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Inflamed tumor-associated adipose tissue is a depot for macrophages that stimulate tumor growth and angiogenesis

Marek Wagner, Rolf Bjerkvig et al.

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Macrophages

- Monocytes develop from myeloid progenitor cells
- Monocytes migrate into tissues and differentiate into macrophages
- Main task is the production of cytokines and chemokines (e.g. IL-1β, TNF-α, IL-6, IL-8, IL-12) phagocytosis and production and release of reactive oxygen species ROS

K Murphy. Janeway´s Immunobiology. 8th ed. New York: Garland Science 2012,pp. 75-113;pp.377-381

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Macrophages

- M1 macrophages
  - Stimulate adaptive immunity
  - Microbial killing
  - Tumor-suppressive
- M2 macrophages
  - Tissue remodeling
  - angiogenesis

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- Adipose tissue consists of
  - Adipocytes
  - Stromal vascular fraction (including monocytes/maccrophages)

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- Peritumoral adipose tissue (AT) show increased fibrosis, angiogenesis and inflammation

- M1 and M2-type macrophages are located in tumor-associated AT

- Tumor growth may be stimulated by highly vascularized AT

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- Injection of B16F10 melanoma cells and Lewis Lung carcinoma into anterior subcutaneous AT and in dorsal midline

- Adipose tissue was obtained by microdissection after 14d

- Adipocytes are cultured and analyzed in size and lipolysis

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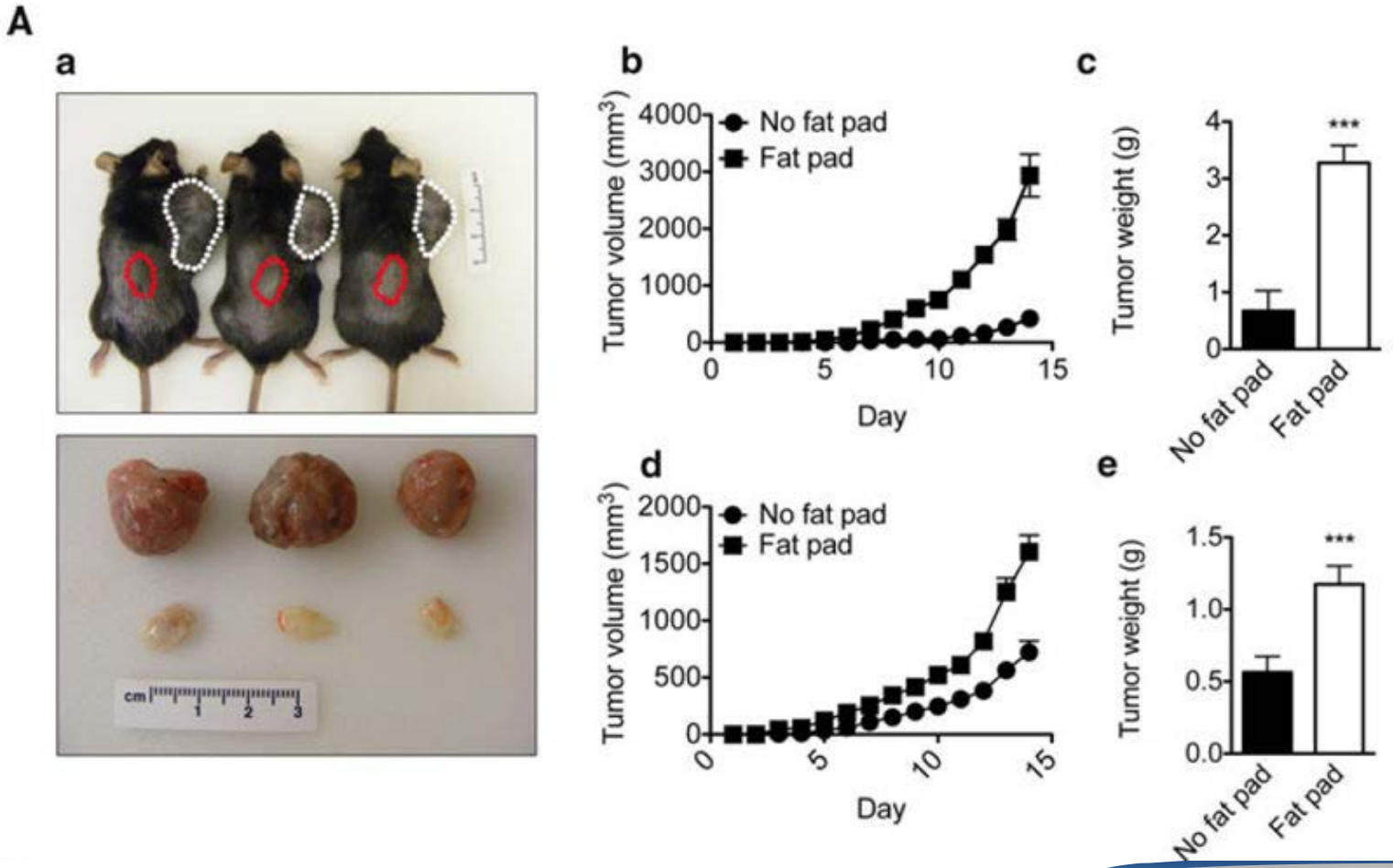

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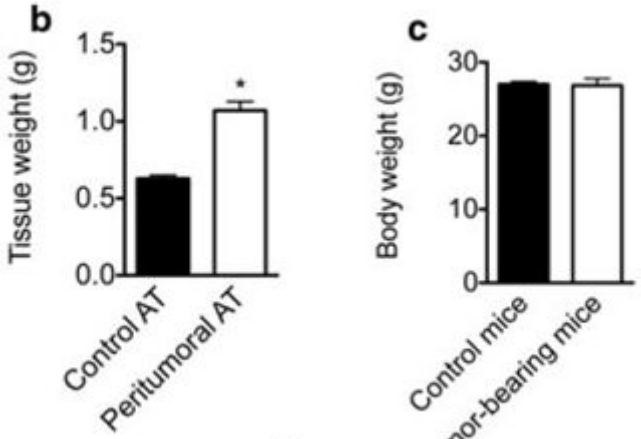

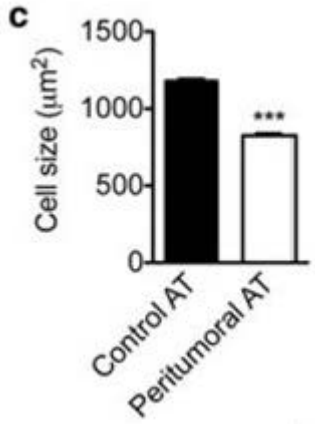

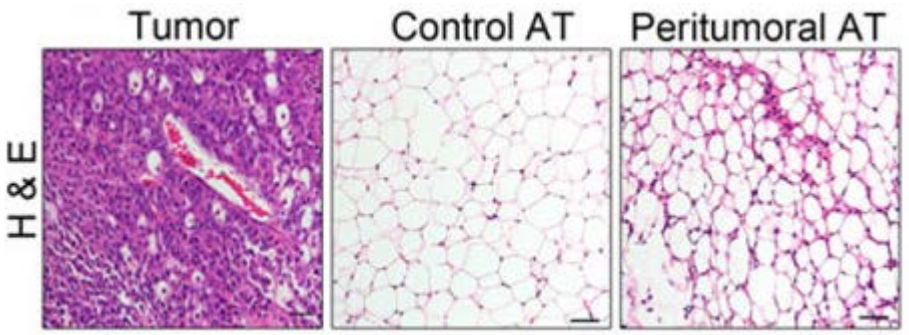

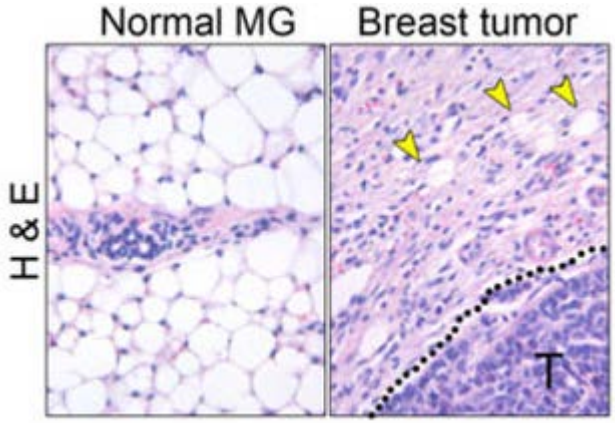

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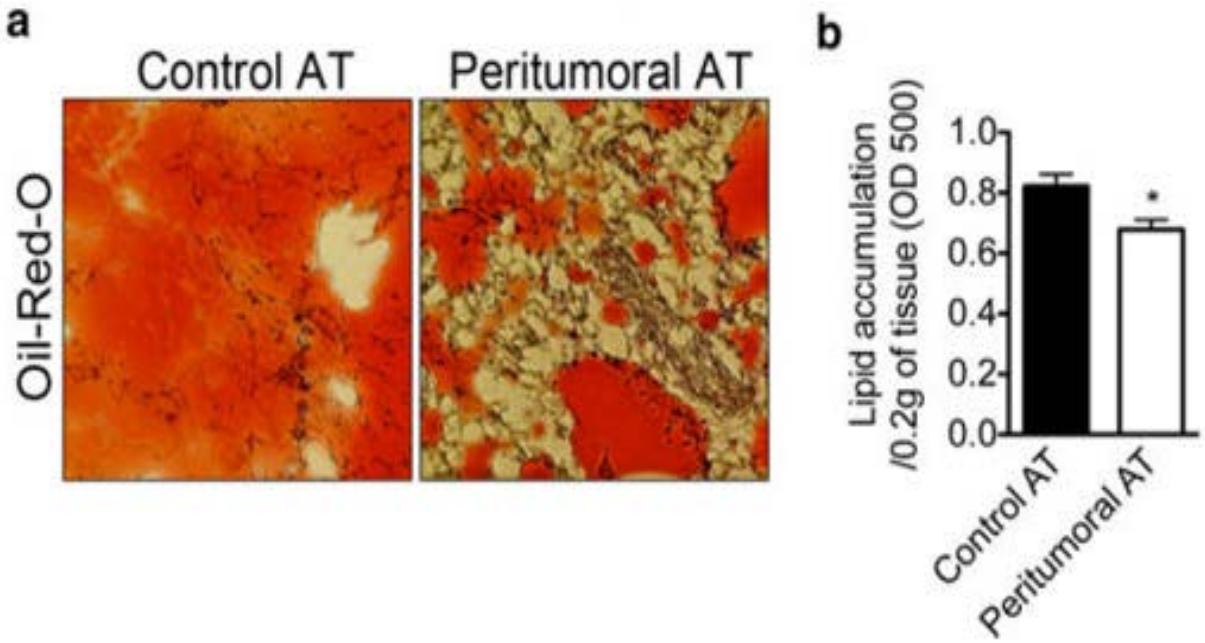

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- Peritumoral adipose tissue displays
  - Inflammation
  - high vascularization
  - Decreased size
  - Areas of dense collagen deposition
  - Decreased lipid accumulation
  - Increased lipolysis

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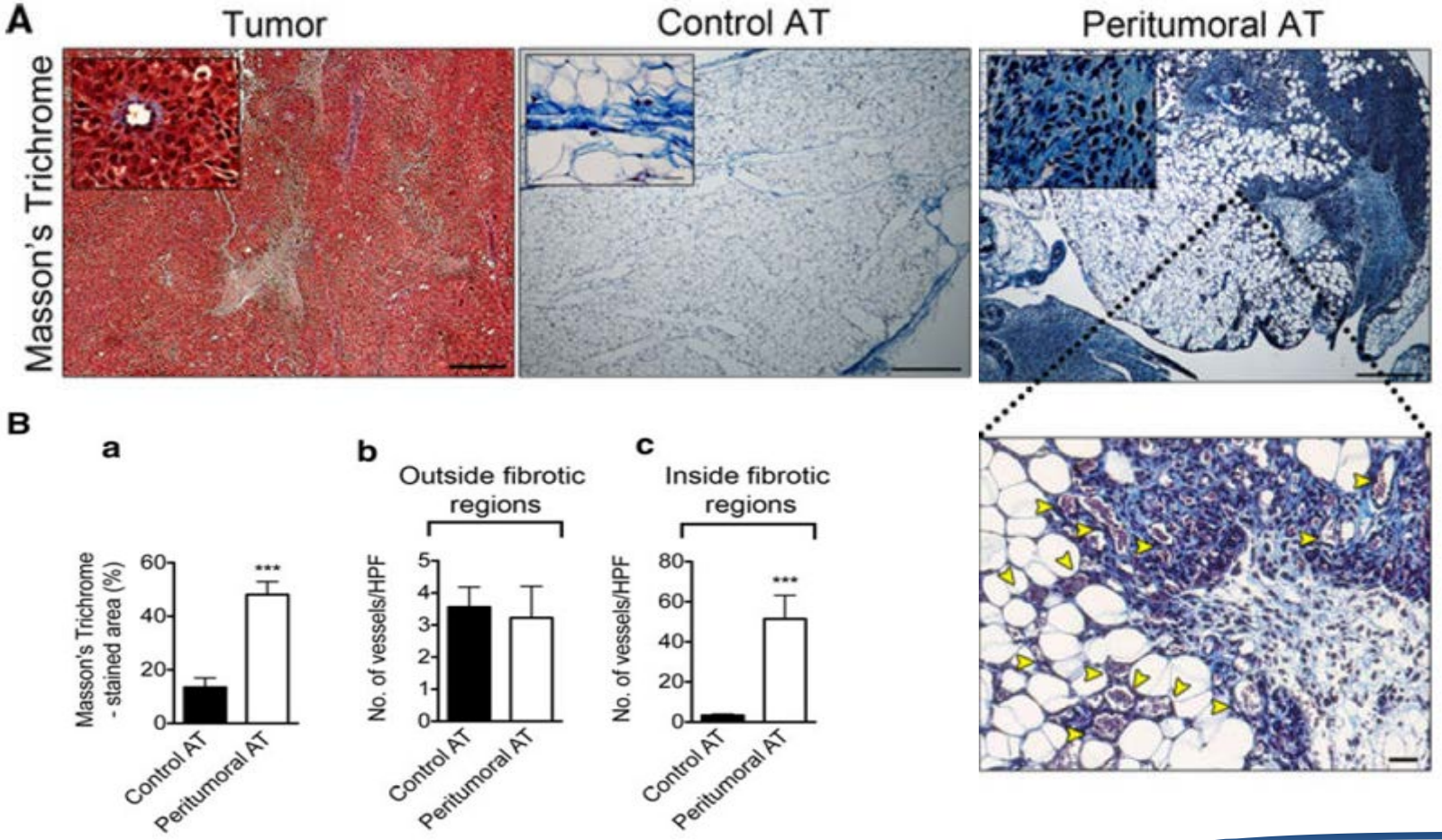

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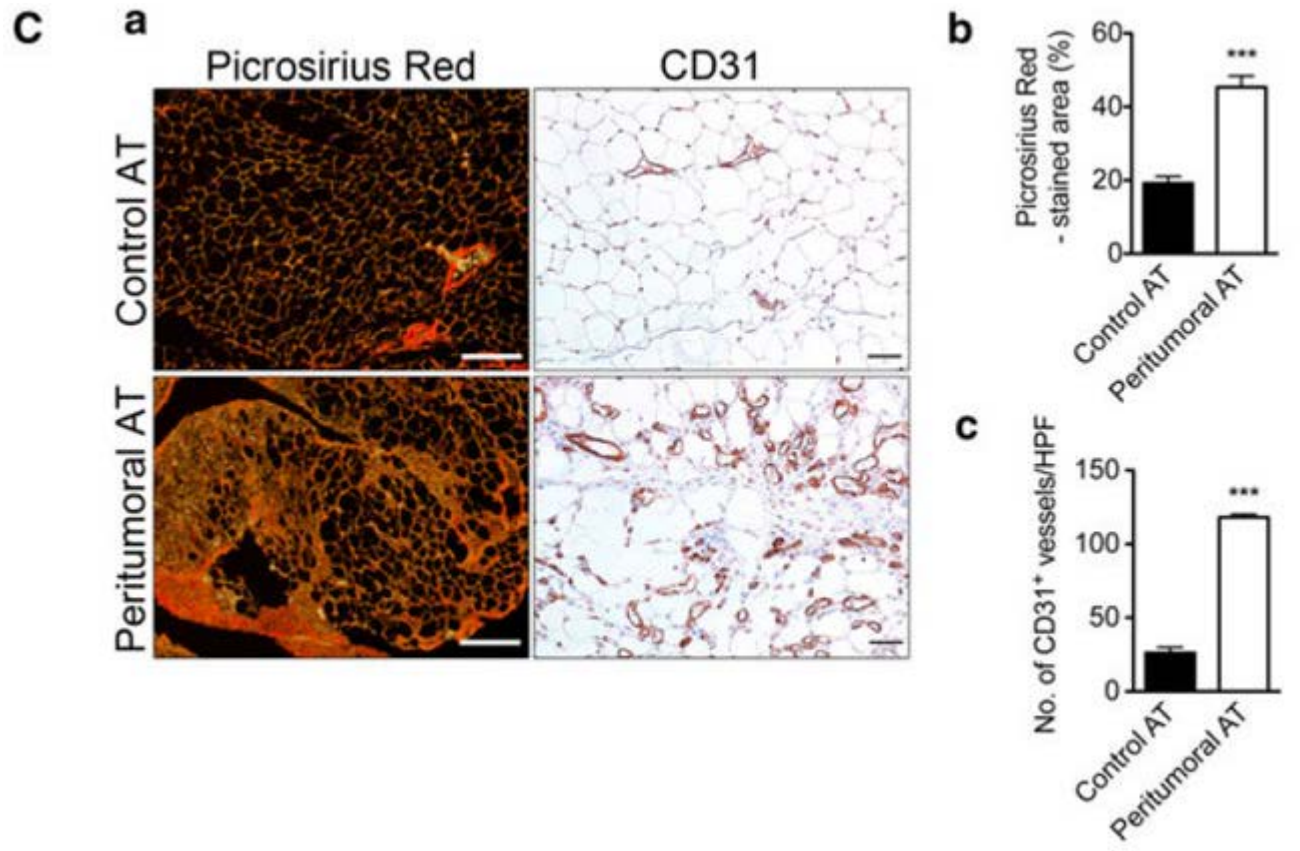

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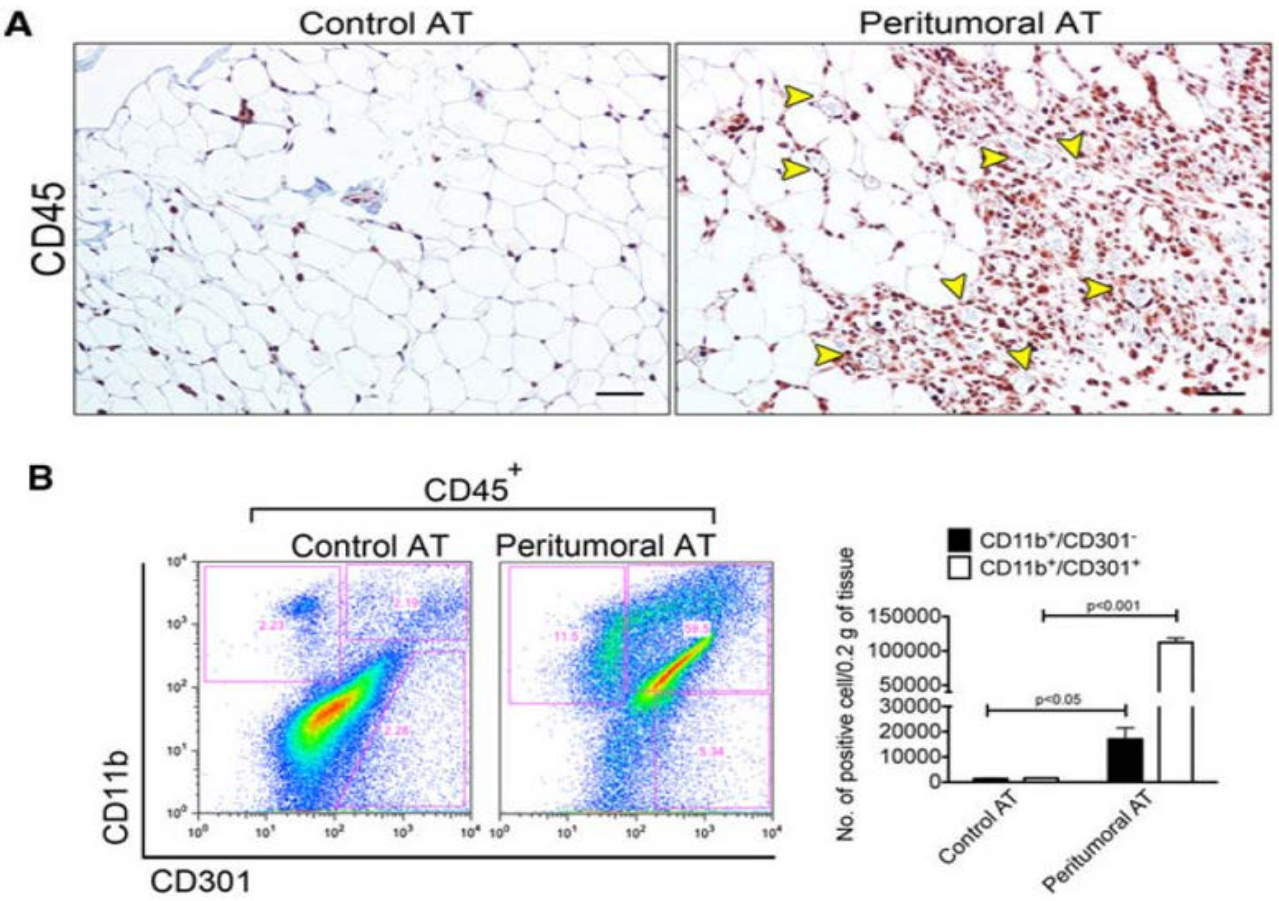

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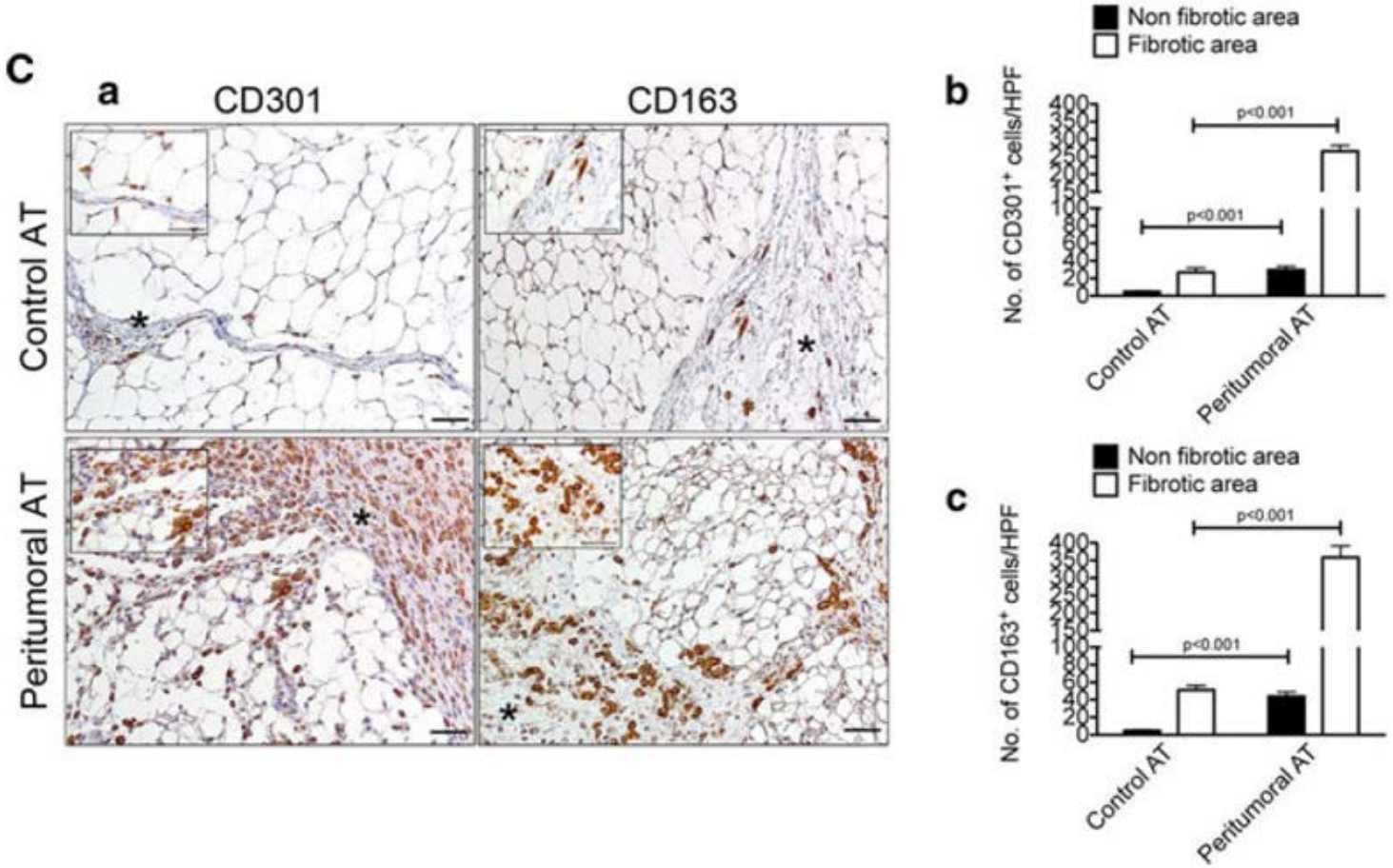

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- Most macrophages are displayed in fibrotic and highly vascularized areas

- The cytokine and chemokine expression-levels are analyzed revealing an increase of IL-6, CXCL1, MCP-1, MIP-2 and TIMP-1

- IL-6 seems to stimulate vascular endothelial cell proliferation

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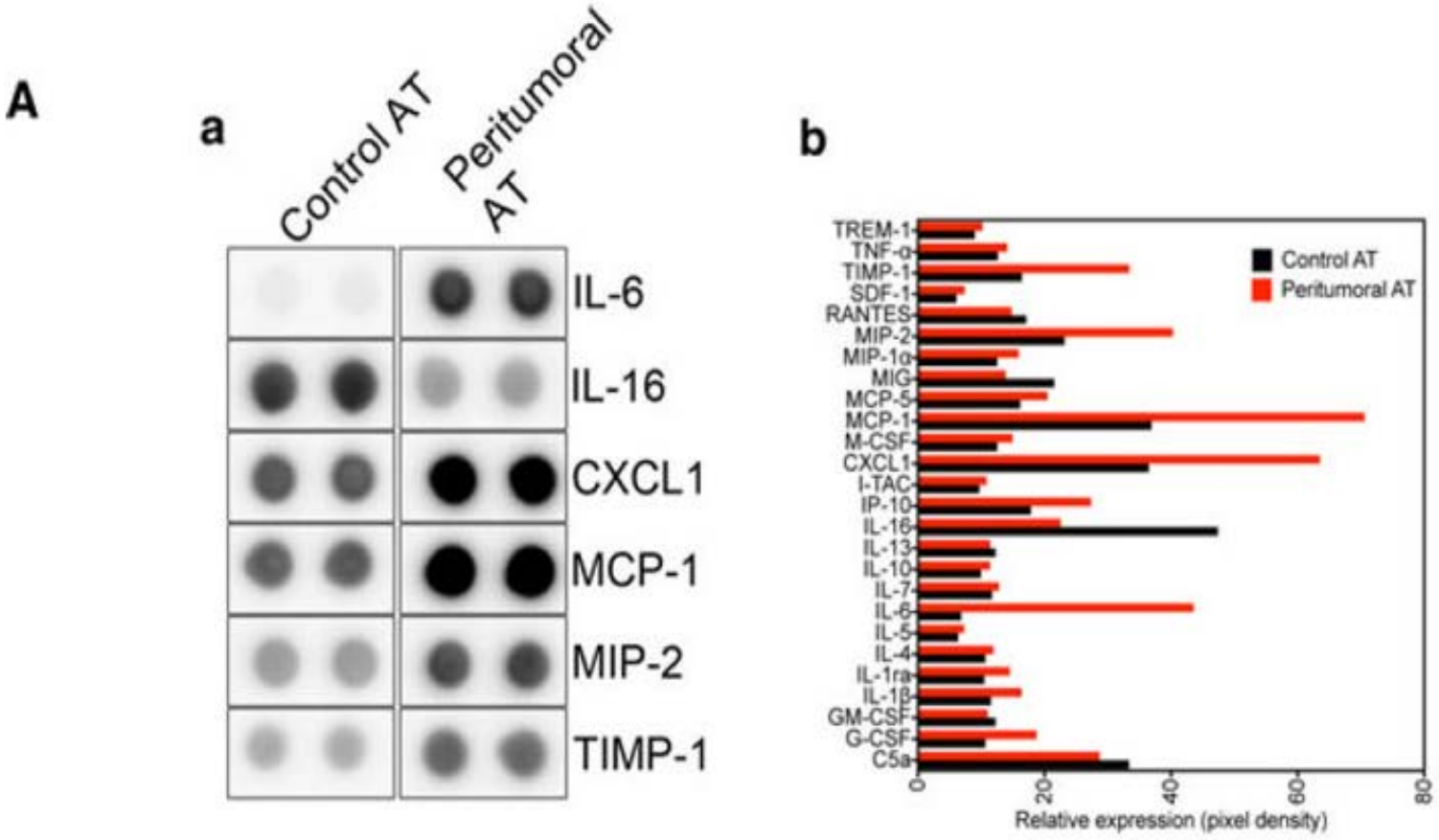

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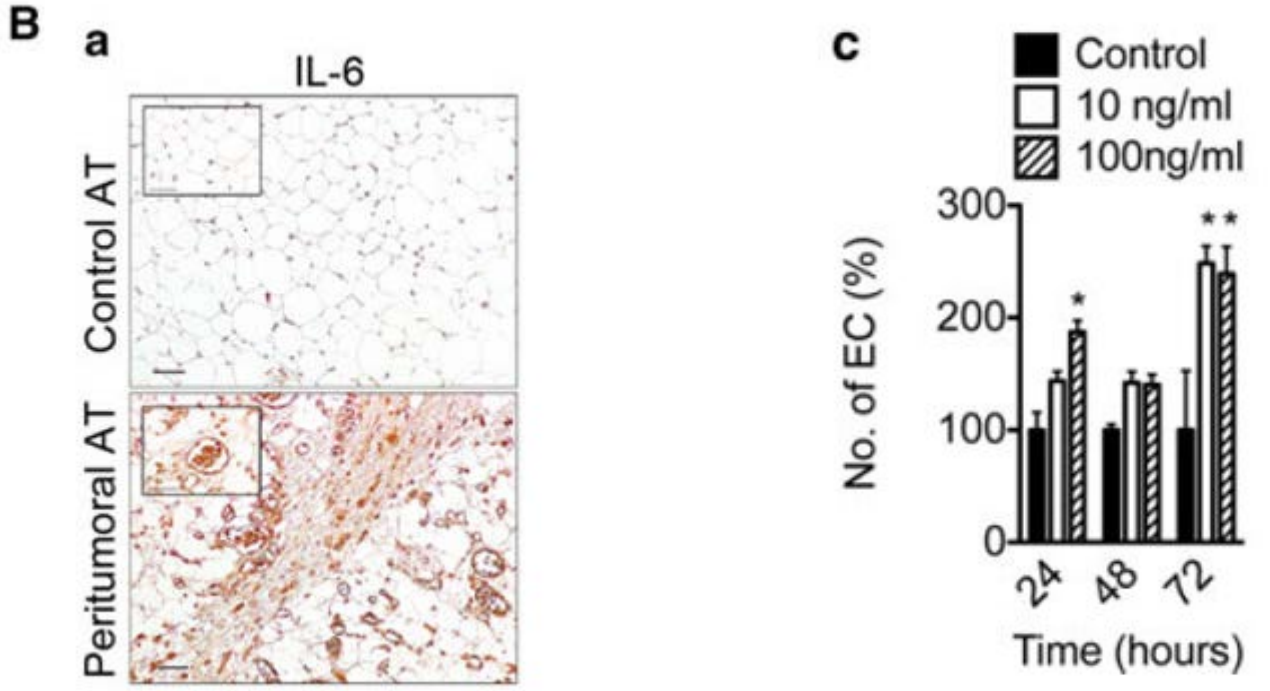

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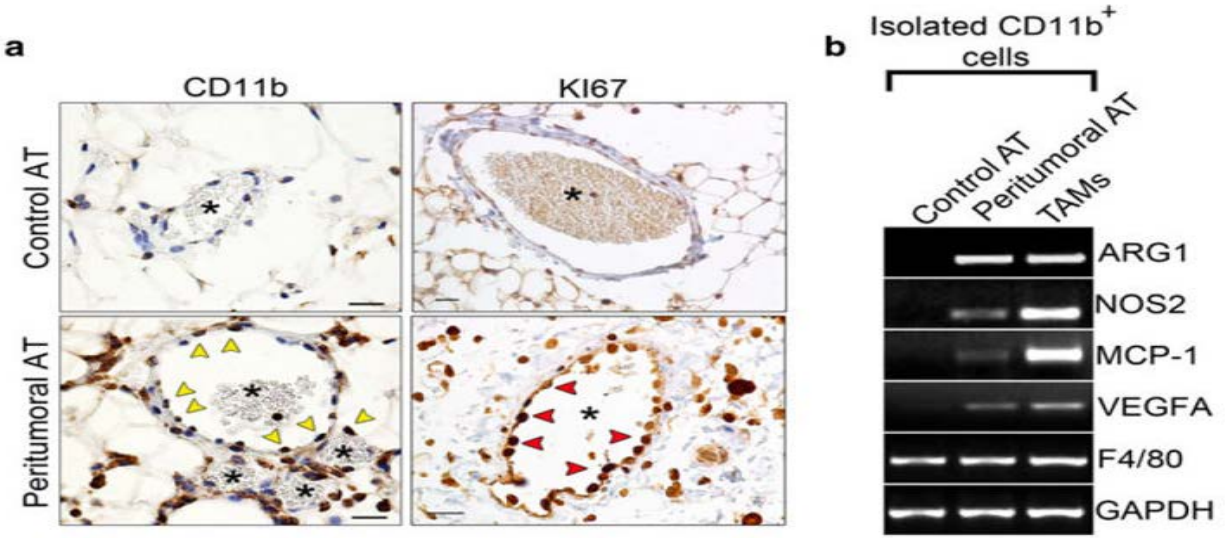

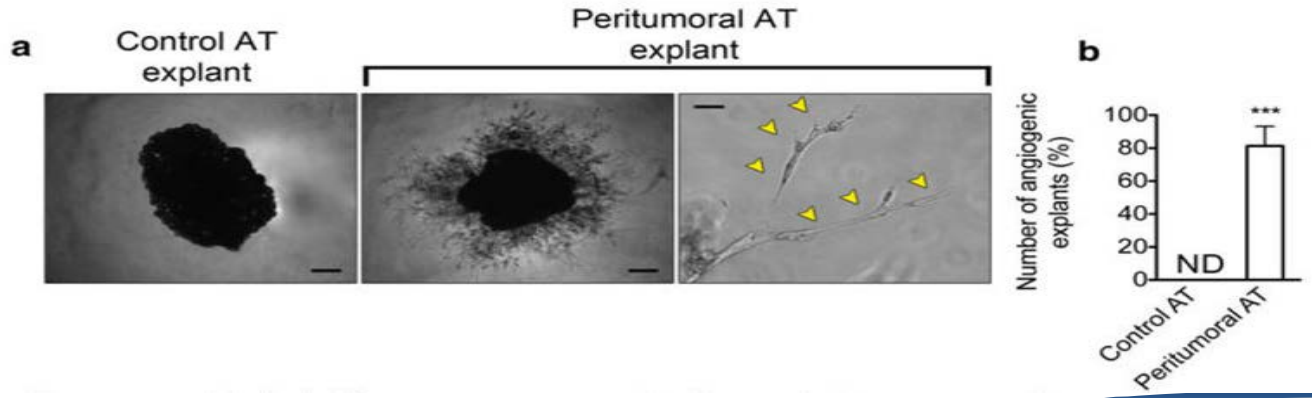

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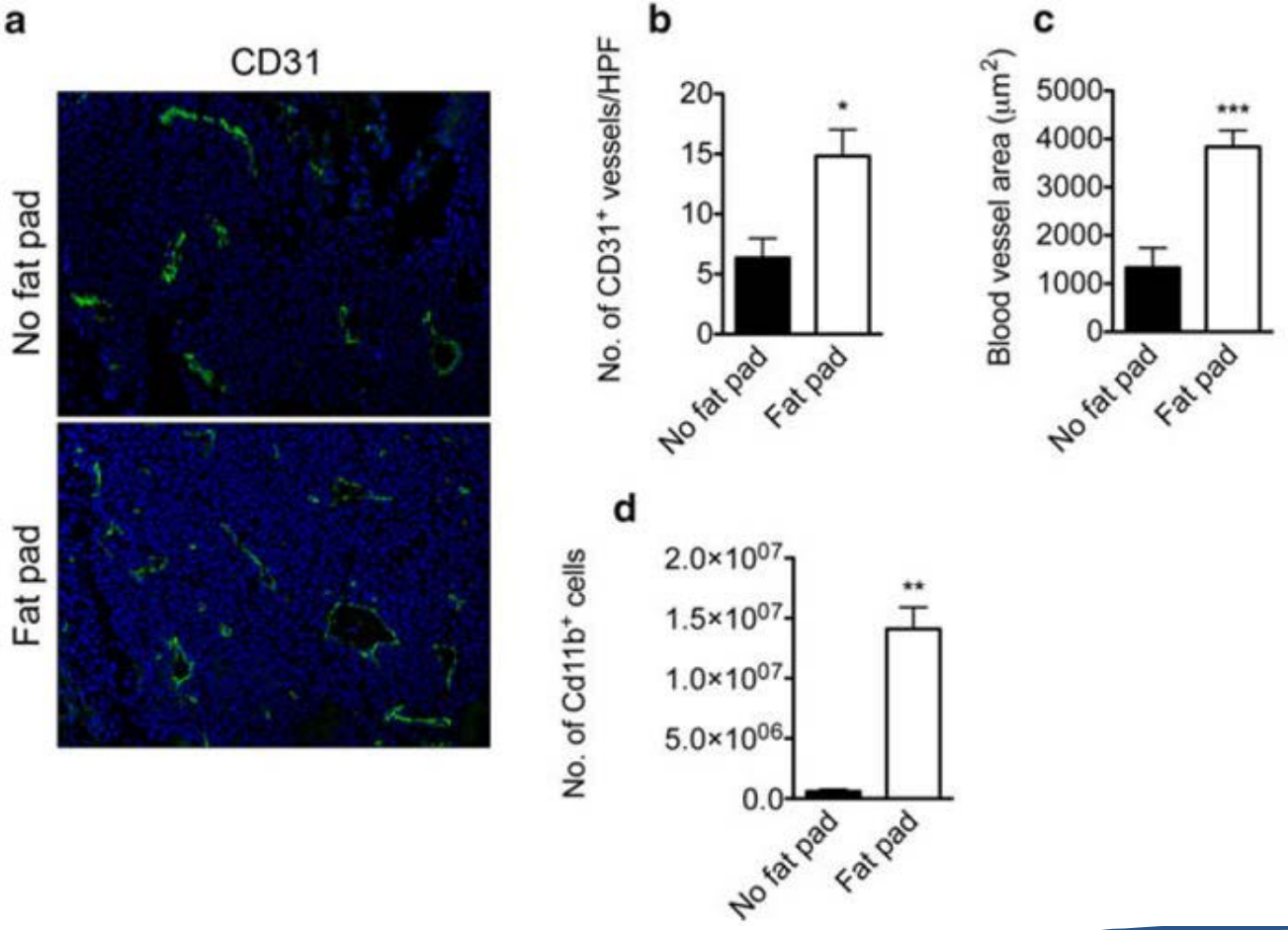

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Discussion

- Lipolysis of adipocytes may provide tumor cells with free fatty acids as energy source
- Adipocytes could dedifferentiate to tumor associated fibroblasts, causing fibrosis
- Overproduction of TIMP-1 block matrix metalloproteinases and induce angiogenesis and fibrosis

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- Both mononuclear and endothelial cells are positive for IL-6
- IL-6 appears to induce angiogenesis
- Peritumoral AT enhances tumor progression especially in lymph node metastasis and breast cancer

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- Peritumoral adipose tissue serves as a depot for neutrophils and macrophages

- Secretion of proangiogenic factors (VEGF, IL-6, IL-8, TNF-α) supports tumor expansion

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Thank you for your attention!