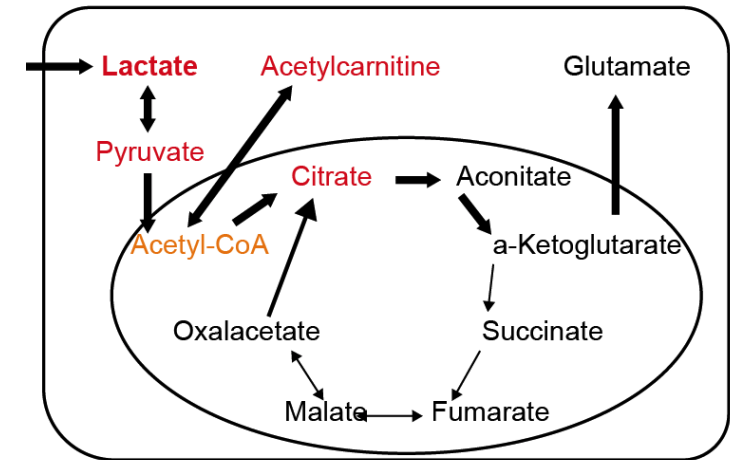
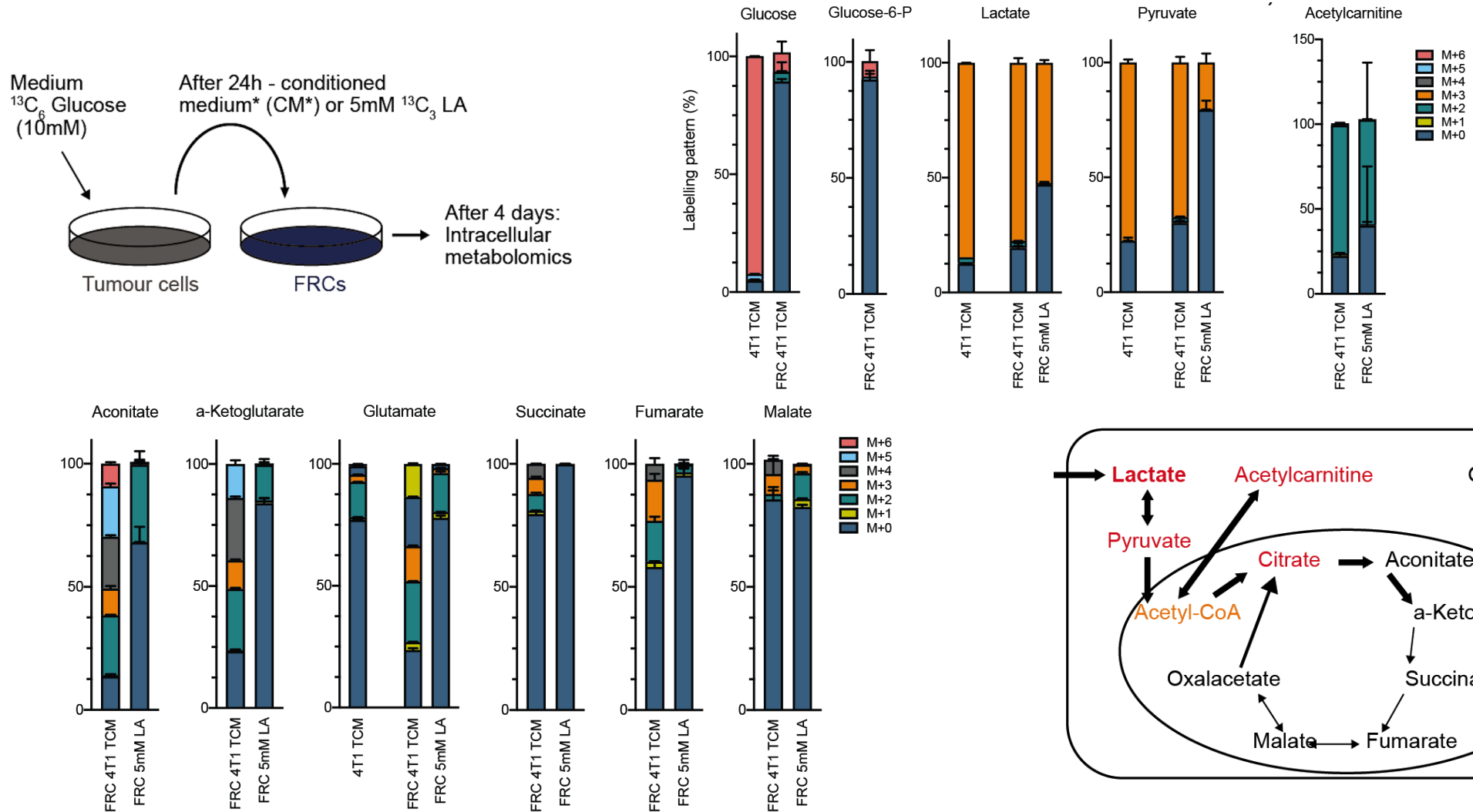
In vitro RNAseq of FRCs



In vitro intra-cellular metabolomics of FRCs



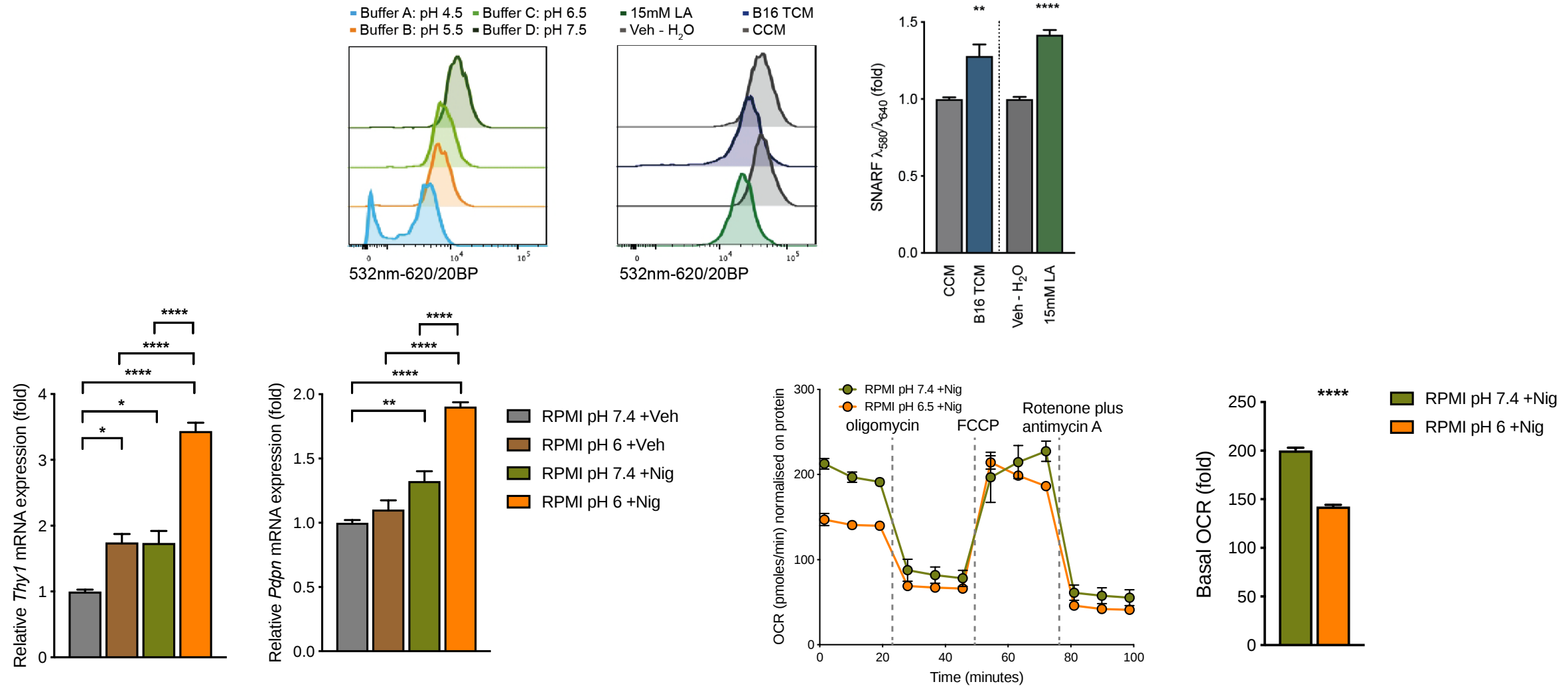
Tumor-derived lactic acid (LA) drives FRC metabolic changes



Riedel et al., Cancer Immunology Research 2022

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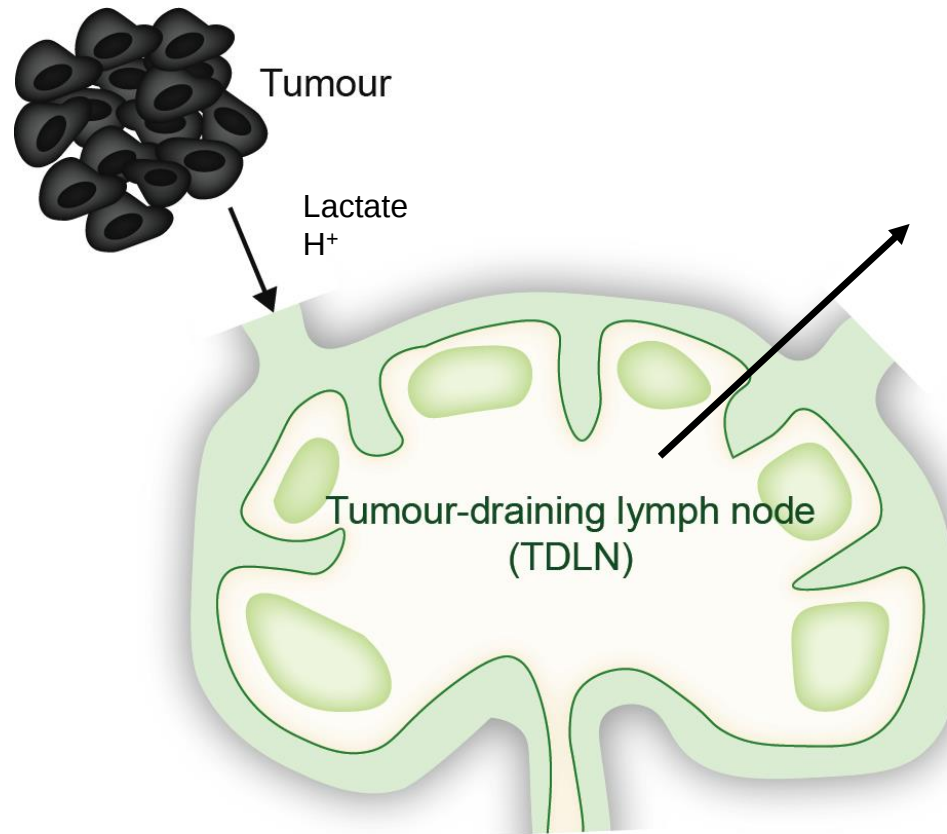
Lactic acid (LA) induced FRC reprogramming depends on intra-cellular pH



Riedel et al., Cancer Immunology Research 2022

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Summary



TDLN FRCs:

Take up lactate/H⁺ (Mct1)
pH is lowered

- 1) Mitochondrial function/ metabolism is changed
- 2) Deregulation of genes/ proteins (RNAseq):
 - Activation markers (Pdpn, Thy1)
 - Cytokines (Il7)
 - ECM
 - Interferon response
 - Metabolic signatures

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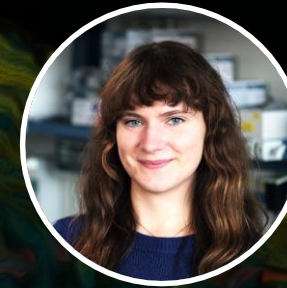
Institute for Systems Immunology:

Georg Gasteiger

Wolfgang Kastenmüller

Institute for Virology and Immunobiology

Manfred Lutz



Poster 34

Multiple Myeloma Microenvironment



Poster 45

TDLN – Myeloid Recruitment

