WHY PIPAC?

Normal and Diseased Peritoneum

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Disclosures

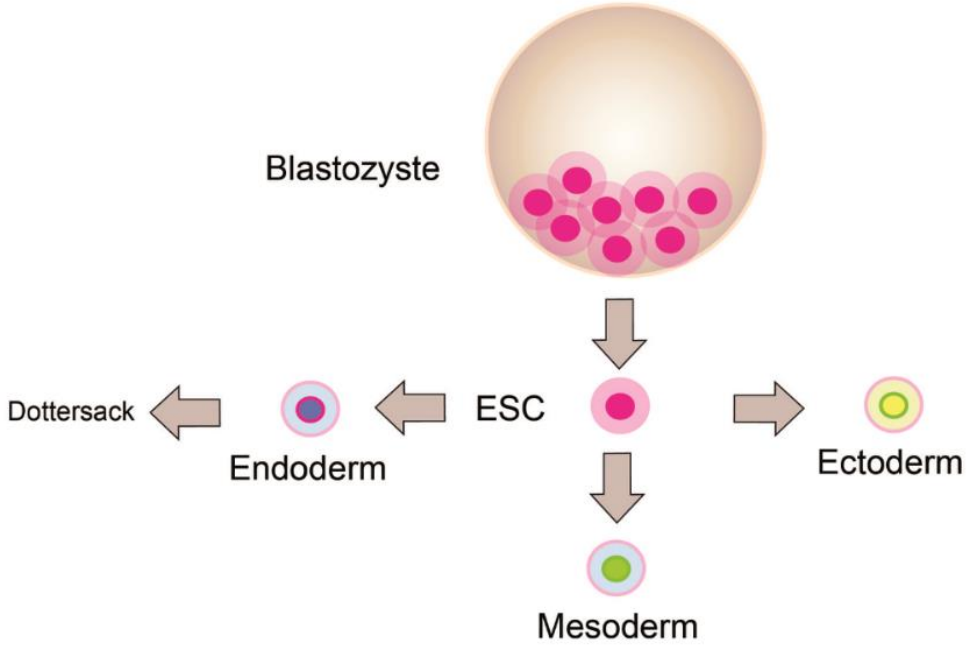
- CEO/Owner of Capnomed GmbH
- CEO/Owner of Capnopharm GmbH

These disclosures have been deemed as irrelevant, as this presentation is limited to basic science research, such as pre-clinical research and drug discovery, or the methodologies of research, and I will not make care recommendations.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their products and/or other business interests.

Peritoneum: Embryology

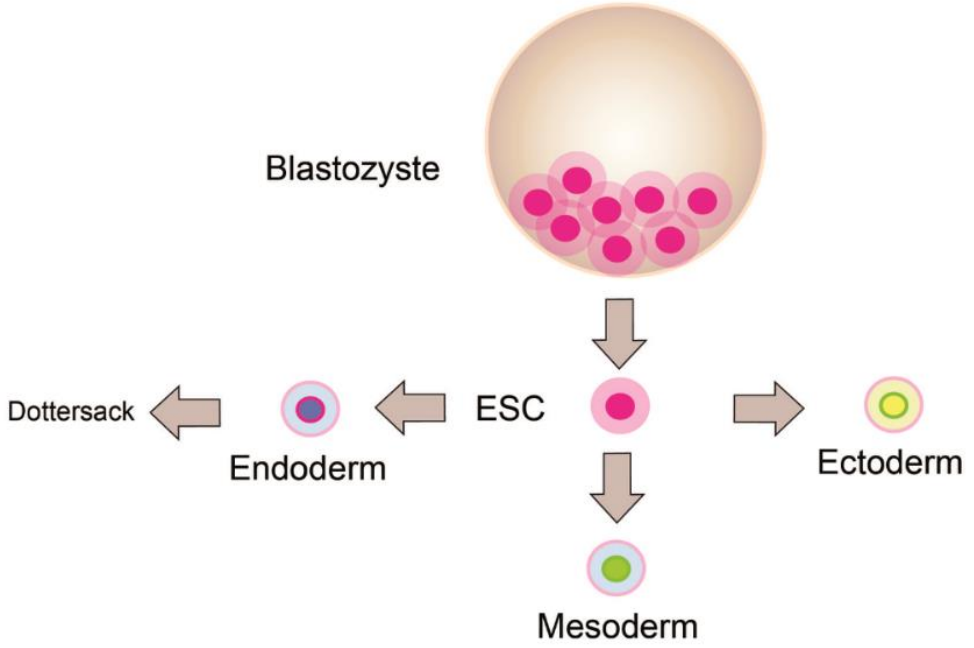
- Human body develops from the three cotyledons



ESC:
Embryonal Stem Cell

Peritoneum: Embryology

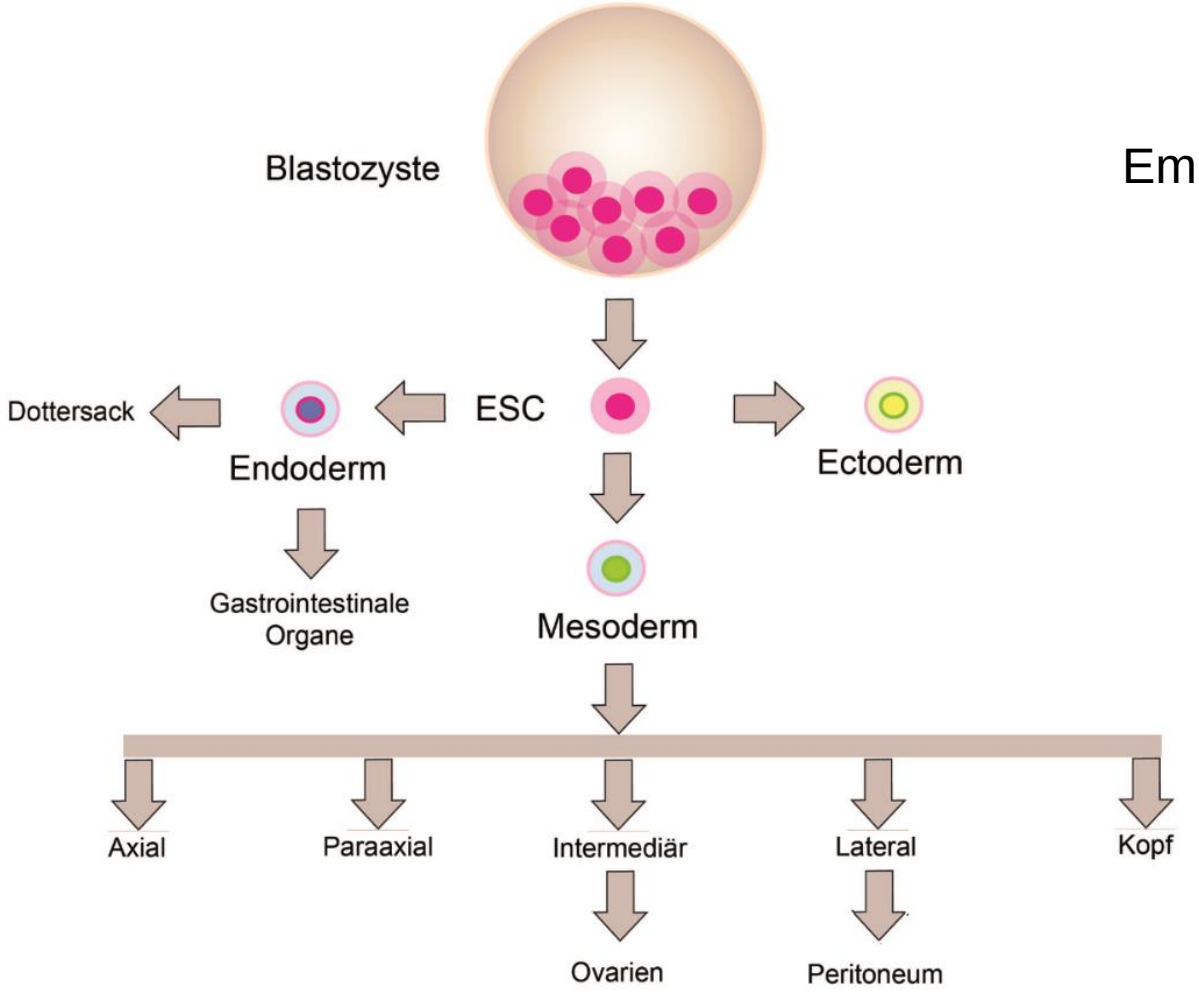
- There is different types of tissue that later differentiate to develop into the various specialized organs of the body.



ESC:
Embryonal Stem Cell

Peritoneum: Embryology

- The peritoneum develops from the lateral plate mesoderm.
- The ovaries also develop from the mesoderm, but from the intermediate plate mesoderm.



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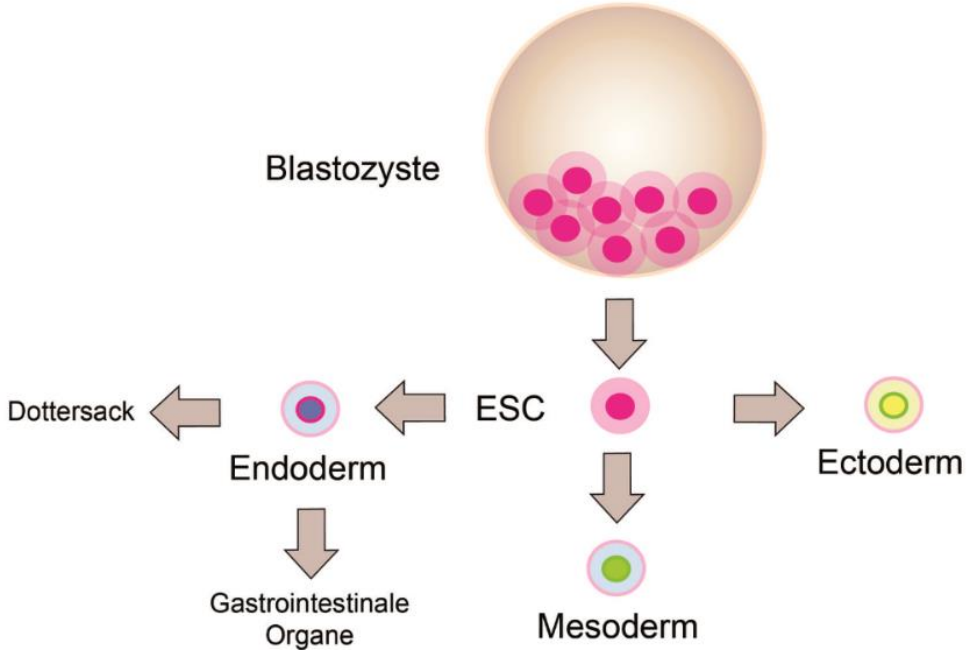


ESC: Embryonal Stem Cell

In clinical routine, these different origins are relevant because the determination of epithelial and mesothelial markers allows the origin of peritoneal tumors to be determined.

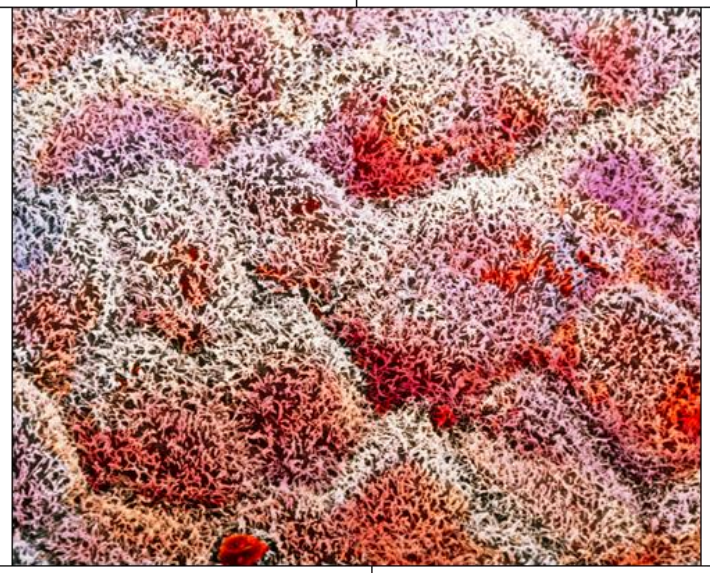
Peritoneal Surface, 6 Major Functions

- Total surface area= 2 m^2
- **The parietal peritoneum**

(around 30%) covers the abdominal wall

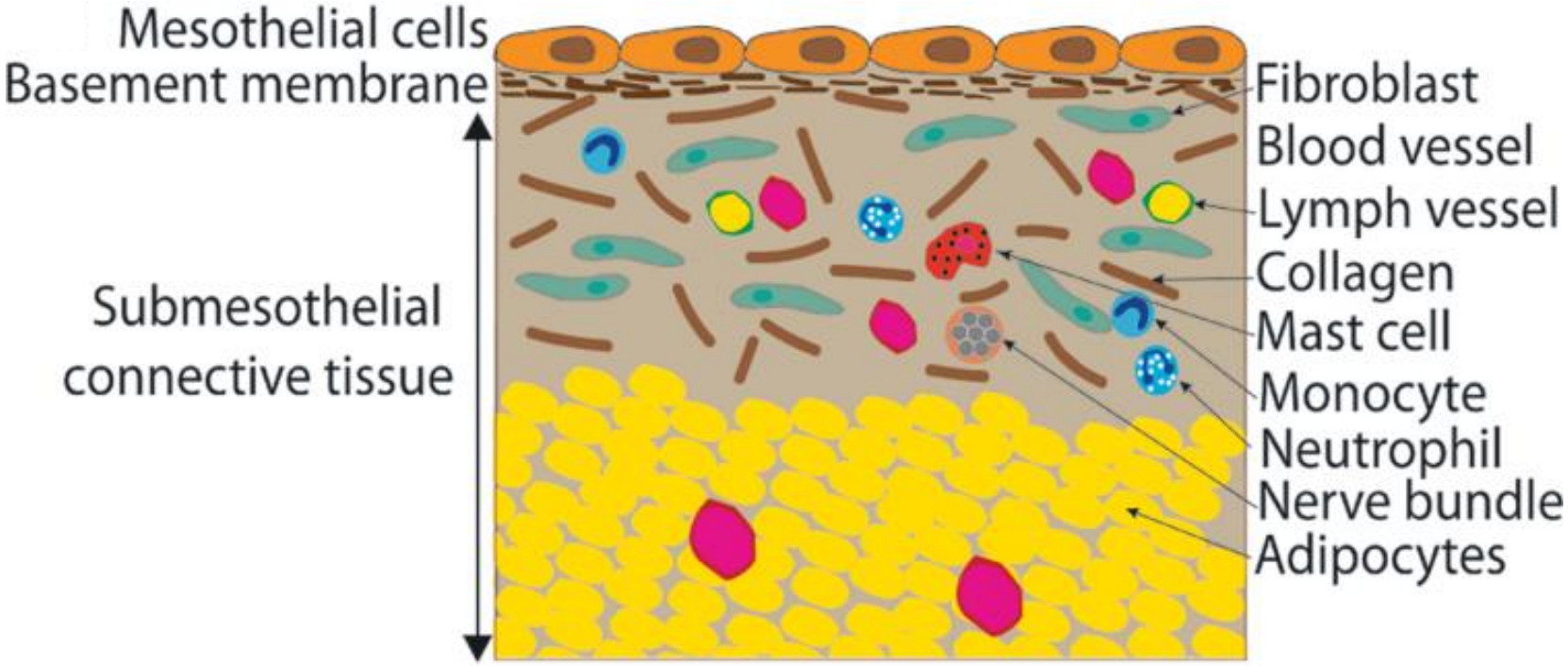
- **The visceral peritoneum**

(around 70%) covers the intra-abdominal organs

Fluid and solute transport	Protection barrier (infection, cancer)
Coagulation and clotting	 Inflammation and healing
Immune response and regulation	Adipose tissue development ?

Peritoneum: Morphology

Mesothelium: a simple layer



Pleura and Peritoneum 2016; 1(2): 79–89

Kunio Kawanishi*

→ Covering the surface of the internal organs and cavities forming the pleura, the pericardium

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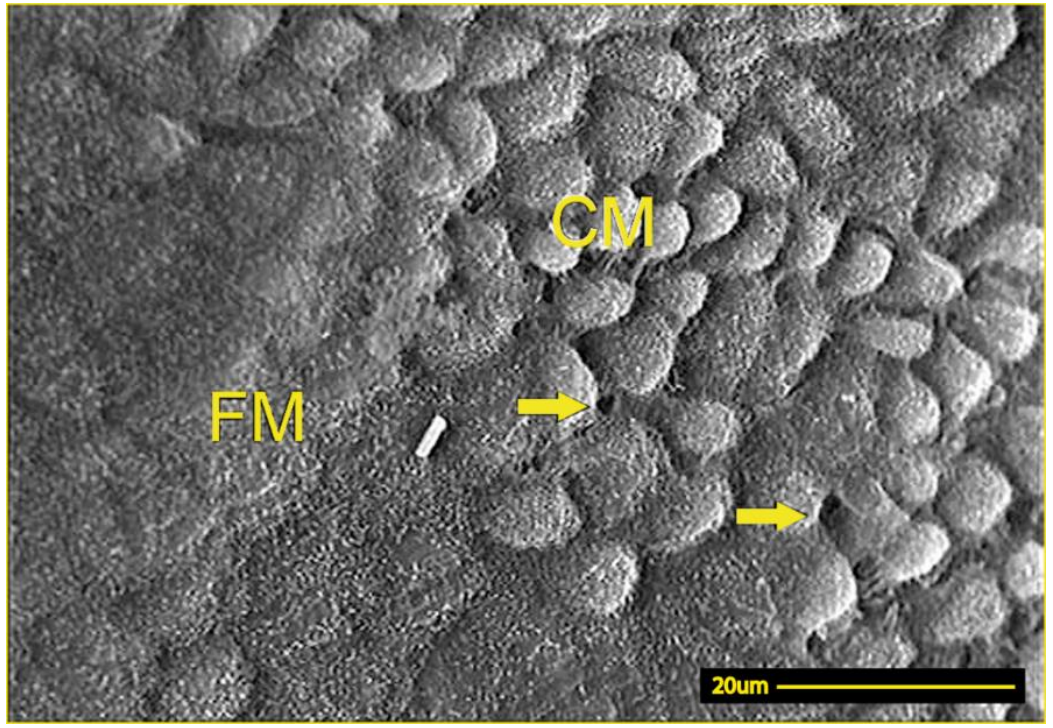
Peritoneum: Morphology

- Serous membranes (pleura, peritoneum) have many similarities with epithelial membranes (skin, mucosae)
  - intercellular junctions
  - apico-basal orientation
  - cytokeratins
  - large surface microvilli
  - rapid turnover



Electron microscope view

Two kind of mesothelials cells:
Flat (visceral peritoneum and peritoneal side of the diaphragm) and cubic (parietal peritoneum),
Arrows: lymphatic stomata.

Solass W et al. In: Rau, Piso, Königsrainer (eds). Springer 2018

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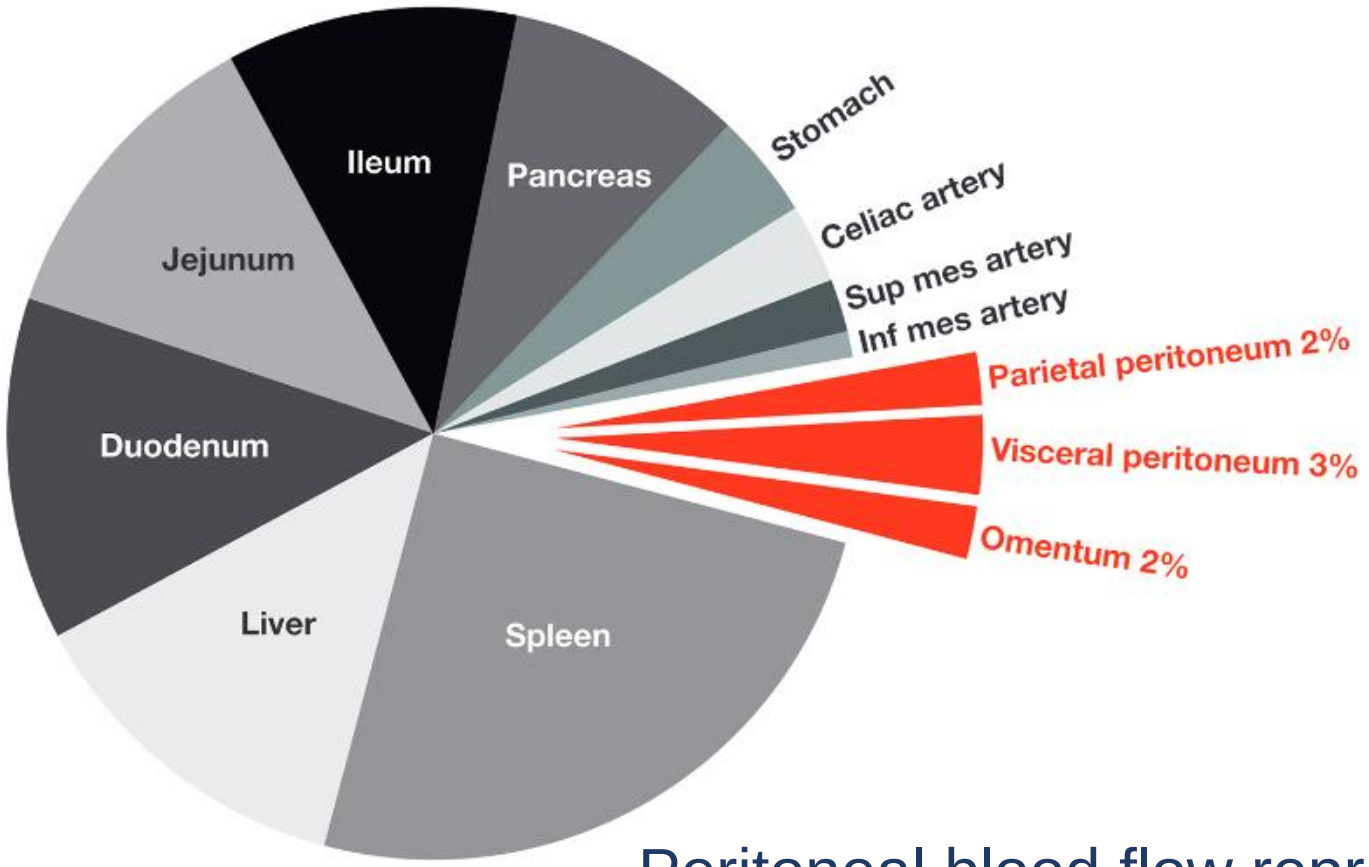
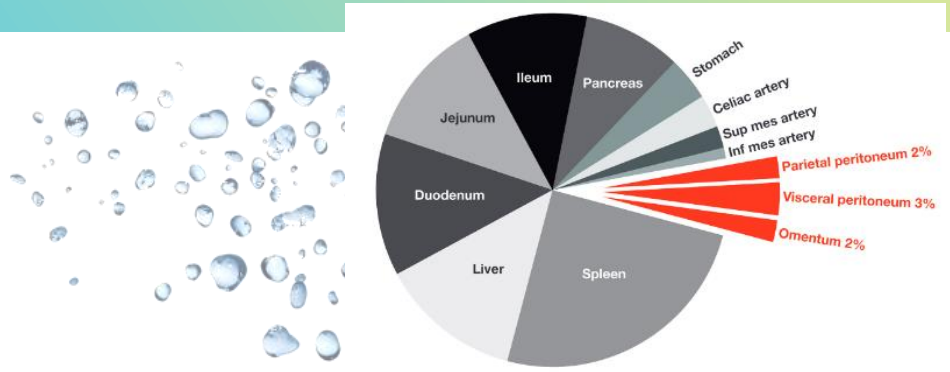
Peritoneum: Vascular Supply



Peritoneal blood flow represents only 1-2% of cardiac output

Solass W et al. Pleura Peritoneum 2016

Peritoneum: Vascular Supply



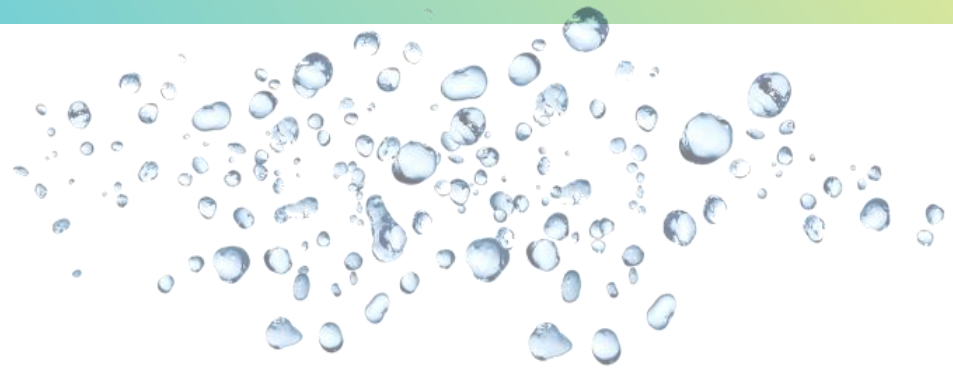
- **The parietal peritoneum** is supplied by the circumflex, iliac, lumbar, intercostal, and epigastric arteries.
- The parietal vessels drain into the inferior vena cava.

- **The visceral peritoneum** receives its blood supply from the three main arteries of the splanchnic organs – the celiac trunk and the superior and inferior mesenteric arteries.
- The visceral peritoneum drains into the portal vein.

- **Both inflammation of the peritoneum and tumor invasion induce neoangiogenesis,** which develops into excessive growth of the microvascular network.

Solass W et al. Pleura Peritoneum 2016

Lymphatic Vessels



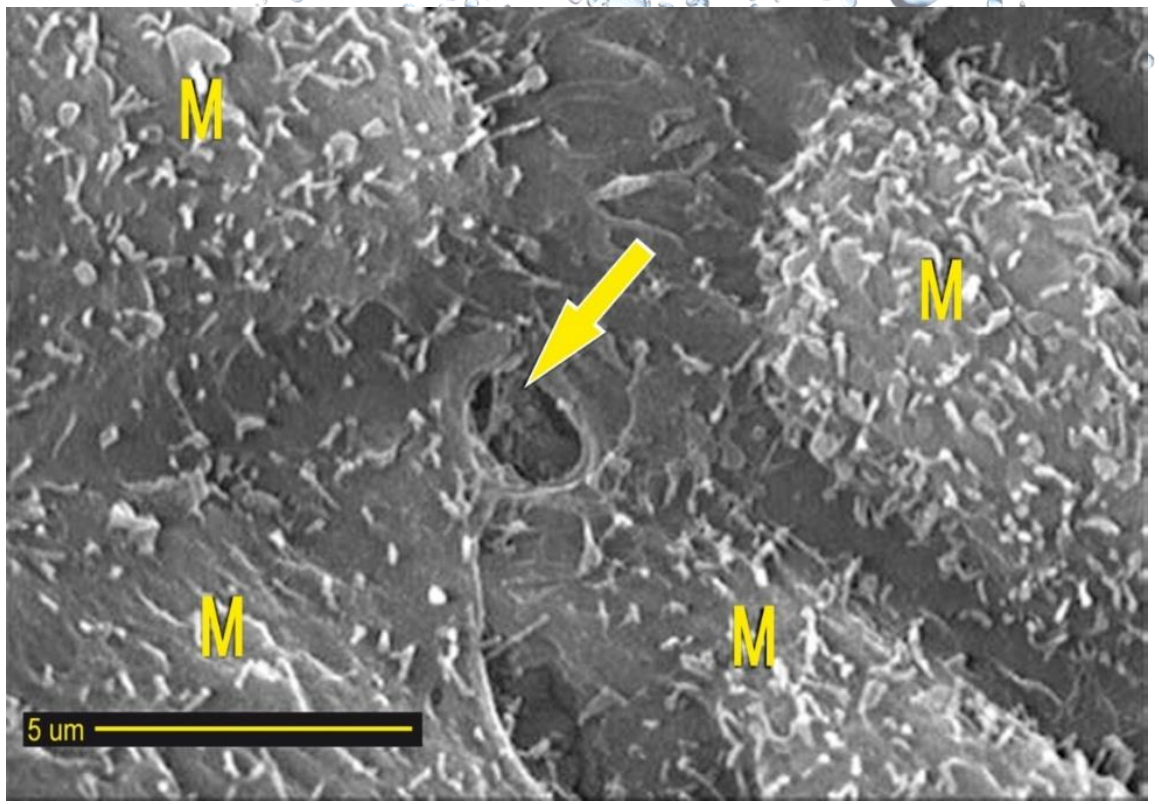
- Has a major role in protein and lipid transport from tissue to blood
- Subdiaphragmatic lymphatics drain 80% from abdominal cavity,
    - then into the lymph ducts into the venous circulation
- Contributes to balance of solutes and fluids in the interstitial tissue by absorbing fluid from the peritoneal cavity

Lymphatic Stomata (LS)

- Small openings of lymphatic capillaries within the basal membrane
- Function: active fluid absorption

  (peritonitis, ascites, PM)
- Connect abdominal and pleural cavities
- High density of LS:

greater omentum, diaphragm, falciform ligament, douglas pouch and interface small bowel/ mesentery



Electron microscope view:
The majority of stomata in normal conditions are not opened

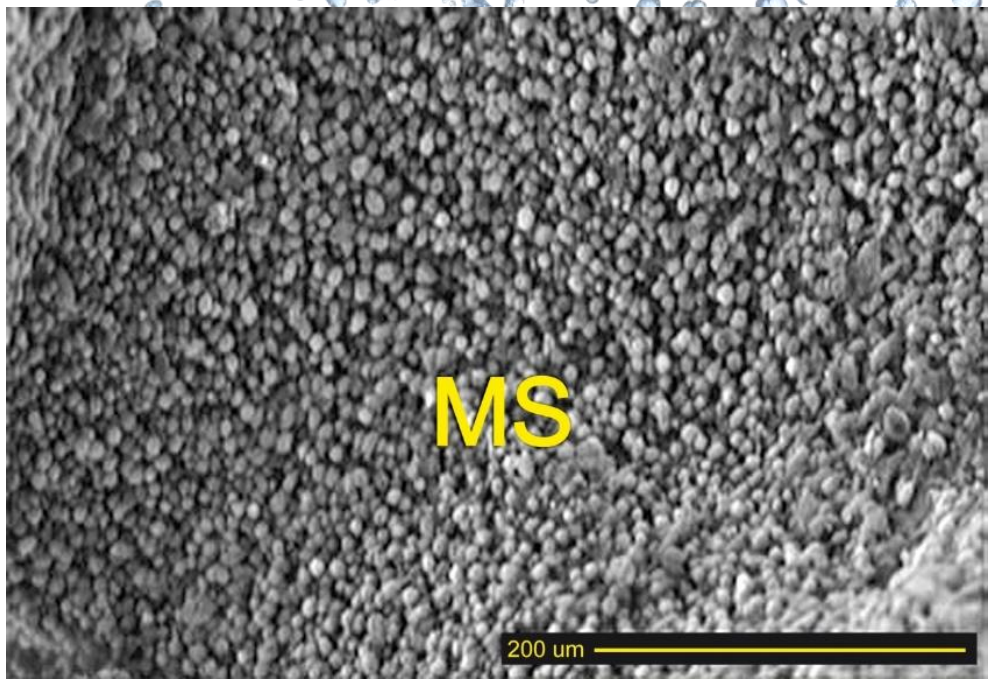
Hort W. et al. Virchow Arch B Zellpat. 1969; 2:280-291
Michailova KN et al (eds). Serosal Membranes (Pleura, Pericardium, Peritoneum). Springer 2006

Immune Defense: Peritoneal Liquid

- Only few milliliters of free liquid
- Contains growth factors, nutriments, cytokines and chemokines
  - Allowing exchange between blood and peritoneal cavity
- Cellular content (sorted by frequency)
  1) leucocytes (monocytes and macrophages)
  2) B- lymphocytes
  3) T- lymphocytes, NK-cells, mastocytes, neutrophils

Immune Defense: Milky Spots (MS)

- Very small lymphatic structures,
- Located around lymphatic stomata,
- Reservoir of macrophages and lymphocytes
- First immune barrier in the peritoneal cavity.



electron microscope view

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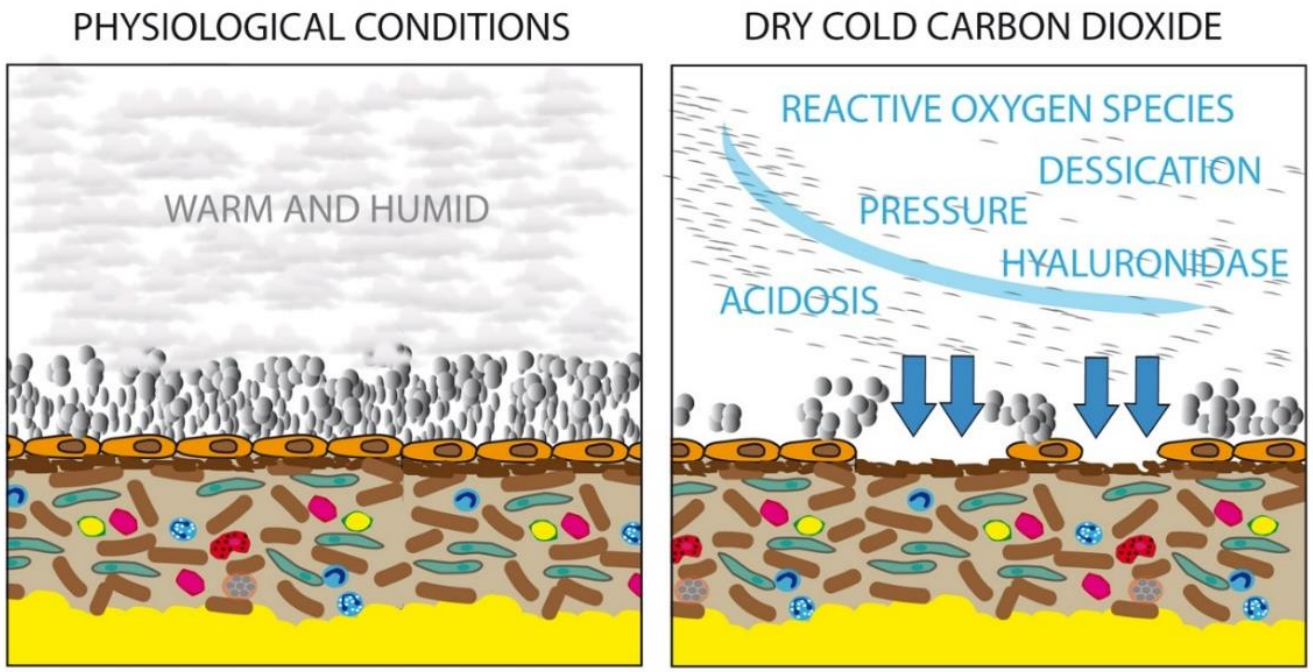
Peritoneal Injury (During Laparoscopy)



Local effects include
Evaporative cooling, oxidative stress,
Desiccation of mesothelium,
Disruption of mesothelial cell junctions and glycocalyx,
Decreased peritoneal blood flow,
Peritoneal acidosis, hypoxia or necrosis

Wilson R, Pleura Peritoneum 2017

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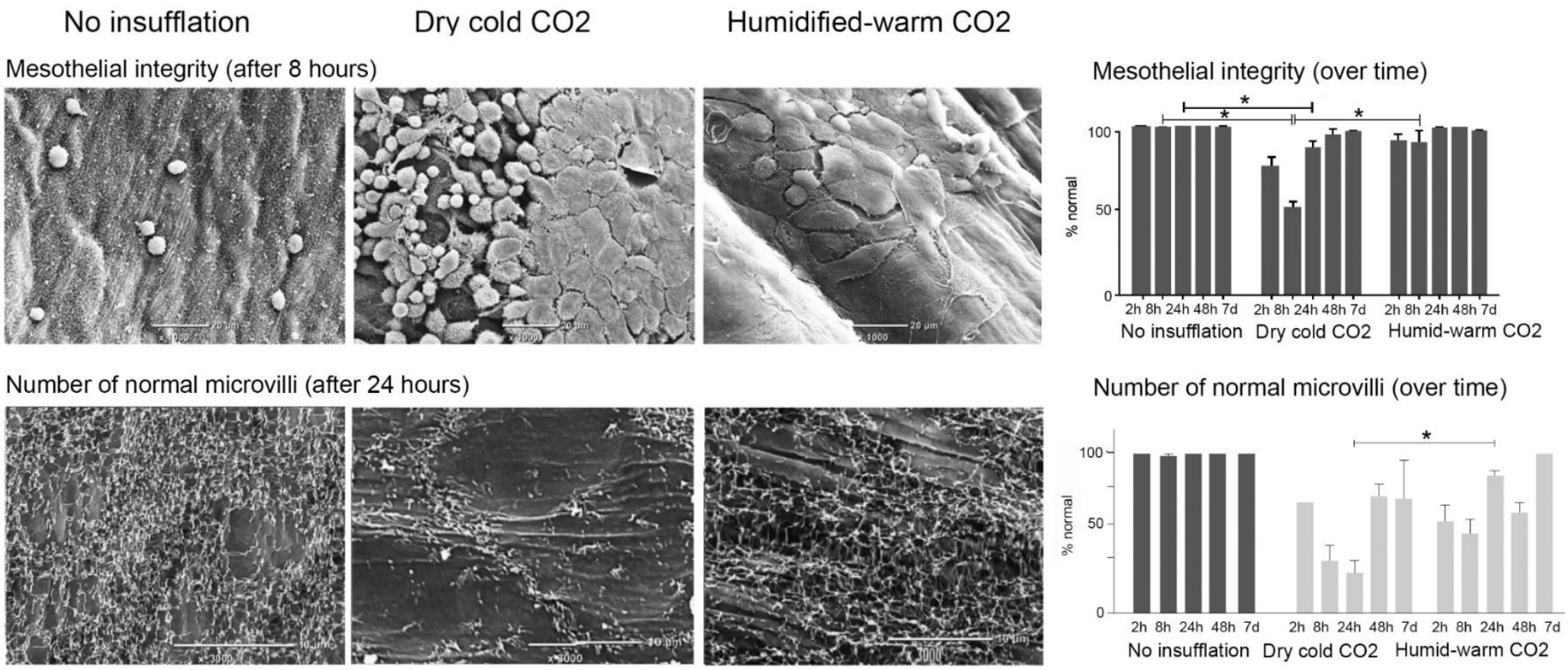
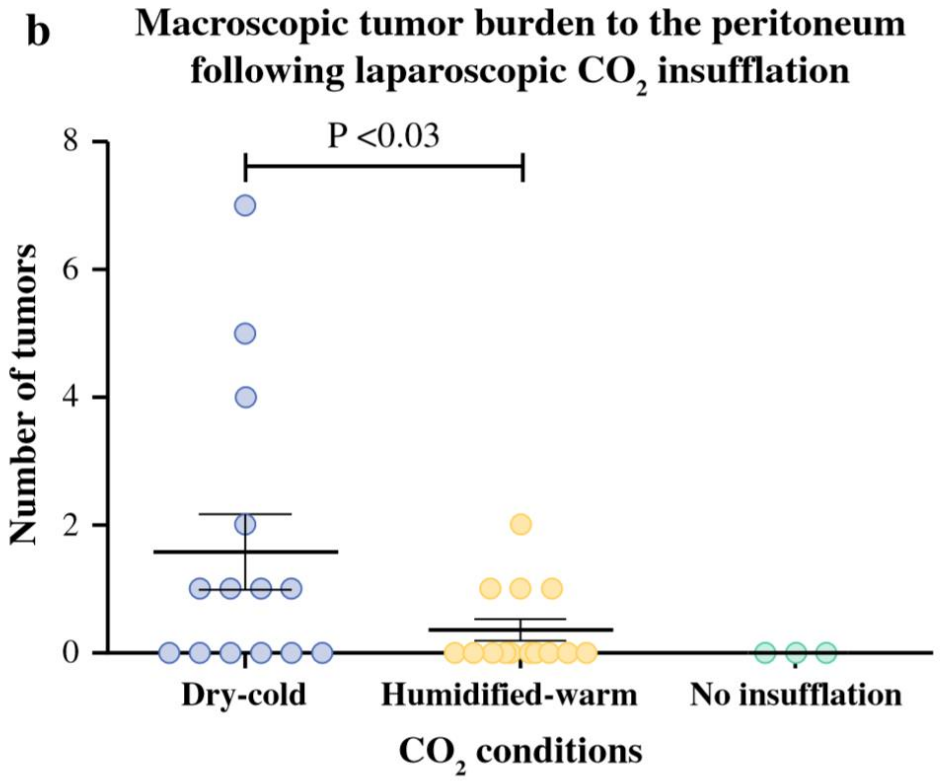
Peritoneal Injury
(During Laparoscopy in Murine Model)

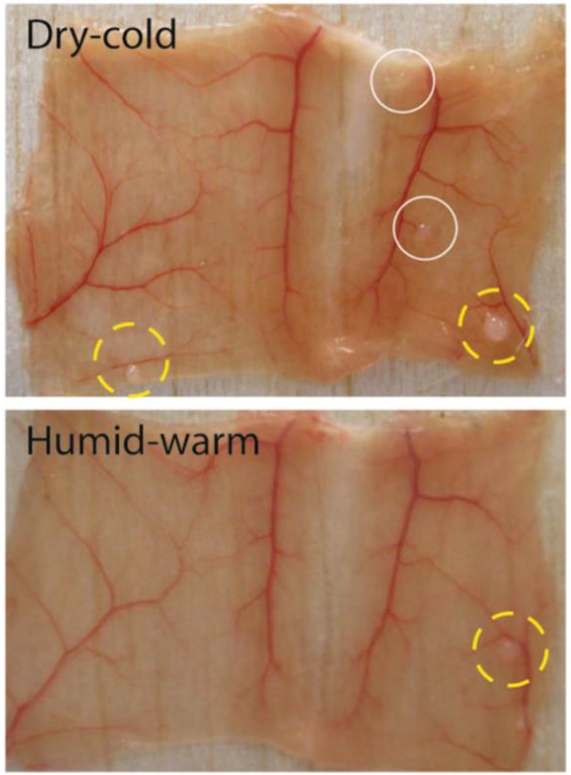
Electron microscope view



Carpinteri S, Ann Surg Oncol (2015) 22:S1540–S1547

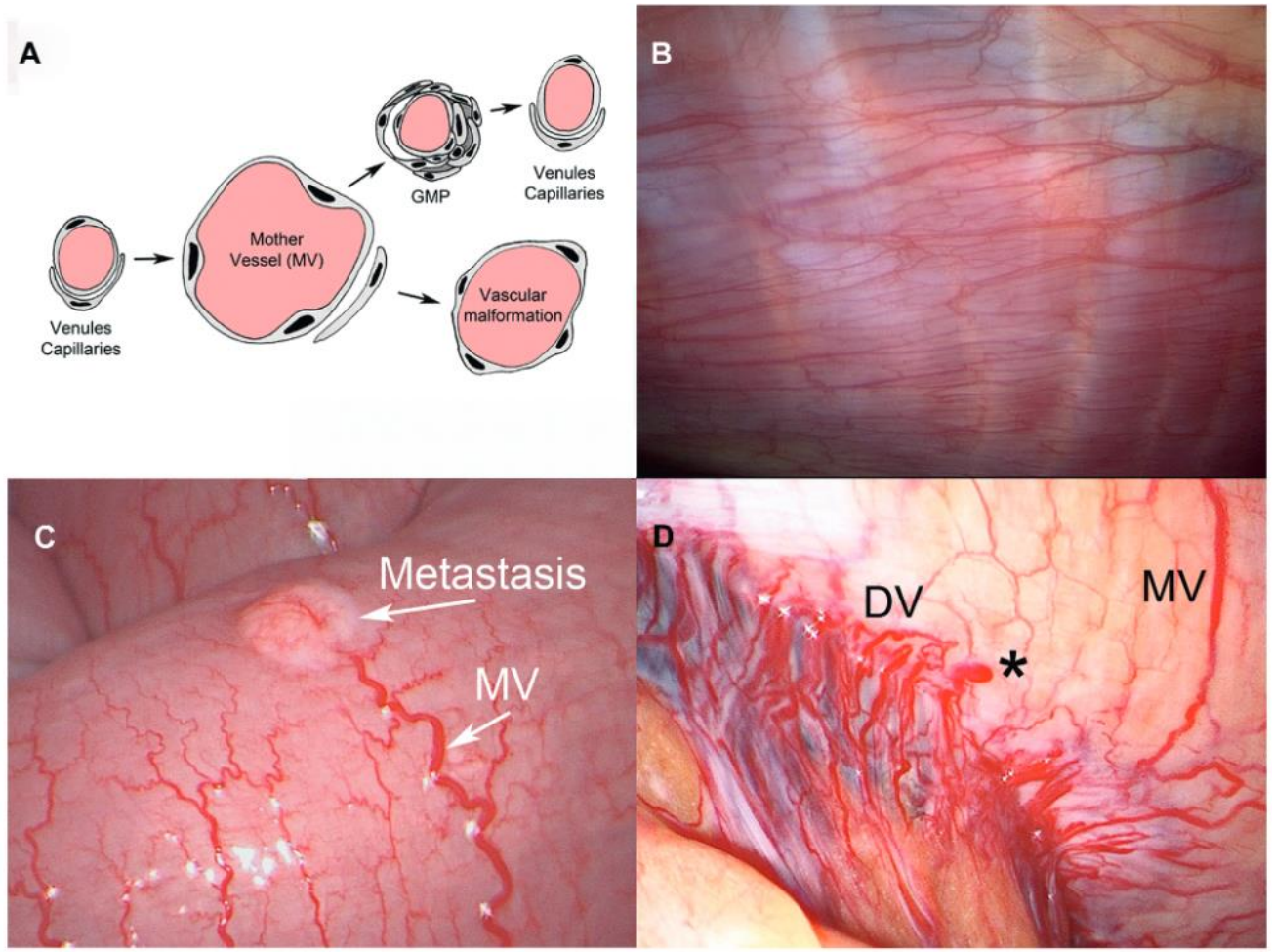
Peritoneal Injury Promotes Tumor Implantation





Carpinteri S, Ann Surg Oncol (2015) 22:S1540–S1547

PM are Accompanied by Angiogenesis



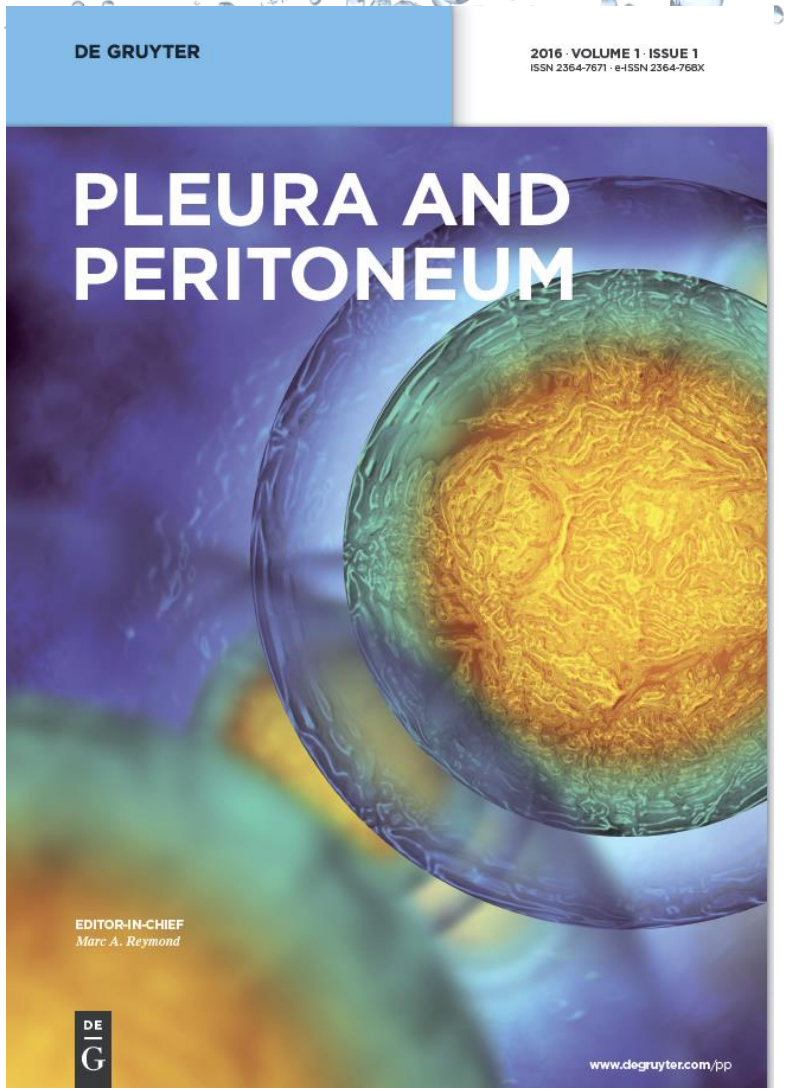
Normal peritoneum

During neoangiogenesis, preexisting normal venules and capillaries evolve within few days into highly abnormal, enlarged “mother” vessels.

Solass W et al Pleura Peritoneum 2016a

Conclusion

- Pleura and peritoneum are not just membranes and should be considered as polyvalent organs.
- For developing effective therapies we first should know more about these organs and pathologies.
- To facilitate this, ISSPP has launched an own, open-access, peer-reviewed journal



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