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Macrophages mediate colon carcinoma cell adhesion in the rat liver after exposure to lipopolysaccharide

Nuray Gül, Simran Grewal et. al.

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Colorectal Cancer

- Incidence rate is 1 million per year
- Patients dying from CRC every year: half a million
- 20-50% develop liver metastases within 5 years after resection

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Toll-like receptors

Toll-like receptor	Ligand
TLR-1:TLR-2 heterodimer	Lipomannans, Lipoproteins Cell-wall β-glucans, lipoteichoic acids, Zymosan
TLR-2:TLR-6 heterodimer	Ligands of TLR-1:TLR-2 heterodimer
TLR-3	Double-stranded RNA
TLR-4	LPS, Lipoteichoic acids
TLR-5	Flagellin
TLR-7	Single-stranded RNA
TLR-8	Single-stranded RNA
TLR-9	DNA with unmethylated CpG
TLR-10	Unknown

K Murphy. Janeway´s Immunobiology. 8th ed. New York: Garland Science 2012,p.86

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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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ROS

- Fusion of phagosome and lysosome forms the NADPH oxidase complex
- NADPH oxidase transfers an electron to molecular oxygen forming the superoxide ion O_2^-
- Superoxide Ion is converted by superoxide dismutase to H_2O_2
- ROS can be released into extracellular environment

K Murphy. Janeway´s Immunobiology. 8th ed. New York: Garland Science 2012,pp. 78-83

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Macrophages and LPS

- Surgery can paradoxically contribute to tumor recurrence and liver metatstases development
- Bacterial spillage during surgery may lead to the growth of metatstases
- Concentration of Lipopolysaccharide in peripheral blood increases 1h after surgery and normalizes 24 h later

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- LPS activates macrophages through TLR-4
- Activated macrophages can release reactive oxygen species (ROS)
- ROS disrupts the endothelial barrier, leading to vascular permeability in tissues and enhanced tumor-cell adhesion in the liver

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- Intraperitoneal injections with PBS (control group) or LPS in rats
- Followed by the inoculation of tumor cells (rat colon carcinoma cell line CC351s- moderately differentiated and immunogenic)
- LPS injections resulted in decreased expression of the thight junction protein zonula occludens 1 (ZO-1)

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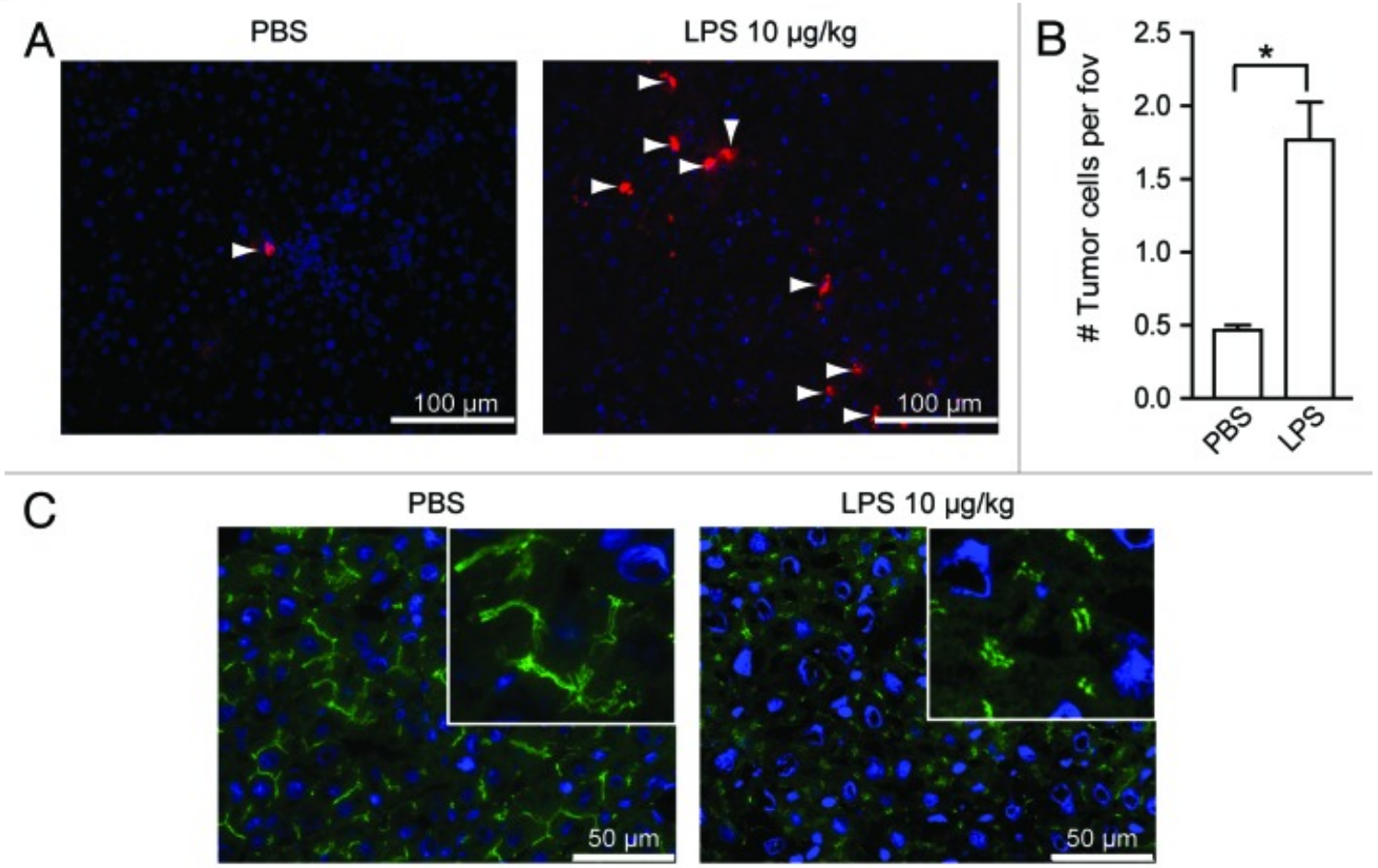

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- Effect of LPS-stimulated macrophages on tumor cell adhesion by disrupting sinus endothelial barriers

- Endothelial cell monolayers (of human umbilical vein endothelial cells; HUVECs) were cultured on the upper side of transwell membranes
- Macrophages on the lower side
- Addition of LPS (and LPS inhibitor polymyxin B; PMB)

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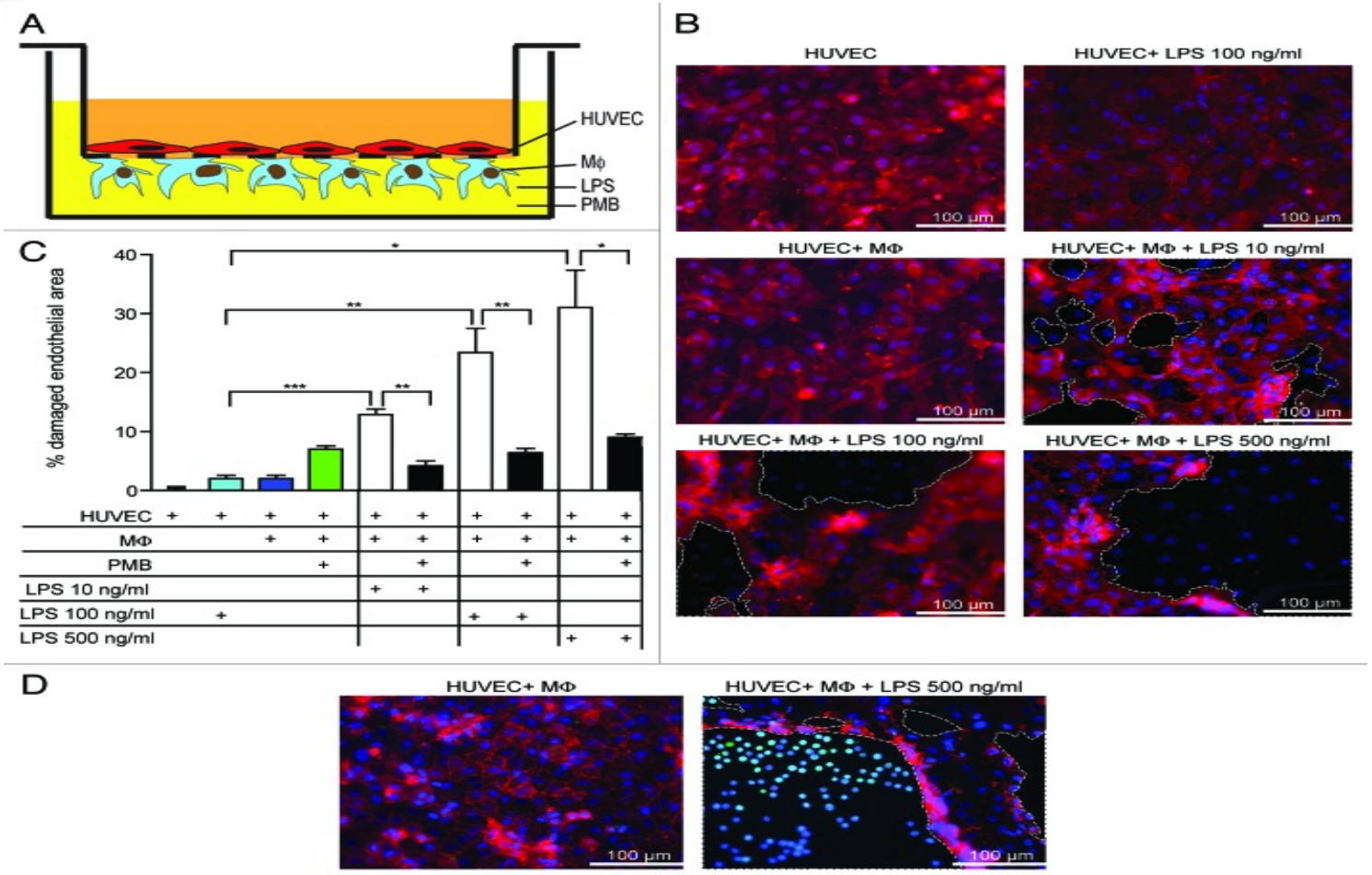

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- Next step: Adding of tumor cells

- The intercellular gaps in the endothelial monolayer, that were formed upon LPS administration, contained a high number of adherent tumor cells

- No tumor cells attached to endothelial monolayer in absence of LPS

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- Role of LPS-activated macrophages in tumor-cell adherence **in vivo**

- liver macrophages (Kupffer cells) had been depleted by injection of clodronate-containing liposomes

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- The absence of Kupffer cells and newly recruited monocytes was confirmed by ED2 (marker for tissue resident macrophages) and ED1 (marker for newly recruited monocytes)

- Less tumor cells were observed in the livers of the KC-depleted rats, pre-treated with LPS and tumor cells

- Higher expression levels of ZO-1 in KC-depleted rats

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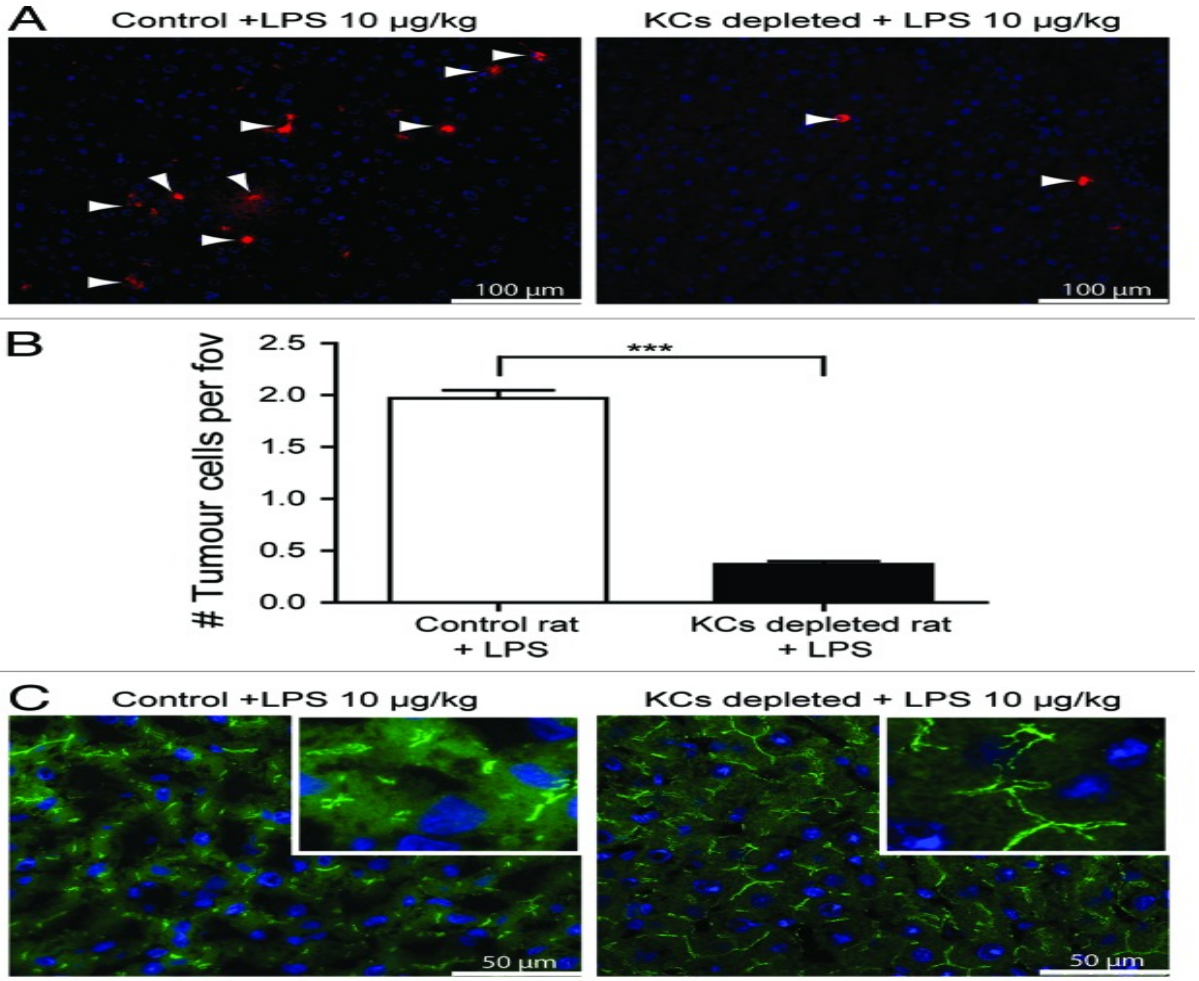

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- Endothelial layer damage induced by macrophage-produced reactive oxygen species (ROS)

- ROS-scavenging enzymes:
  - Superoxide dismutase (SOD)
  - Catalase

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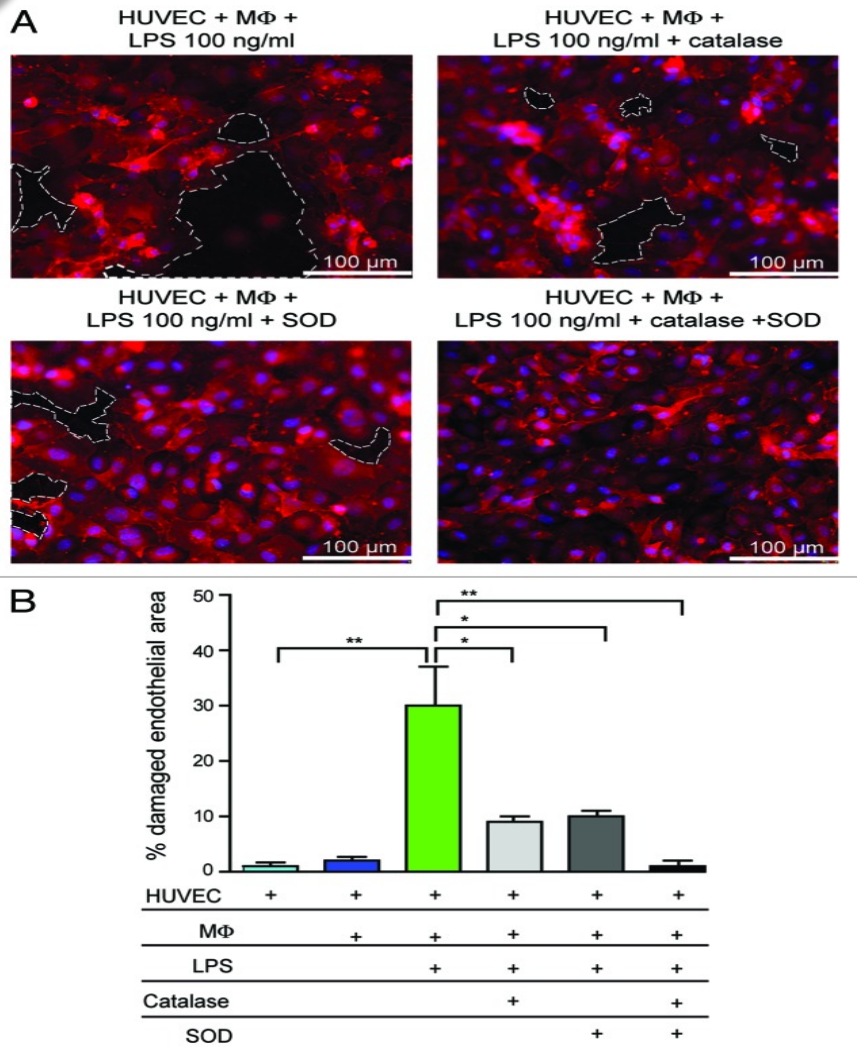

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- Role of ROS in LPS-induced tumor-cell adhesion in vivo

- Rats were treated with the anti-oxidant edaravone (which is used to treat ischemic stroke)

- This resulted in lower numbers of tumor cells and the expression levels of ZO-1 did not decrease

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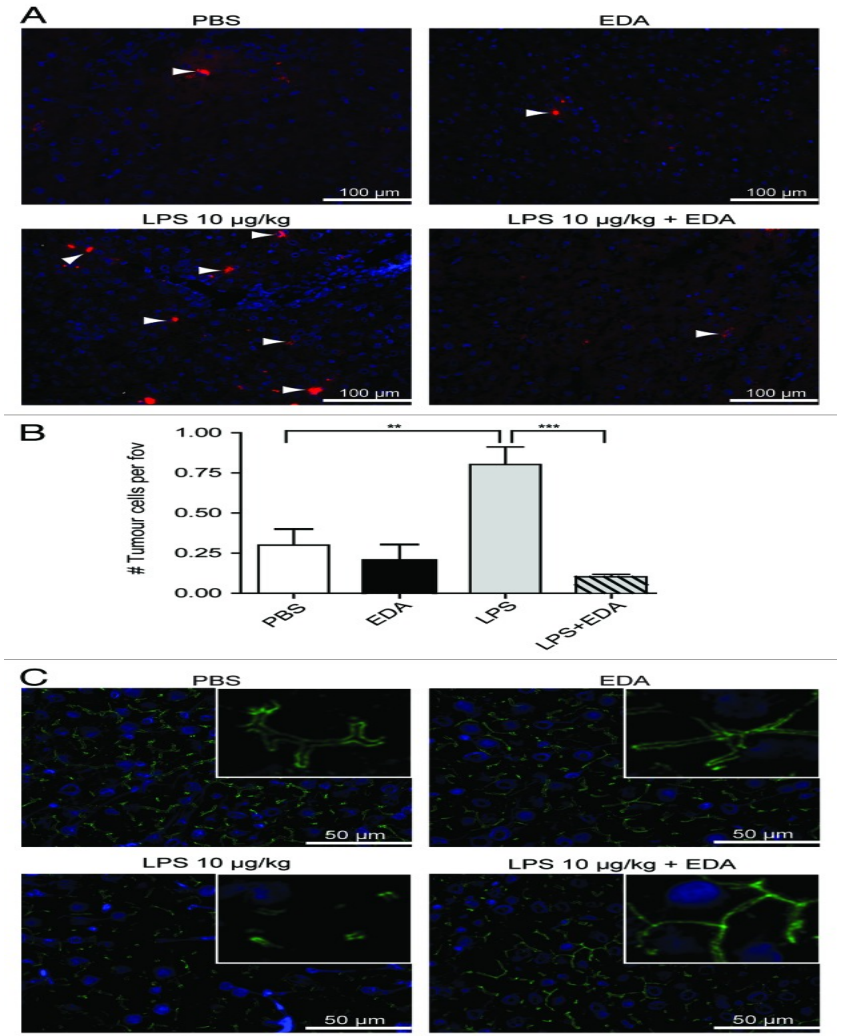

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Discussion

- Polymorphonuclear cells (PMNCs) also produce ROS
- In both cancer patients and tumor-bearing mice, an impairment of ROS-scavenging systems has been found

- Rats that received LPS developed less liver metastases, compared with PBS treated mice
- LPS may stimulate immune responses against immunogenic CC351s cells

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Thank you for your attention!