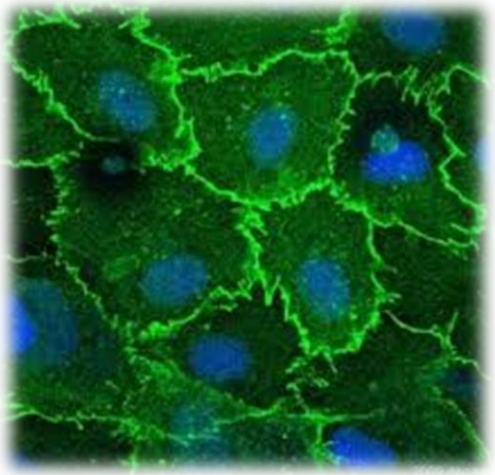
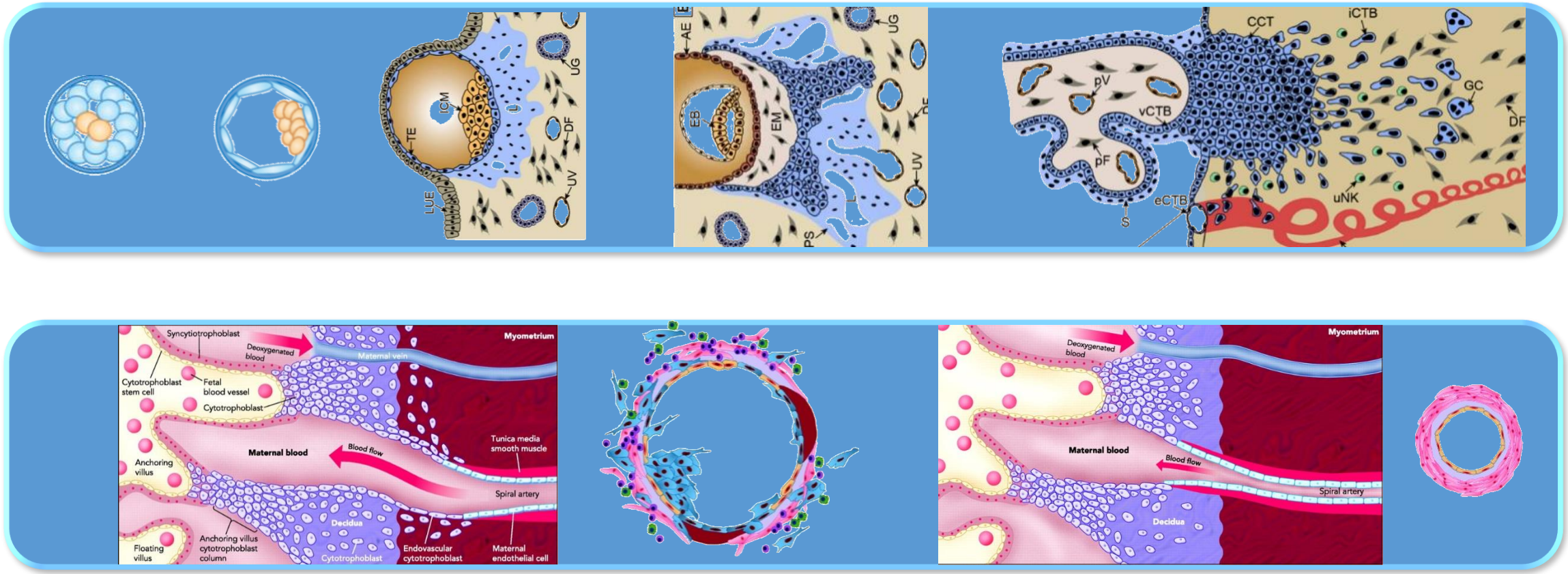


Klaudin 5 szerepe a várandósságban és az extracelluláris vezikulák

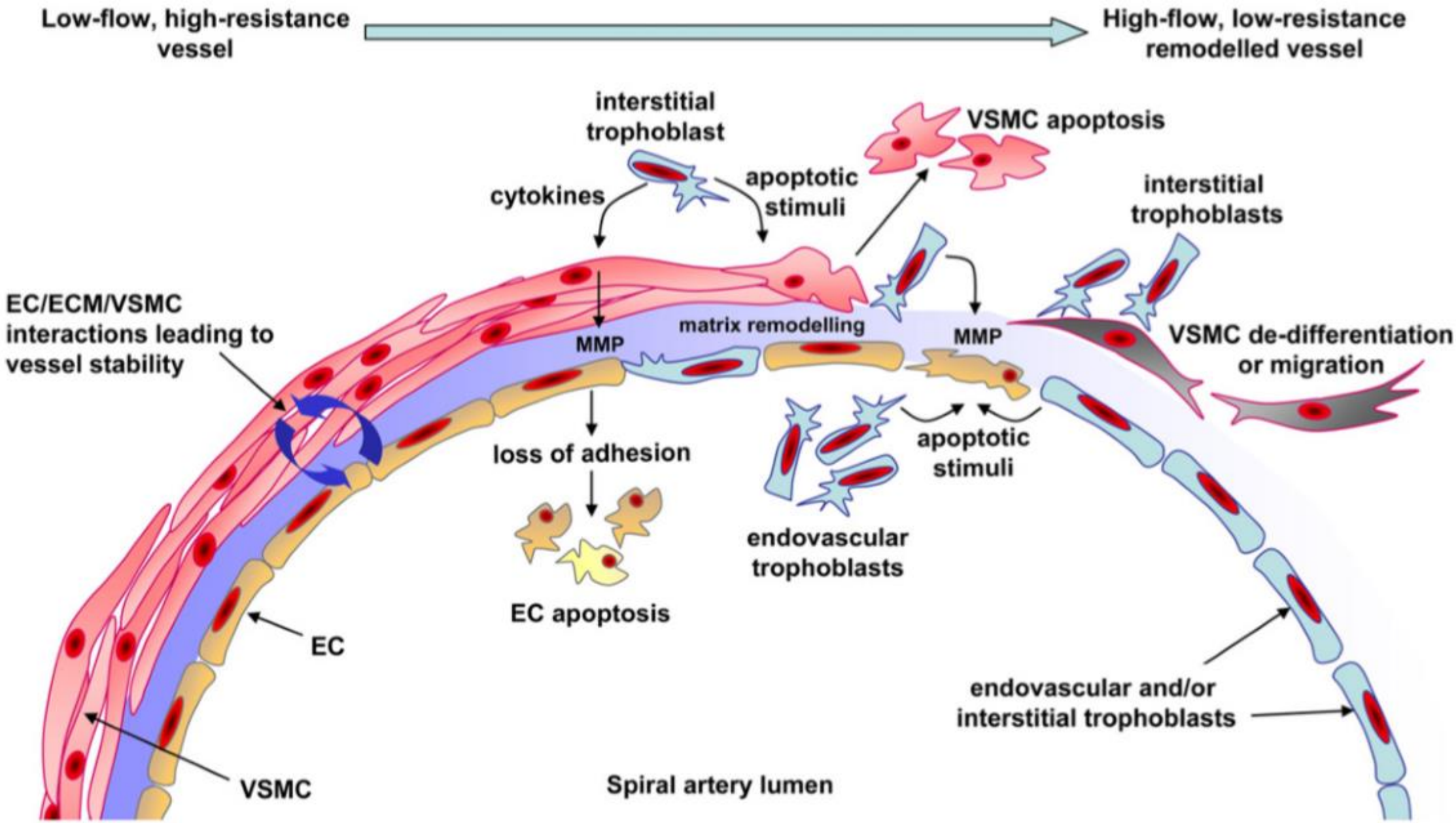
Dr. Kovács Árpád Ferenc

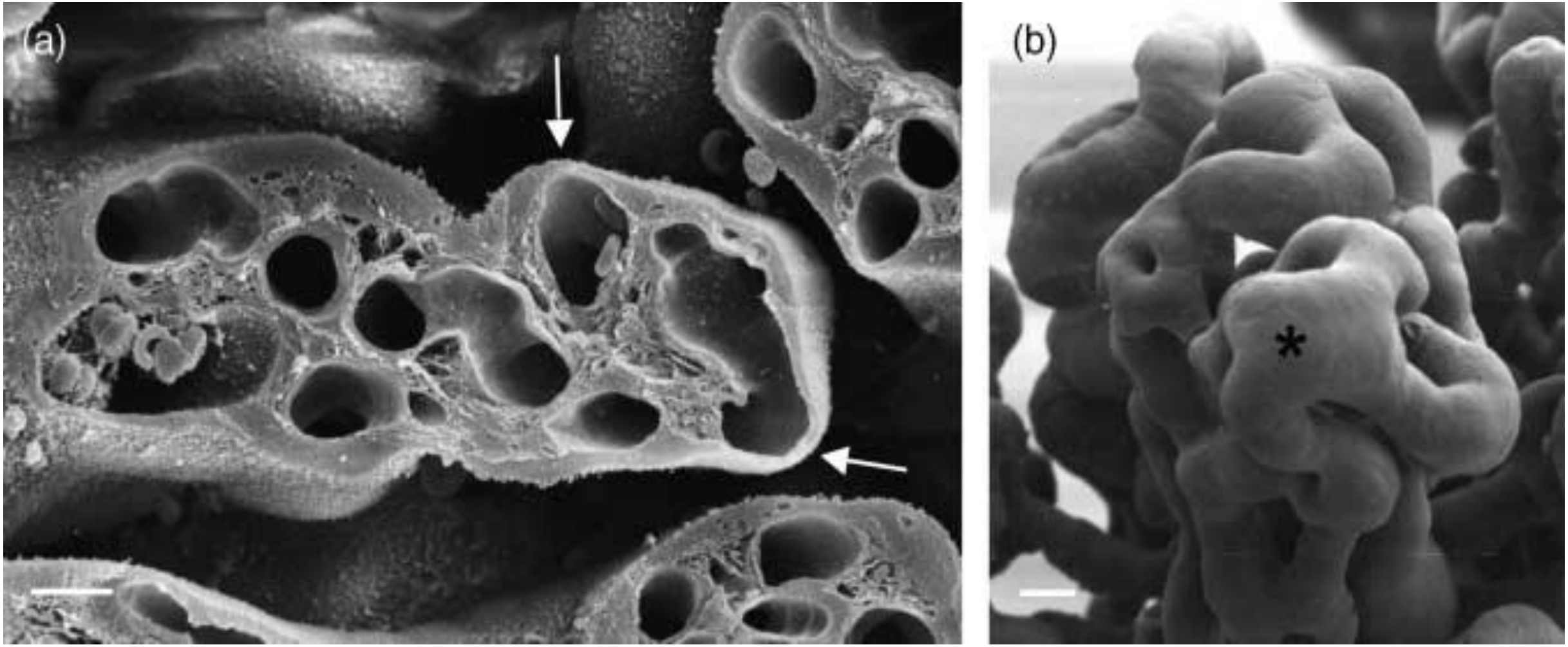
2015. 11. 23.

Trophoblast differenciáció és funkció

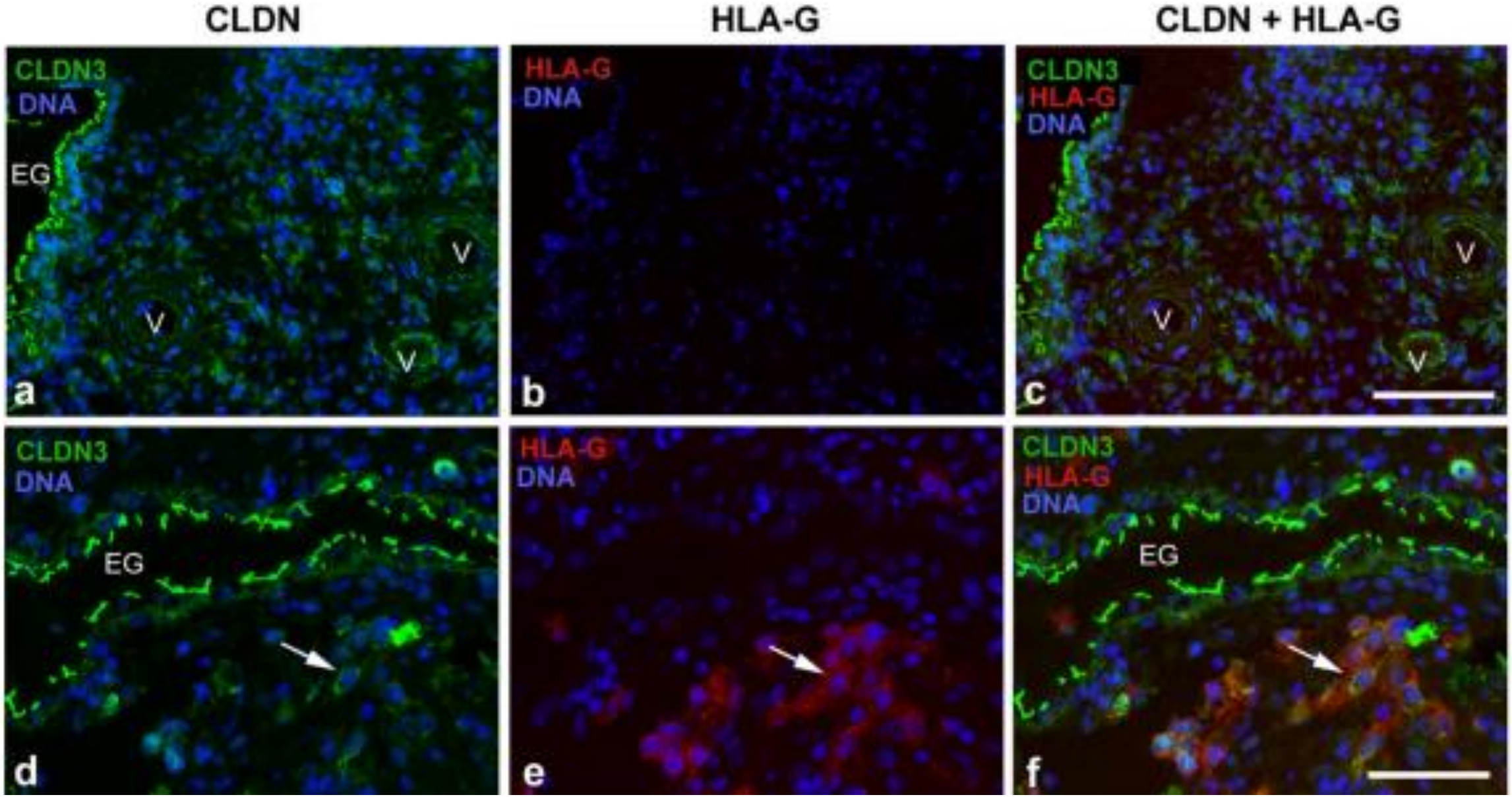


Judith E Cartwright et al. – Remodelling at the maternal–fetal interface: relevance to human pregnancy disorders Reproduction 140 (6) 803-813


Low-flow, high-resistance vessel
High-flow, low-resistance remodelled vessel
interstitial trophoblast
cytokines
apoptotic stimuli
VSMC apoptosis
interstitial trophoblasts
EC/ECM/VSMC interactions leading to vessel stability
MMP
matrix remodelling
MMP
VSMC de-differentiation or migration
loss of adhesion
apoptotic stimuli
endovascular trophoblasts
EC apoptosis
EC
endovascular and/or interstitial trophoblasts
VSMC
Spiral artery lumen



G J Burton, D S Charnock-Jones and E Jauniaux - Regulation of vascular growth and function in the human Placenta, Reproduction (2009) 138 895–902


CLDN
HLA-G
CLDN + HLA-G
CLDN3
DNA
EG
V
V
V
a
HLA-G
DNA
b
CLDN3
HLA-G
DNA
V
V
V
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CLDN3
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EG
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HLA-G
DNA
e
CLDN3
HLA-G
DNA
EG
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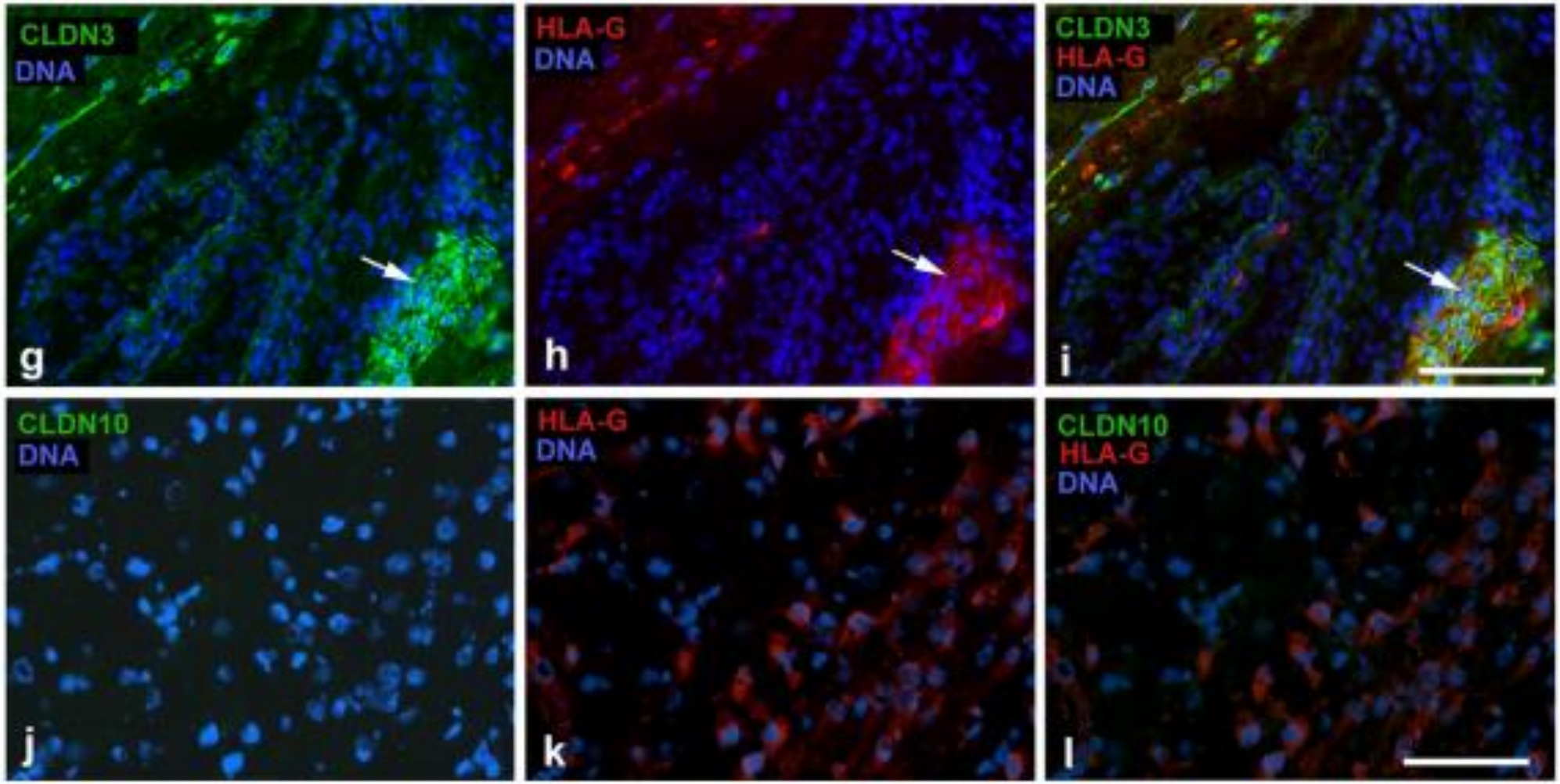
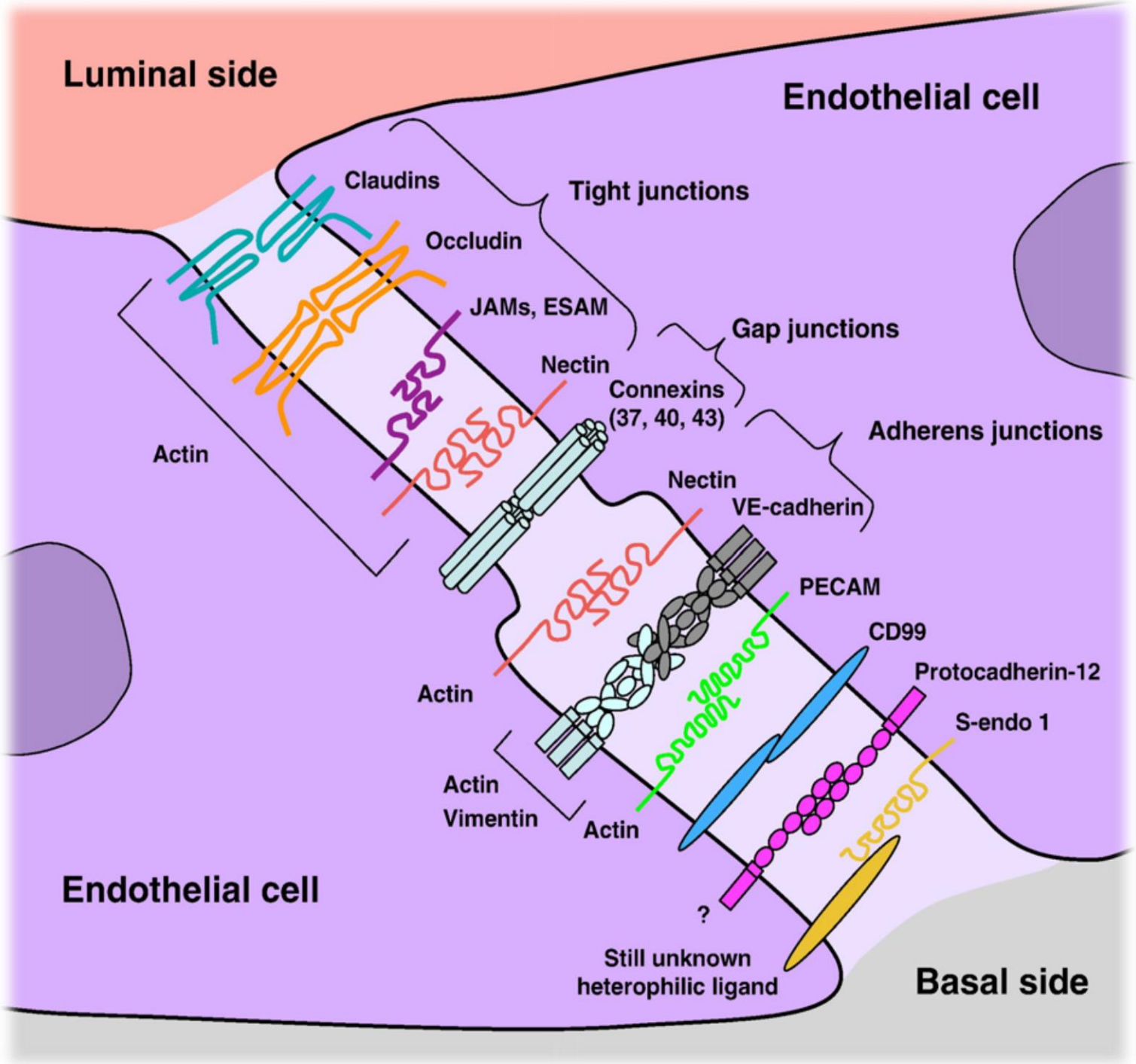
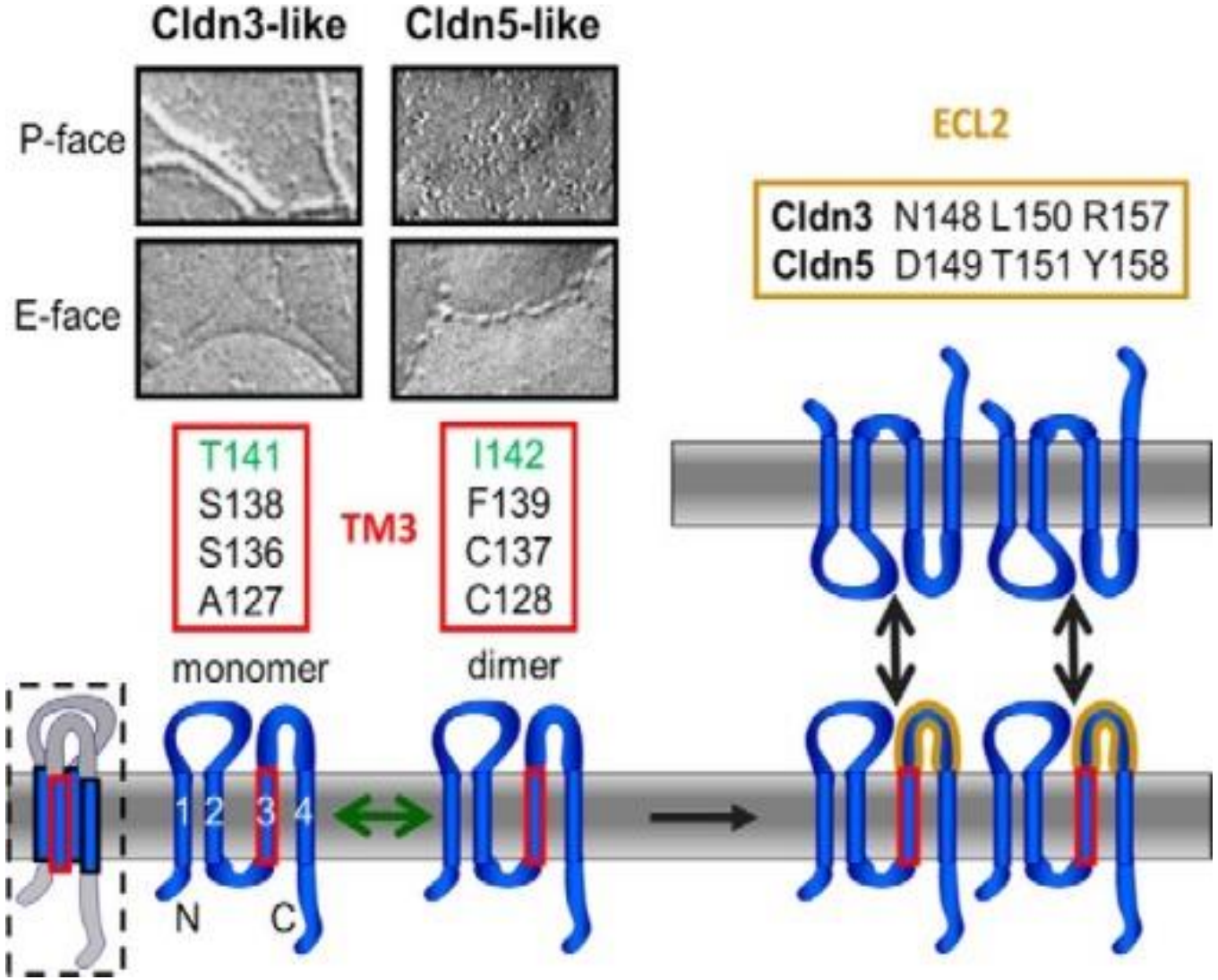


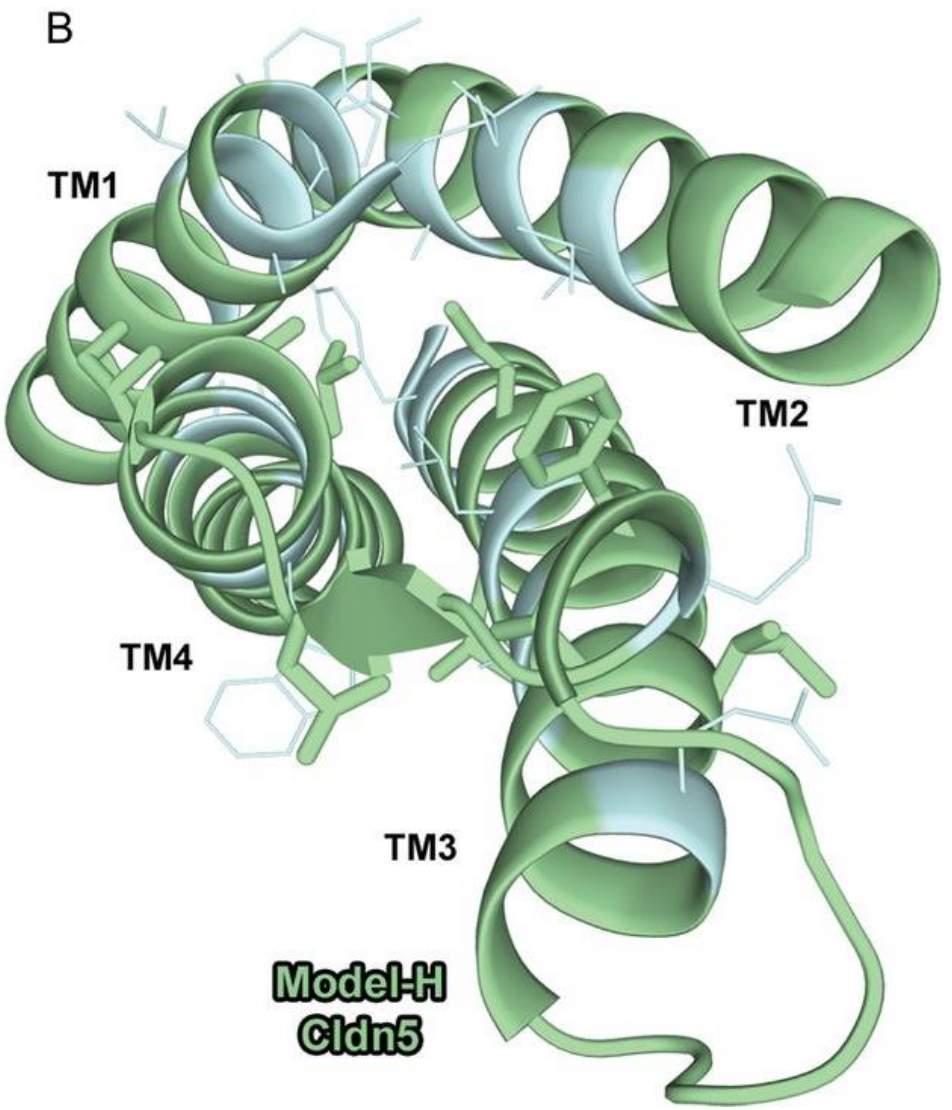
Fig. 6 Immunofluorescence staining of Cldn3 (**a–i**) and Cldn10 (**j–l**) in the decidua basalis of human first trimester placentas of week 8 (**a–f**, **j–l**) and week 9 (**g–i**) of gestation. In placental tissue of 8th and 9th weeks of gestation, abundant extravillous trophoblast cells were identified by HLA-G staining (**e**, **h**, **k**). Cldn3 protein was detected in vascular endothelial cells (*V* in **a**, **c**) and endometrial glandular epithelium (*EG* in **d**, **f**), but also in extravillous trophoblast cells as identified by HLA-G staining (**d–i**, *arrows*). No expression of Cldn10 was observed neither in decidual nor in trophoblast cells (**j–l**). *EG* endometrial gland, *V* vessel. *Bar* in **a–c**, **g–i**: 100 μm, *bar* in **d–f**, **j–l**: 60 μm

Sejtkapcsoló struktúrák



Y. Wallez, P. Huber / Biochimica et Biophysica Acta 1778 (2008) 794–809

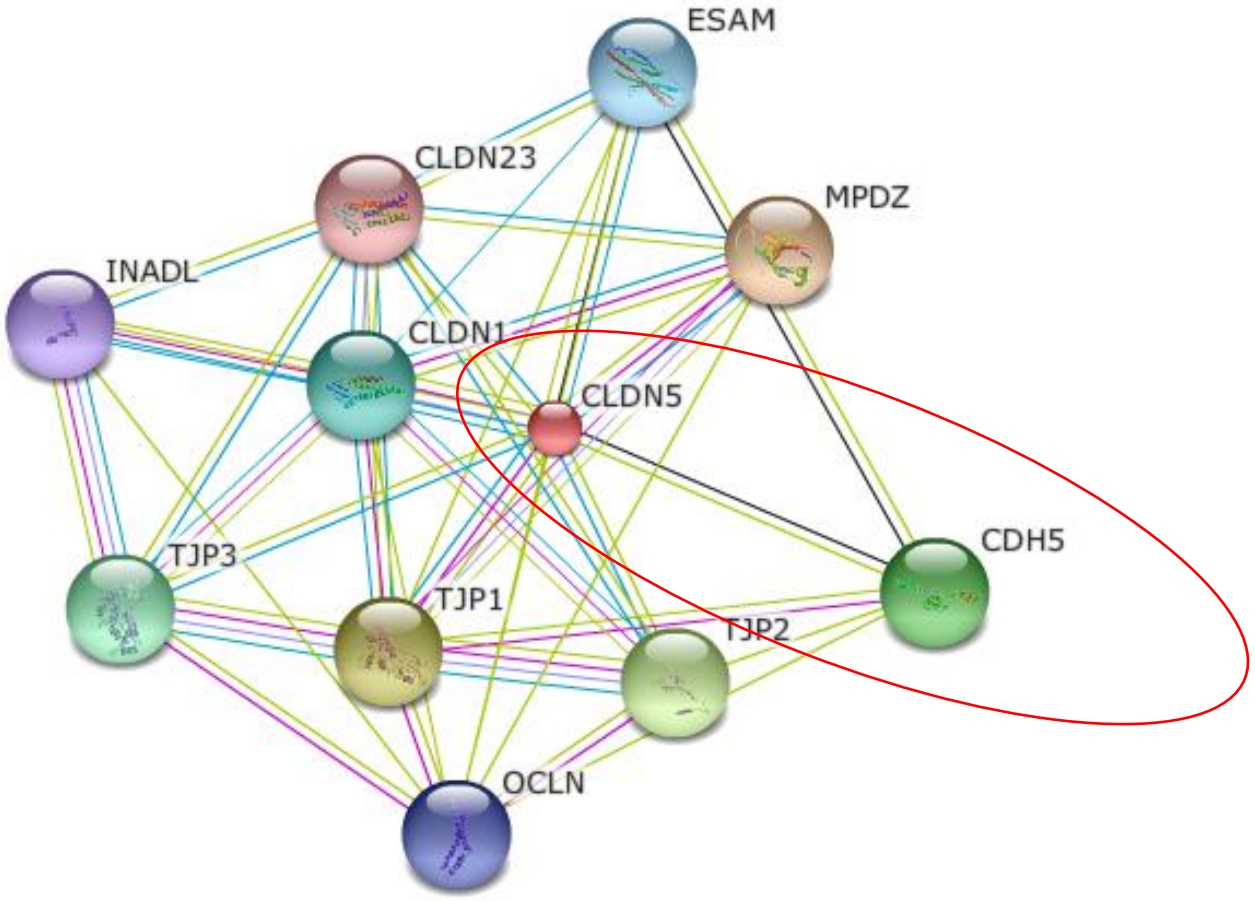




Rossa J, Ploeger C, Vorreiter F, et al. Claudin-3 and Claudin-5 Protein Folding and Assembly into the Tight Junction Are Controlled by Non-conserved Residues in the Transmembrane 3 (TM3) and Extracellular Loop 2 (ECL2) Segments. *The Journal of Biological Chemistry*. 2014;289(11):7641-7653.

Rossa, J., et al. (2014). "Molecular and structural transmembrane determinants critical for embedding claudin-5 into tight junctions reveal a distinct four-helix bundle arrangement." Biochemical Journal **464**(1): 49-60.

Uniprot (1)

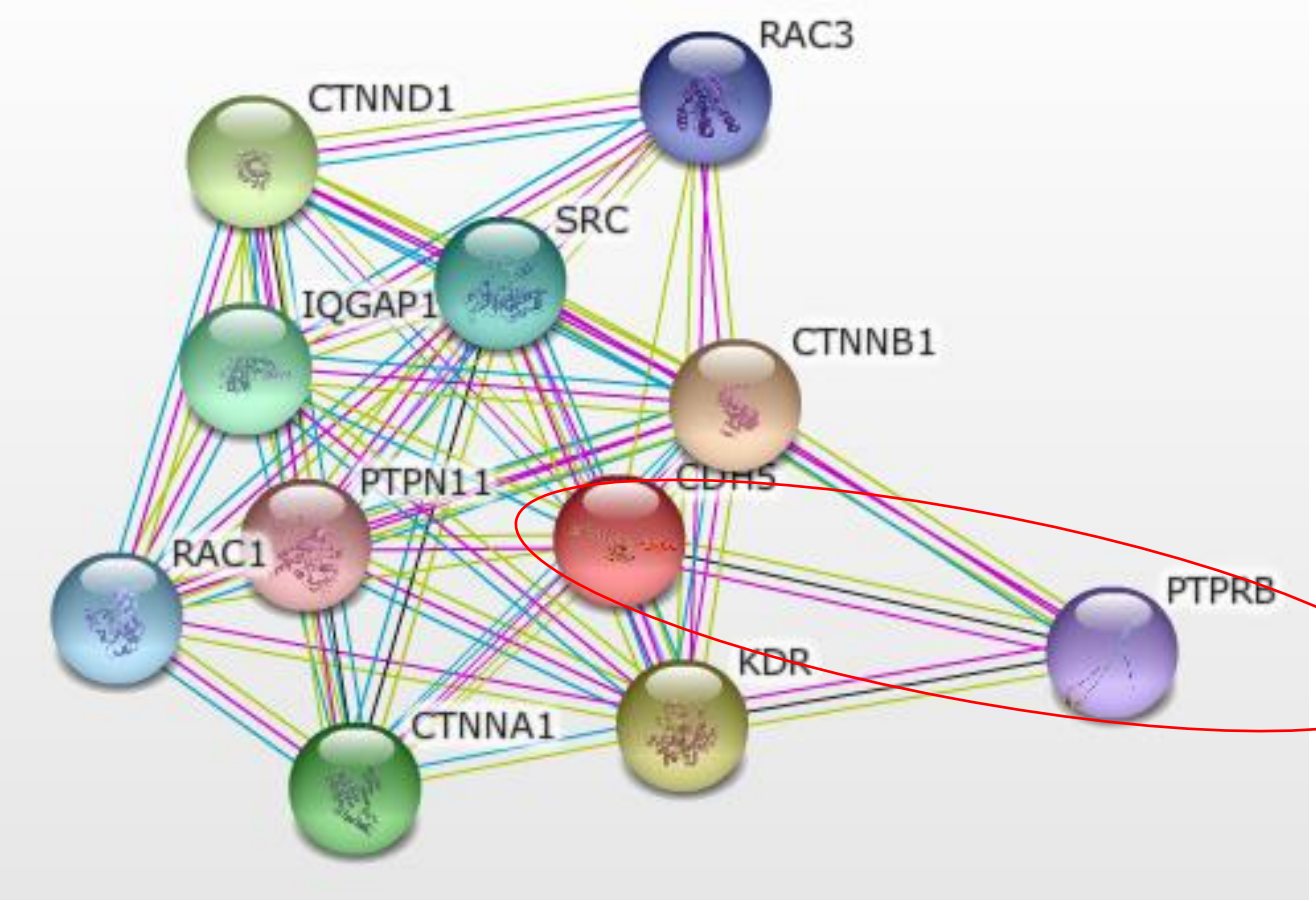


Claudin 5- Plays a major role in tight junction-specific obliteration of the intercellular space

CDH5 cadherin 5, type 2 (vascular endothelium);

Cadherins are calcium-dependent cell adhesion proteins. They preferentially interact with themselves in a homophilic manner in connecting cells; cadherins may thus contribute to the sorting of heterogeneous cell types. This cadherin may play a important role in endothelial cell biology through control of the cohesion and organization of the intercellular junctions. It associates with alpha-catenin forming a link to the cytoskeleton. **Acts in concert with KRIT1 to establish and maintain correct endothelial cell polarity and vascular lumen**

Uniprot (2)



PTPRB

Protein tyrosine phosphatase, receptor type, B; Plays an important role in blood vessel remodeling and angiogenesis. Not necessary for the initial formation of blood vessels, **but is essential for their maintenance and remodeling**. Can induce dephosphorylation of TEK/TIE2, CDH5/VE-cadherin and KDR/VEGFR-2. Regulates angiopoietin-TIE2 signaling in endothelial cells. Acts as a negative regulator of TIE2, and controls TIE2 driven endothelial cell proliferation, which in turn affects **blood vessel remodeling during embryonic development and determines blood vessel size** during perinatal growth

ARTICLE

doi:10.1038/nature15756

Tumour exosome integrins determine organotropic metastasis

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Ever since Stephen Paget's 1889 hypothesis, metastatic organotropism has remained one of cancer's greatest mysteries. Here we demonstrate that exosomes from mouse and human lung-, liver- and brain-tropic tumour cells fuse preferentially with resident cells at their predicted destination, namely lung fibroblasts and epithelial cells, liver Kupffer cells and brain endothelial cells. We show that tumour-derived exosomes uptaken by organ-specific cells prepare the pre-metastatic niche. Treatment with exosomes from lung-tropic models redirected the metastasis of bone-tropic tumour cells. Exosome proteomics revealed distinct integrin expression patterns, in which the exosomal integrins $\alpha_6\beta_4$ and $\alpha_6\beta_1$ were associated with lung metastasis, while exosomal integrin $\alpha_v\beta_5$ was linked to liver metastasis. Targeting the integrins $\alpha_6\beta_4$ and $\alpha_v\beta_5$ decreased exosome uptake, as well as lung and liver metastasis, respectively. We demonstrate that exosome integrin uptake by resident cells activates Src phosphorylation and pro-inflammatory *S100* gene expression. Finally, our clinical data indicate that exosomal integrins could be used to predict organ-specific metastasis.

Despite Stephen Paget's 126-year-old "seed-and-soil" hypothesis[1], insufficient progress has been made towards decoding the mechanisms governing organ-specific metastasis. In experimental metastasis assays, Fidler *et al.* demonstrated that cancer cells derived from a certain metastatic site displayed enhanced abilities to metastasize to that specific organ, providing support for Paget's organ-specific metastasis theory[2]. Subsequent studies investigating organ-specific metastasis focused largely on the role of intrinsic cancer cell properties, such as genes and pathways regulating colonization, in directing organotropism[3–8]. Breast cancer cells express chemokine receptors, such as C-X-C motif receptor 4 (CXCR4) and C-C motif receptor 7 (CCR7), which partner with chemokine ligands expressed in lymph nodes (CXCL12) and lung (CCL21), thus guiding metastasis[3,4]. Tumour-secreted factors can also increase metastasis by inducing vascular leakiness[5], promoting the recruitment of pro-angiogenic immune cells[6], and influencing organotropism[7]. Furthermore, the ability of breast cancer to form osteolytic lesions depends on osteoclast-stimulating growth factors (for example, PTHRP and GM-CSF) released into the bone microenvironment[4,8]. Therefore, our previous observation that metastatic melanoma-derived factors dictate organotropism is not surprising[9]. We found that medium conditioned by highly metastatic murine B16-F10 melanoma cells was sufficient to expand the metastatic repertoire of Lewis lung carcinoma cells that would typically metastasize to the lung[9]. We also showed that pre-metastatic niche formation requires S100 protein and fibronectin upregulation by lung resident cells, and the recruitment of bone-marrow-derived

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Review

Extracellular vesicles as modulators of the cancer microenvironment

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Institute of Cancer and Genetics, School of Medicine, Cardiff University, Velindre Cancer Centre, Whitchurch, Cardiff CF14 2TL, United Kingdom

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ABSTRACT

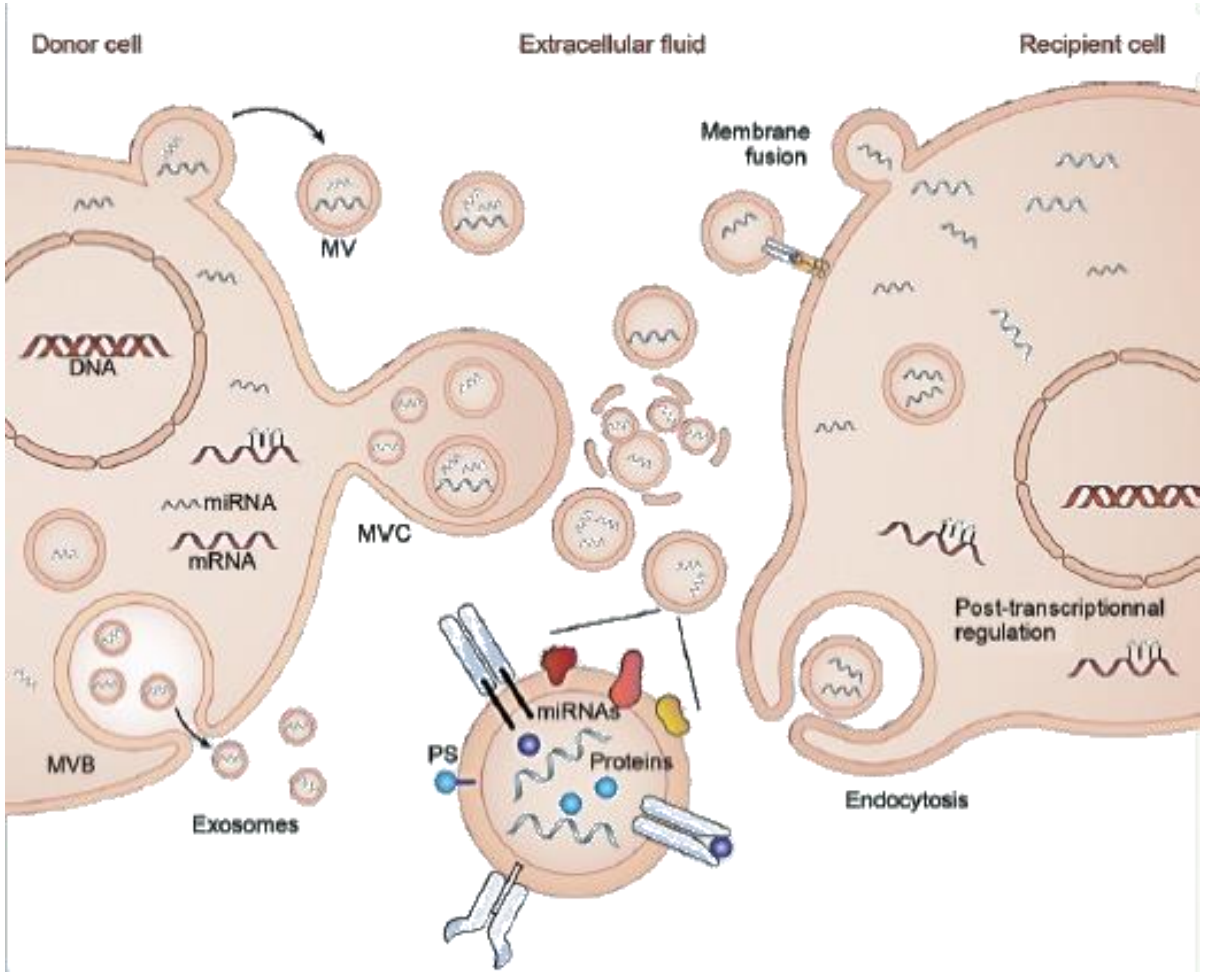
The tumour microenvironment is a highly complex and dynamic tissue. It comprises not only neoplastic cells, but also other resident cells within the milieu such as stroma and vascular cells in addition to a variable cellular infiltrate from the periphery. A host of soluble factors such as growth factors, chemokines, eicosanoids soluble metabolites and extracellular matrix components have been extensively documented as factors which modulate this environment. However, in recent years there has also been growing interests in the potential roles of extracellular vesicles (EV) in many of the processes governing the nature of cancerous tissue. In this brief review, we have assembled evidence describing several distinct functions for extracellular vesicles in modulating the microenvironment with examples that include immune evasion, angiogenesis and stromal activation. Whilst there remains a great deal to be learnt about the interplay between vesicles and the cancerous environment, it is becoming clear that vesicle-mediated communication has a major influence on key aspects of cancer growth and progression. We conclude that the design of future therapeutics should acknowledge the existence and roles of extracellular vesicles, and seriously consider strategies for circumventing their effects *in vivo*.

Contents

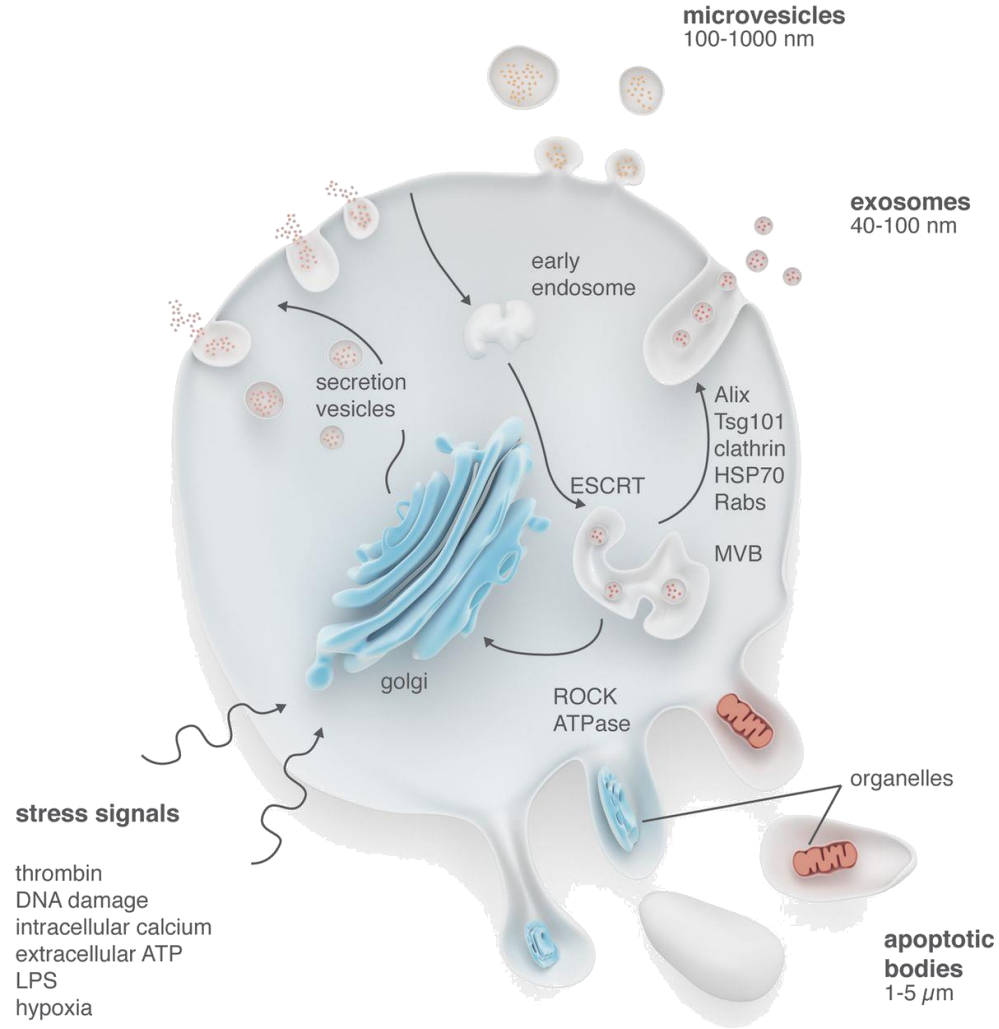
1. Introduction

Like most cell types, neoplastic cells release small lipid-bounded vesicles into the extracellular space, but they may do so extensively compared to their non-neoplastic counterparts [1]. Genotoxic, hypoxic, metabolic and other forms of cellular stress [2–4] lead to heightened levels of vesicle secretion, together with alterations in vesicle-cargo molecules. In cancer therefore, where such conditions are particularly rife, the vesicle secretion pathway appears to be a major feature.

Extracelluláris vezikulák (1)

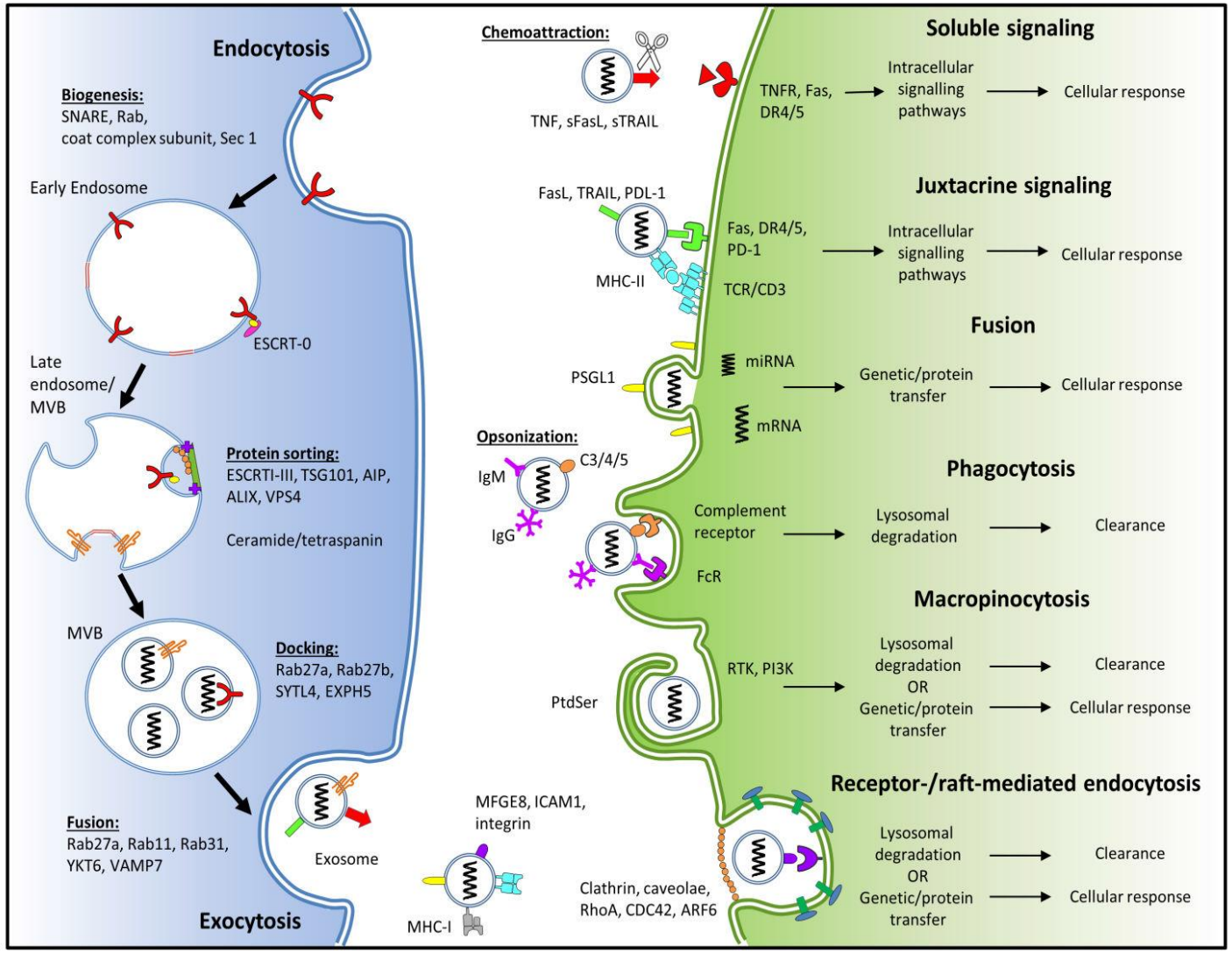


Belleannée Clémence -Extracellular microRNAs from the epididymis as potential mediators of cell-to-cell communication-Asian J Androl 2015;17:730-6



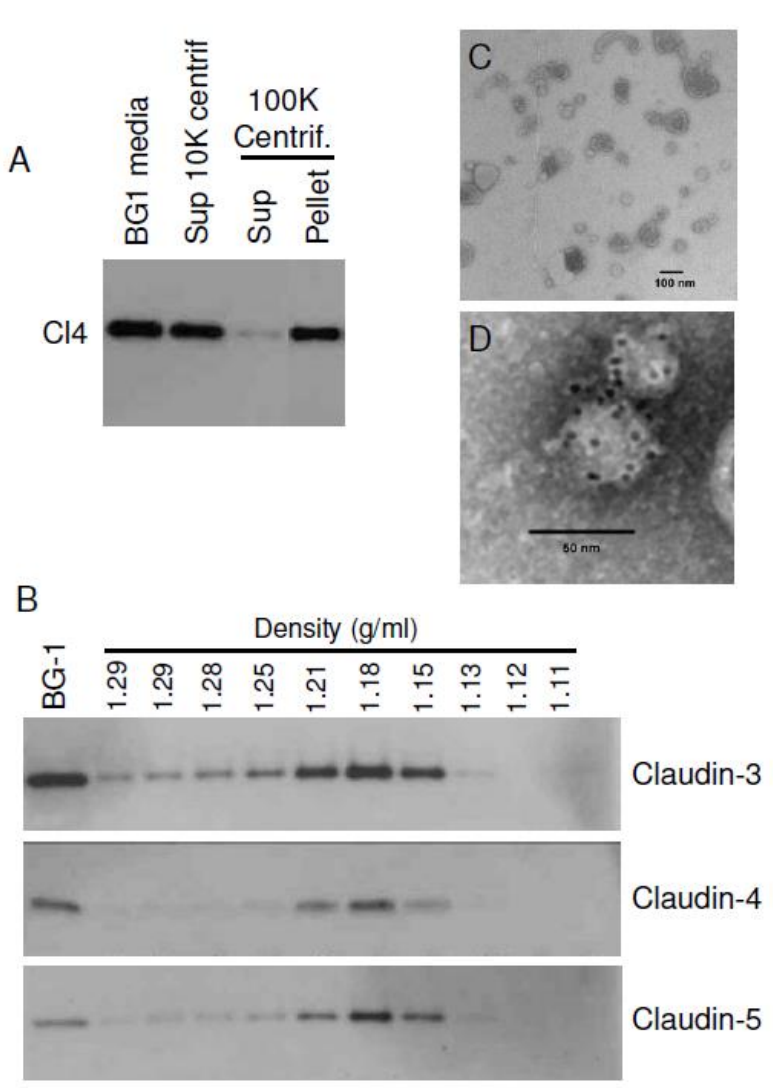
Joost P.G. Sluijter et al. - Microvesicles and exosomes for intracardiac communication, Cardiovascular Research Feb 2014

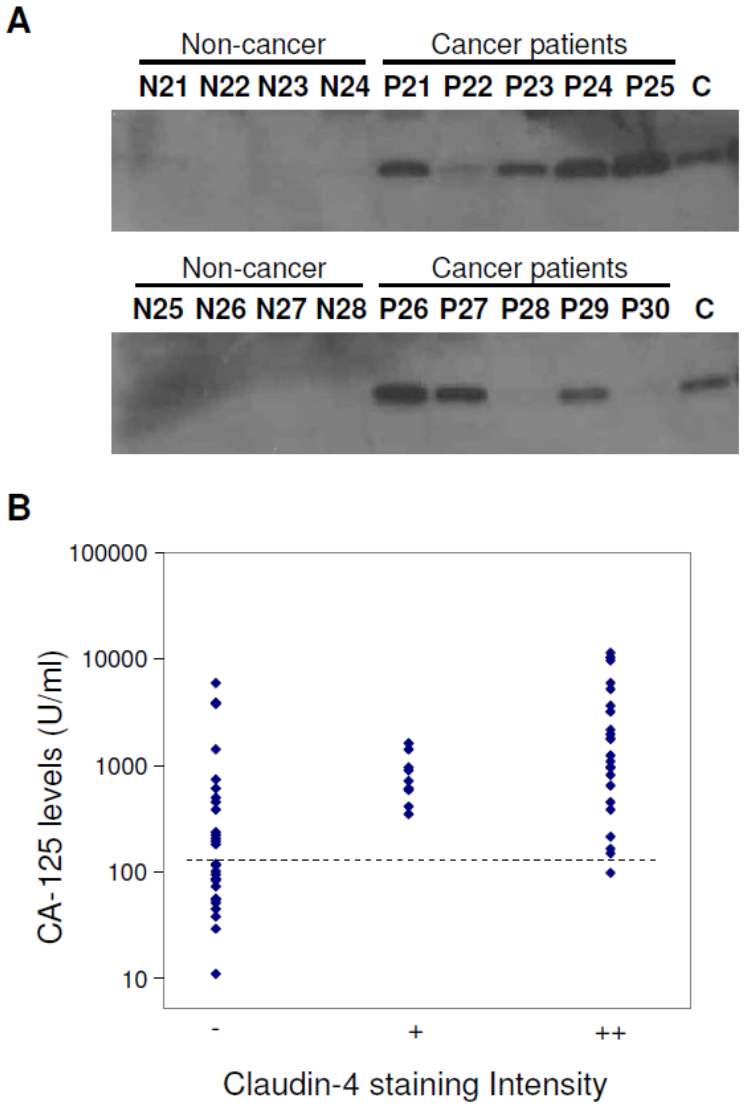
Extracelluláris vezikulák (2)



Kelly J. McKelvey et al - Exosomes: Mechanisms of Uptake J Circ Biomark, 2015, 4:7

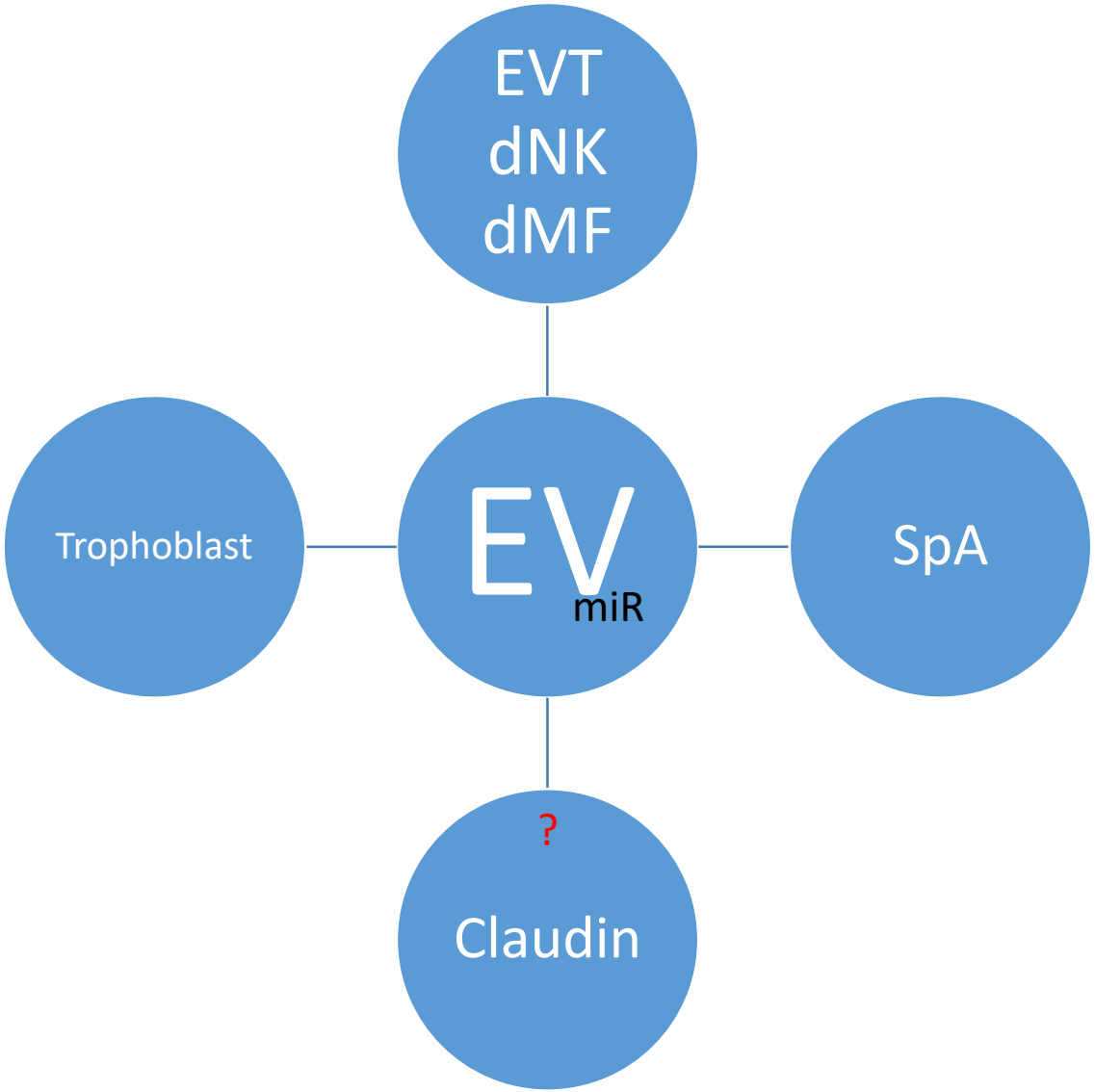
EV és claudinok





Jianghong Li et al - **Claudin-containing exosomes in the peripheral circulation of women with ovarian cancer,** *BMC Cancer* 2009, **9**:244

Konklúzió



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