Сеченовский Университет

Role of exosomes in pregnancy loss (miscarriage) CD 9, 81, 63

Assambayeva Ailar

Plan

I Extracellular vesicles
II Types of EVs
III Function
IV Placental exosome
V Oocyte extracellular vesicles
VI Endometrial EVs
VII Role of EVs during embryo implantation
VIII Pregnancy loss
IX Role of EVs in miscarriage

Extracellular vesicles:

- Secreted from different types of cells including blood cells, endothelial, trophoblast, cardiac and tumor cells.
- Present in the blood circulation and other biological fluids under normal physiologic conditions
- Level of EVs increase in a wide range of disease states

Types of Evs:

- **Exosomes** (less than 150 nm in diameter)
- Microvesicles
- Apoptotic bodies

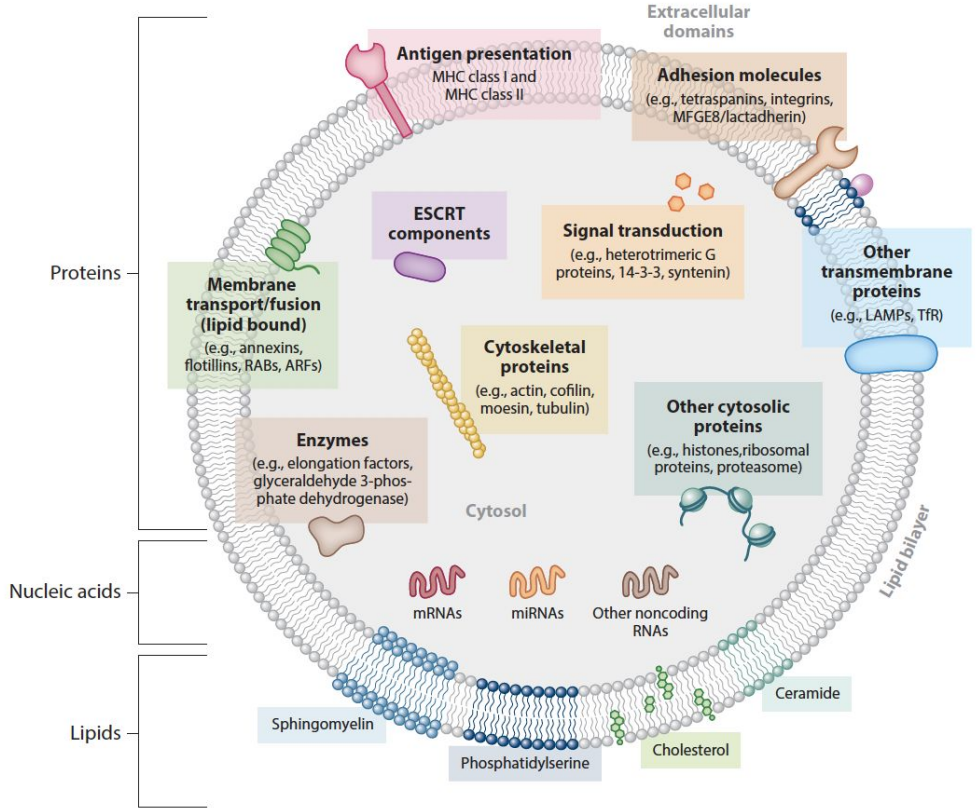

Figure 2

Overall composition of extracellular vesicles (EVs). Schematic representation of the composition (families of proteins, lipids, and nucleic acids) and membrane orientation of EVs. Examples of tetraspanins commonly found in EVs include CD63, CD81, and CD9. Note that each listed component may in fact be present in some subtypes of EVs and not in others. For instance, histones and proteasome and ribosome components are probably secreted in large plasma membrane–derived EVs and/or apoptotic vesicles rather than exosomes. Abbreviations: ARF, ADP ribosylation factor; ESCRT, endosomal sorting complex required for transport; LAMP, lysosome-associated membrane protein; MHC, major histocompatibility complex; MFGE8, milk fat globule–epidermal growth factor-factor VIII; RAB, Ras-related proteins in brain; TfR, transferrin receptor.

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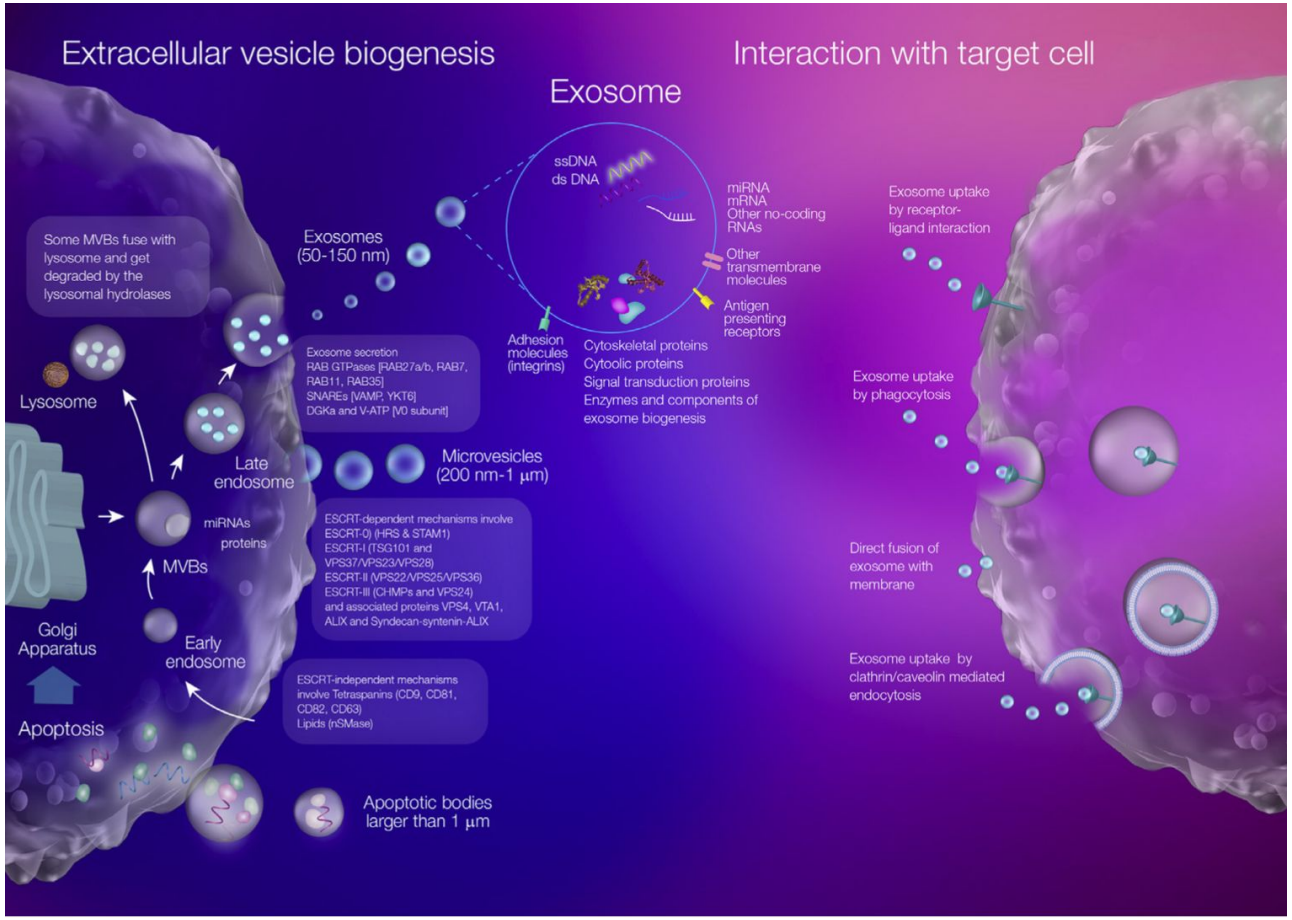
Cellular and Molecular Life Sciences

REVIEW

Current knowledge on exosome biogenesis and release

Nina Pettersen Hessvik[1,2] · Alicia Llorente[1,2]

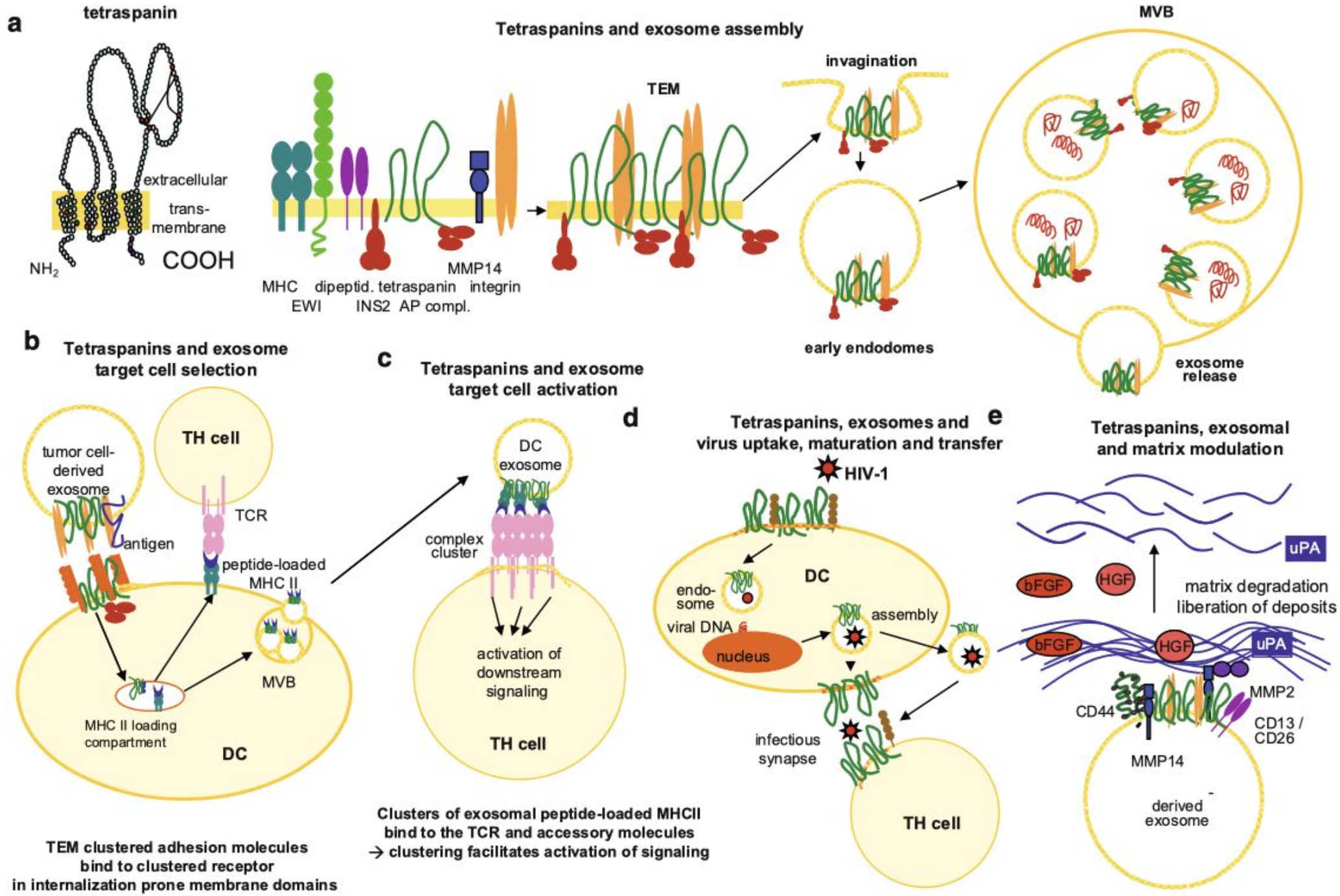
- Contains RNA and proteins, that is secreted into the extracellular space by exocytosis when multivesicular bodies fuse with the plasma membrane
- Consist of lipid bilayer

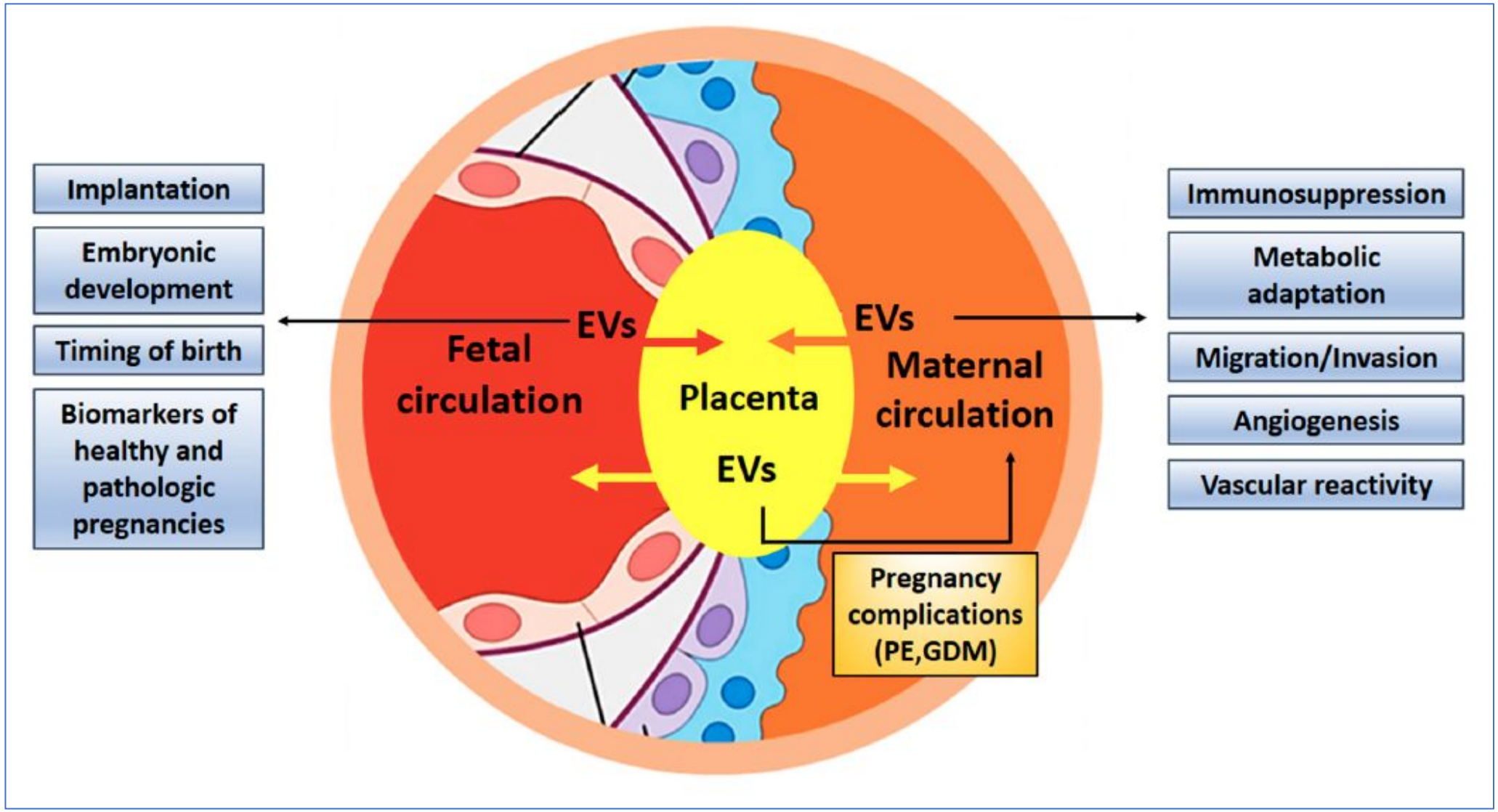


Exosomes can regulate target cell activity via:

- Alteration in translational activity
- Angiogenesis
- Proliferation
- Metabolism,
- Apoptosis

Functioning as a mechanism for intercellular communication.


a
tetraspanin
extracellular
trans-
membrane
NH2
COOH
Tetraspanins and exosome assembly
MHC
EWI
dipeptid.
INS2
tetraspanin
AP compl.
integrin
MMP14
TEM
invagination
early endodomes
MVB
exosome
release
b
Tetraspanins and exosome
target cell selection
tumor cell-
derived
exosome
antigen
TH cell
TCR
peptide-loaded
MHC II
MVB
MHC II loading
compartment
DC
TEM clustered adhesion molecules
bind to clustered receptor
in internalization prone membrane domains
c
Tetraspanins and exosome
target cell activation
DC
exosome
complex
cluster
activation of
downstream
signaling
TH cell
Clusters of exosomal peptide-loaded MHCII
bind to the TCR and accessory molecules
→ clustering facilitates activation of signaling
d
Tetraspanins, exosomes and
virus uptake, maturation and transfer
HIV-1
DC
endo-
some
viral DNA
nucleus
assembly
infectious
synapse
TH cell
e
Tetraspanins, exosomal
and matrix modulation
uPA
bFGF
HGF
matrix degradation
liberation of deposits
bFGF
HGF
uPA
MMP2
CD44
CD13 /
CD26
MMP14
derived
exosome



International Journal of
Molecular Sciences

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Review

Exosomes as Messengers between Mother and Fetus in Pregnancy

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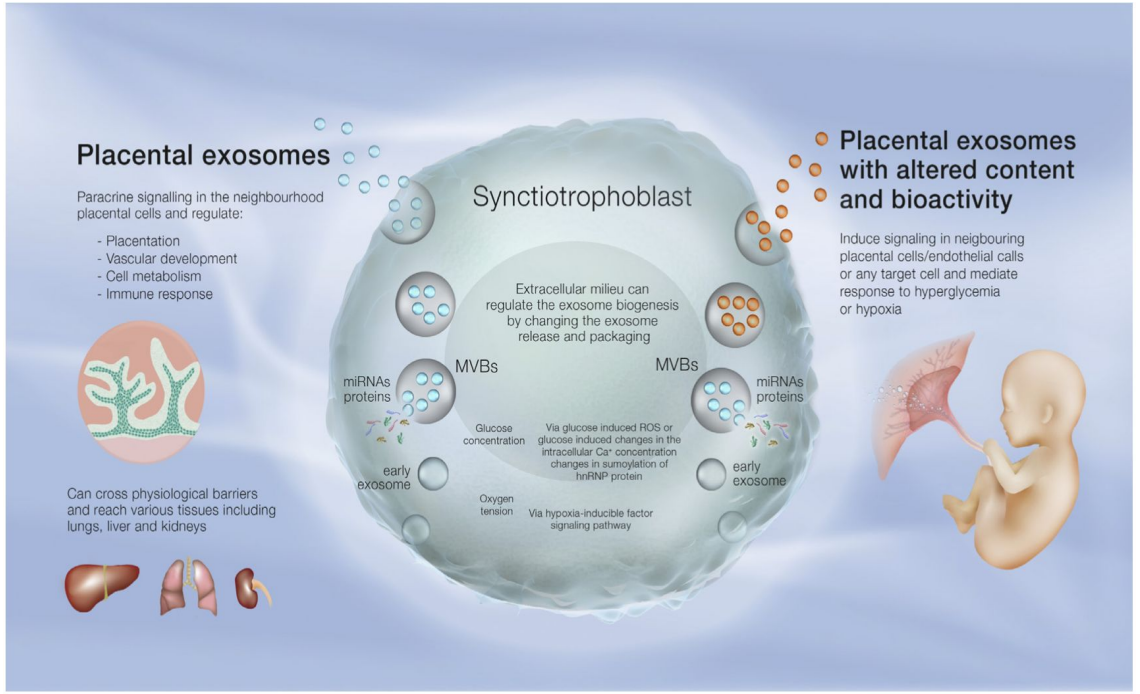
check for updates

- Placenta secretes exosomes into maternal circulation and play important roles in several different aspects of pregnancy including feto-maternal signaling.
- Size 40-120 nm
- Released via exocytosis into maternal plasma
- Contain many signaling molecules including proteins, mRNA, microRNA, and noncoding RNAs
- Regulate target cell activity, angiogenesis, proliferation, metabolism, and apoptosis



Placental exosome

- Can be detected in maternal plasma from as early as 6 weeks of gestation
- Number increases with advancing gestation
- Increases in number in complicated pregnancies
- Contain members of the chromosome 19 microRNA cluster

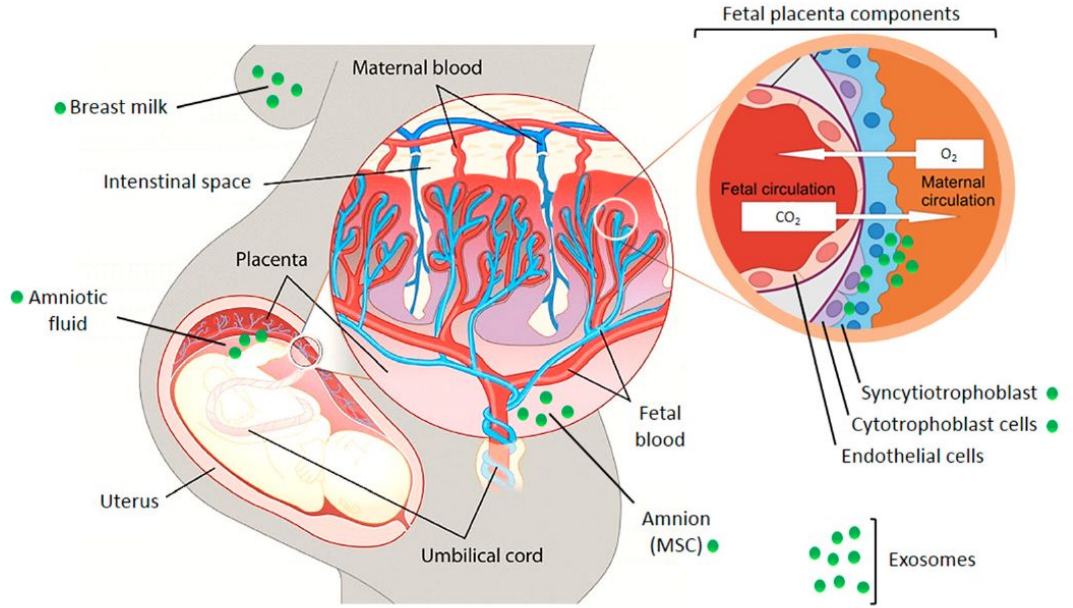


Figure 2. Illustration of the fetal placental barrier that separates fetal and maternal circulations in the human placenta. Places of exosome appearance are indicated. MSC—mesenchymal stem cells. The picture was composed using publicly available graphics from The Alcohol Pharmacology Education Partnership at the Duke University Medical Center [13] and from Christiane Albrecht, University of Bern, with her friendly permission [14].

Oocyte extracellular vesicles

- Tetraspanin CD9 play an important role in gamete fusion
- Oocytes transfer CD9 to the sperm head via “exosome-like” vesicles
- CD9 associated EVs localized in perivitelline space of the oocyte

- Expression of CD9 and CD81 are predominantly localized in the Perivitelline space and zona pellucida respectively.
- CD9 is primarily produced by the oocyte
- CD81 is produced in the surrounding cumulus cells

- Expressed on the surface of the oocyte and surrounding somatic cells
- Play role in a sperm-oocyte membrane fusion

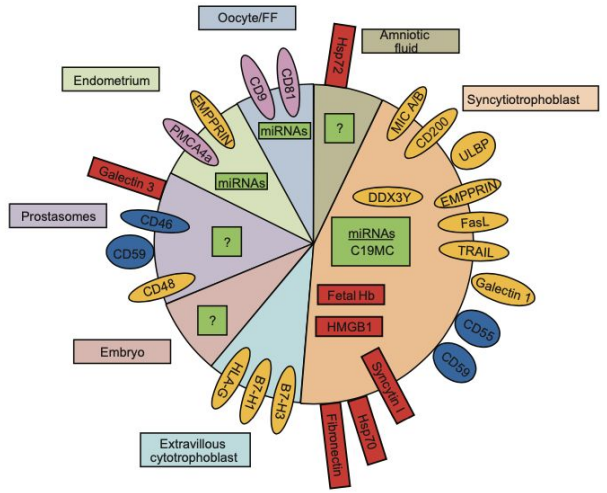


Figure 3 Schematic diagram summarizing various functional moieties carried by reproductive EVs. Proinflammatory mediators (red fill) include HSP70, HSP72, HMGB1, fibronectin, fetal haemoglobin and Syncytin 1. Reproductive EVs have also been shown to contain immunoregulatory molecules (orange fill), with the potential to suppress NK and T cell responses, such as MIC A/B, EMPPRIN, CD200, minor histocompatibility antigen DDX3Y and galectin 1 and complement regulatory proteins (blue fill) CD46, CD55 and CD59. Finally, follicular fluid, endometrial and STB EVs contain miRNAs (green fill) with the potential to further modulate recipient cell responses. HMGB1, high mobility group box 1; MIC A/B, MHC class I chain-related proteins A and B; miRNA, micro-interfering RNA; MV, microvesicle; NK, natural killer; STB, syncytiotrophoblast.

doi: 10.1242/bio.20121420

cells

MDPI

Article

MicroRNAs in Small Extracellular Vesicles Indicate Successful Embryo Implantation during Early Pregnancy

Qiang Tan [1,†], Shuang Shi [1,†], Jingjie Liang [1], Xiaowei Zhang [2], Dingren Cao [1] and Zhengguang Wang [1,*]

Extracellular Vesicles are present and secreted by the endometrium

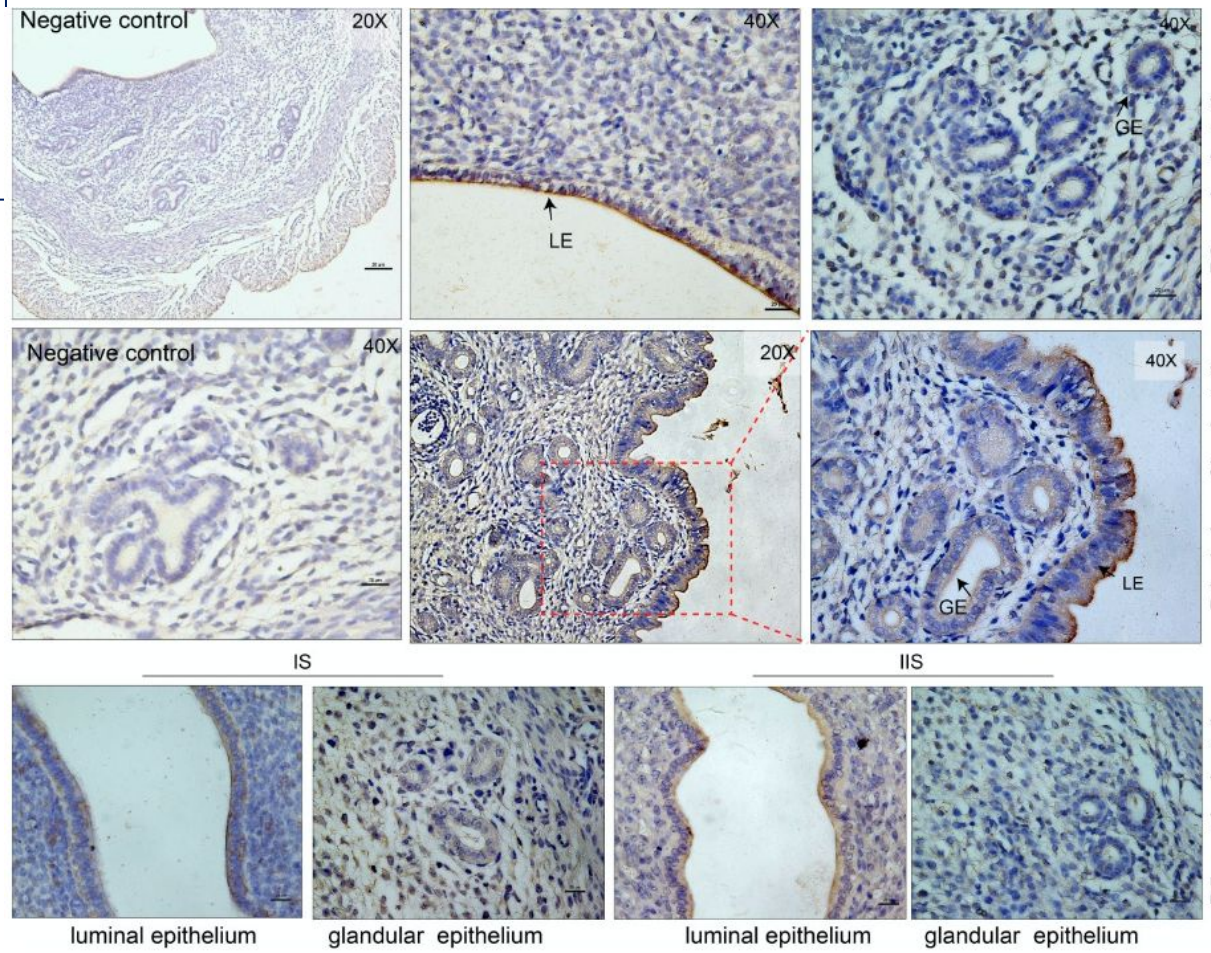


Figure 2. Immunohistochemical staining of CD63 in mouse glandular and luminal epithelium during pre-implantation (D2), window of implantation (WOI) (D4), post-implantation (D5) stage, and in the negative control (no primary antibody). LE: luminal epithelium. GE: glandular epithelium. IS: implantation site. IIS: inter implantation site.

Сеченовский Университет

Circulating Exosomal miRNA Profile During Term and Preterm Birth Pregnancies: A Longitudinal Study

Ramkumar Menon,[1]* Chirantan Debnath,[2]* Andrew Lai,[3] Dominic Guanzon,[3] Shinjini Bhatnagar,[2] Pallavi K. Kshetrapal,[2] Samantha Sheller-Miller,[1] and Carlos Salomon,[3,4] The Garbhini Study Team

[1]Division of Maternal-Fetal Medicine and Perinatal Research, Department of Obstetrics and Gynecology, University of Texas Medical Branch at Galveston, Galveston, Texas 77555; [2]Translational Health Science and Technology Institute, Faridabad, Haryana 121001, India; [3]Exosome Biology Laboratory, Centre for Clinical Diagnostics, University of Queensland Centre for Clinical Research, Royal Brisbane and Women's Hospital, University of Queensland, Brisbane, Queensland 4029, Australia; and [4]Department of Clinical Biochemistry and Immunology, Faculty of Pharmacy, University of Concepción, Concepción, Chile

ORCiD numbers: 0000-0001-9213-6105 (R. Menon); 0000-0002-3991-1747 (S. Sheller-Miller).

Exosomal miRNAs in pre-term birth play role in cell-to-cell signaling and interaction, cellular growth and proliferation, and cellular development.

The data suggest that the miRNA content of circulating exosomes in maternal blood might represent a biomolecular "fingerprint" of the progression of pregnancy.

VIA MEDICA

ORIGINAL PAPER / GYNECOLOGY

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The correlation between unexplained infertility and exosomes

Yıldız Uyar, Melike Özgül, Sevtap Gökalp, Gülay Ok, Ayça Tan, Hafize Seda Vatansever

Manisa Celal Bayar University Medical Faculty, Manisa, Turkey

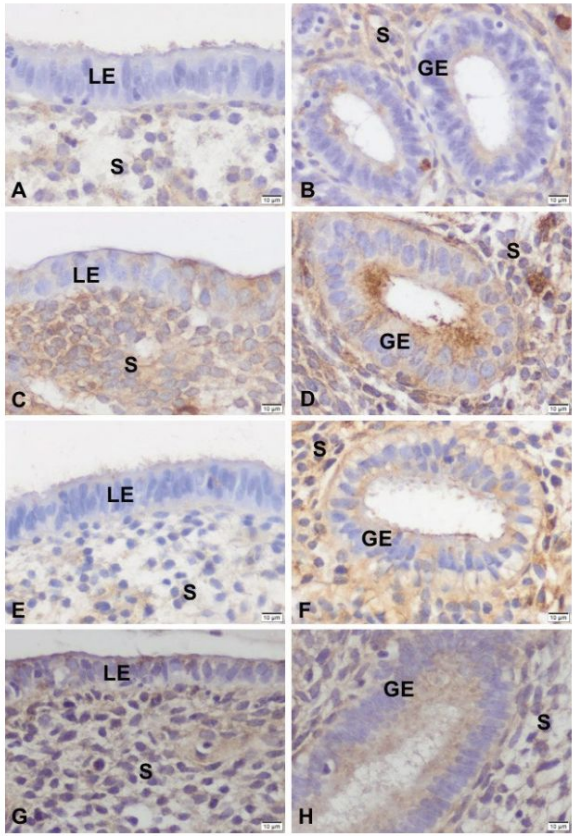

Figure 2. Immunohistochemical distribution of CD63. Scale Bars: 10 µm

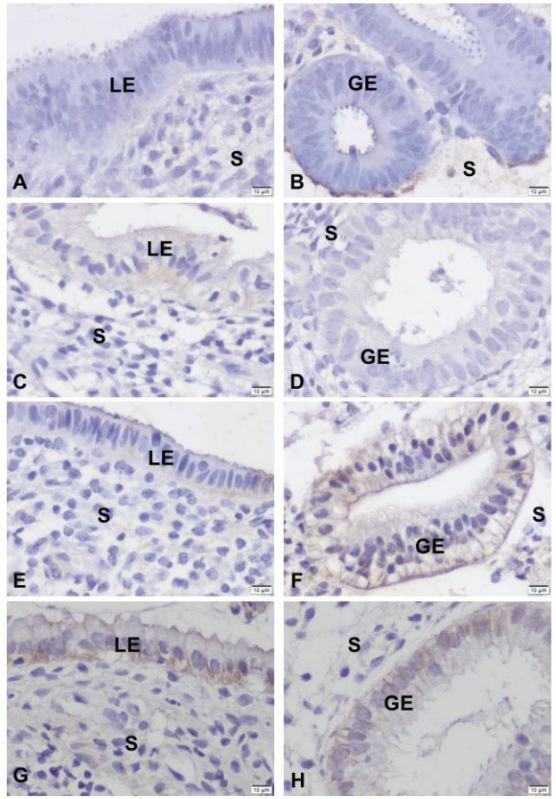

Figure 4. Immunohistochemical distribution of CD9. Scale Bars: 10 µm

Table 1. p values of statistical comparisons of CD63 and CD9 HSCORE results

CD63	
Compared Groups	**p Value**
Fertile proliferation vs infertile proliferation (luminal epithelium)	p = 0.009
Fertile proliferation vs infertile proliferation (glandular epithelium)	p = 0.008
Fertile secretion vs infertile secretion (luminal epithelium)	p = 0.034
Fertile secretion vs infertile secretion (glandular epithelium)	p = 0.037
CD9	
Compared Groups	**p Value**
Fertile proliferation vs infertile proliferation (luminal epithelium)	p = 0.025
Fertile proliferation vs infertile proliferation (glandular epithelium)	p = 0.005
Fertile secretion vs infertile secretion (luminal epithelium)	p = 0.037
Fertile secretion vs infertile secretion (glandular epithelium)	p = 0.037

Pregnancy loss

Pregnancy loss (miscarriage): Risk factors, etiology, clinical manifestations, and diagnostic evaluation

Authors: Sarah Prager, MD, MAS, Elizabeth Micks, MD, MPH, Vanessa K Dalton, MD, MPH
Section Editors: Robert L Barbieri, MD, Courtney A Schreiber, MD, MPH
Deputy Editor: Kristen Eckler, MD, FACOG

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Nov 2020.** | This topic last updated: **Jun 29, 2020.**

Pregnancy loss, also referred to as miscarriage or spontaneous abortion, is generally defined as a nonviable intrauterine pregnancy up to 20 weeks gestation.

The major cause of SA is fetal chromosomal abnormalities, contributing to about 50-60% of the cases

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2

The biological basis and prevention of preterm birth

Gian Carlo Di Renzo*, Valentina Tosto, Irene Giardina

Department of Obstetrics and Gynecology, Centre for Perinatal and Reproductive Medicine, University of Perugia, Perugia, Italy

OPEN ACCESS Freely available online

PLOS ONE

Cell-Free Fetal DNA and Cell-Free Total DNA Levels in Spontaneous Abortion with Fetal Chromosomal Aneuploidy

Ji Hyae Lim[1], Min Hyoung Kim[2], You Jung Han[2], Da Eun Lee[1], So Yeon Park[1], Jung Yeol Han[2], Moon Young Kim[2], Hyun Mee Ryu[1,2]*

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Spontaneous miscarriage in first trimester pregnancy is associated with altered urinary metabolite profile

Chee Wai Ku[a,*,1], Zhen Wei Tan[b,*,1], Mark Kit Lim[c], Zhi Yang Tam[d], Chih-Hsien Lin[d], Sean Pin Ng[d], John Carson Allen[e], Sze Min Lek[a], Thiam Chye Tan[a], Nguan Soon Tan[a,b,c,f,**]

RESEARCH ARTICLE

New evidence that a large proportion of human blood plasma cell-free DNA is localized in exosomes

M. Rohan Fernando[1,2]*, Chao Jiang[1], Gary D. Krzyzanowski[1,2], Wayne L. Ryan[2]

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PLOS ONE

Cell-Free Fetal DNA and Cell-Free Total DNA Levels in Spontaneous Abortion with Fetal Chromosomal Aneuploidy

Ji Hyae Lim[1], Min Hyoung Kim[2], You Jung Han[2], Da Eun Lee[1], So Yeon Park[1], Jung Yeol Han[2], Moon Young Kim[2], Hyun Mee Ryu[1,2*]

1 Laboratory of Medical Genetics, Medical Research Institute, Cheil General Hospital and Women's Healthcare Center, Seoul, Korea, 2 Department of Obstetrics and

- Fetal cfDNA is produced
- by the apoptosis of placental cells of the trophoblast.
- Produced during normal pregnancies; however, the process of apoptosis is likely increased during complicated pregnancies, due to increased oxidative stress and inflammatory response

Noninvasive prenatal testing for chromosomal abnormalities can be performed using only a blood sample collected from the mother, which brings about new possibilities for prenatal diagnostics. Such a new technique is beneficial also when the increased concentrations of cell-free fetal DNA are detected in the circulation of mothers with various pregnancy complications

Take home message:

TABLE 1 Biogenesis, characteristics and functions of different sub-populations of EVs

Types of EV	Mechanism of biogenesis	Size	Proteins present[a]	Cargo	Method of isolation[b]	Reported functions
Exosomes	Correspond to the ILVs formed inside the late endosomes. Released by fusion of MVBs with the plasma membrane. Proteins belonging to the ESCRT and ESCRT-independent mechanisms (lipids and tetraspanins), Rab GTPases and SNARE are involved in the biogenesis [12]	Present a diameter of 50–150 nm, similar to the diameter of ILVs on electron microscopy [13]	Tetraspanins (CD81, CD63, CD9), ESCRT components, Alix, TSG101, syntenins, flotillins, integrins, disintegrin and metalloproteinase domain-containing protein 10/ADAM10/ADA10, HSC70/HSPA8/HSPC7 [13–15]	Proteins, miRNAs, mRNAs, lncRNAs, small fragments of DNA Devoid of nuclear, mitochondrial, endoplasmic reticulum and golgi complex proteins [13, 14]	Differential centrifugation and ultracentrifugation at 100,000 g for 90 m, flotation in density gradient (sucrose or iodixanol), ultrafiltration, size exclusion chromatography, immunoisolation using antibodies and commercial kits (using precipitation) [16, 17]	Cell to cell communication by transfer of molecular cargo to recipient cells [18, 19] Immunoregulation [20, 21] Tumor progression and metastasis [22, 23]

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[a]*Exosome Biology Laboratory, Centre for Clinical Diagnostics, UQ centre for Clinical Research, Royal Brisbane and Women's Hospital, The University of Queensland, St Lucia, QLD, Australia,* [b]*Department of Clinical Biochemistry and Immunology, University of Concepción, Concepción, Chile,* [c]*Department of Obstetrics and Gynecology, Ochsner Baptist Hospital, New Orleans, LA, United States*

Thank you

Any questions?

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