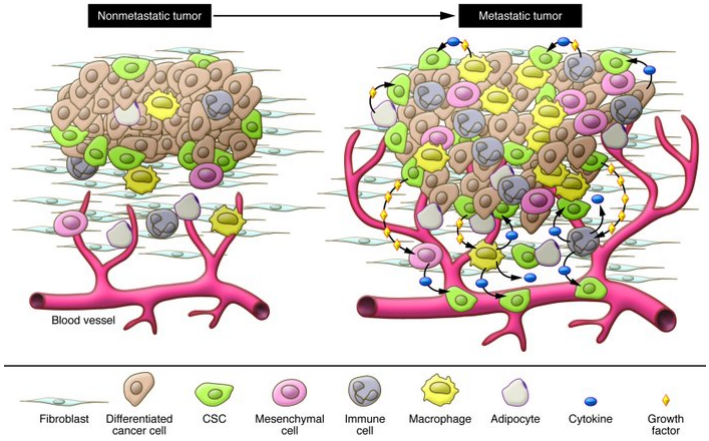
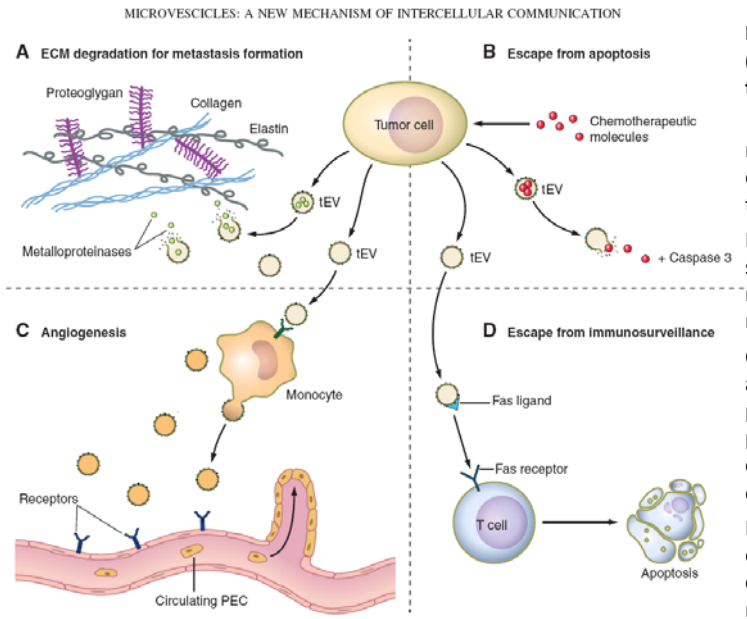


MICROVESCICOLE: Seminari

Microambiente tumorale

http://www.jci.org/articles/view/57099/figure/1



Turturici G, Tinnirello R, Sconzo G, Geraci F. Extracellular membrane vesicles as a mechanism of cell-to-cell communication: advantages and disadvantages. Am J Physiol Cell Physiol. 2014 Apr 1;306(7):C621-33.

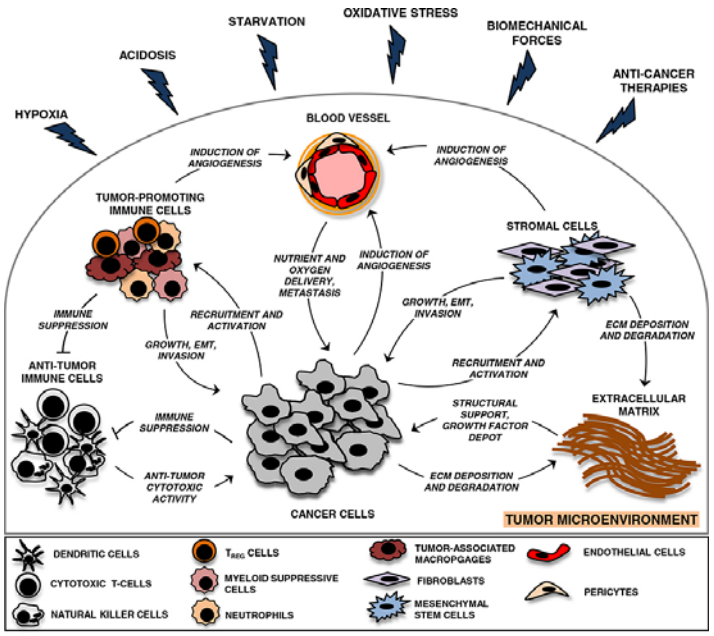
Le vescicole extracellulari (Evs) derivate dai tumori (tEVs) influenzano diversi aspetti della progressione tumorale.

A: Le EVs versate dai tumori contengono metalloproteinasi che sono responsabili dalla degradazione della matrice facilitando l'invasione tumorale;

B: le tEVs permettono alle cellule tumorali di sopravvivere alla chemioterapia e all'apoptosi mediante efflusso dei farmaci e della caspasi 3, rispettivamente;

C: Le tEVs stimolano la secrezione di fattori pro-angiogenci dalle cellule stromali e facilitano la proliferazione delle cellule endoteliali con ciò promuovendo l'angiogenesi e permettendo la crescita tumorale. L'angiogenesi è inoltre influenzata dal rilascio di mRNA e miRNA mediante tEVs.

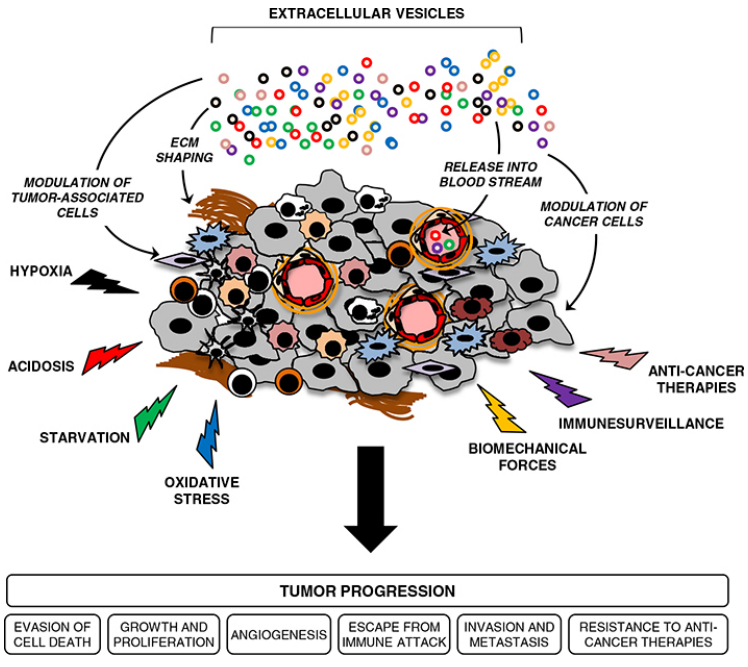
D: Le tEVs rilasciate da molte cellule tumorali espongono Fas ligand, che induce l'apoptosi delle cellule T e inibisce la funzione delle cellule della risposta immunitaria adattativa perciò permettendo alle cellule tumorali di evadere l'immunosorveglianza.



Heterotypic cellular interactions in the tumour microenvironment.

The tumour microenvironment is a complex scaffold of an extracellular matrix (ECM) and various cell types. In addition to malignant cells, vascular cells, stromal cells and immune cells are common cellular residents of the tumour niche. Tumour cells mould this environment for their own needs via intercellular communication pathways, such as direct cell-to-cell contacts and the release of growth factors, matrix metalloproteases, ECM proteins and extracellular vesicles (EVs). Tumour cell-mediated stromal modifications include: suppression of anti-tumoural immune responses, deposition and degradation of ECM components, induction of vascular network formation and recruitment of stromal cells and tumour-promoting immune cells. In turn, heterogeneous tumour microenvironmental components create a favourable environment for tumour growth and dissemination. Various tumour microenvironmental stressors are inherent features of solid tumours that profoundly modify the tumour milieu and accelerate tumour progression towards malignancy.

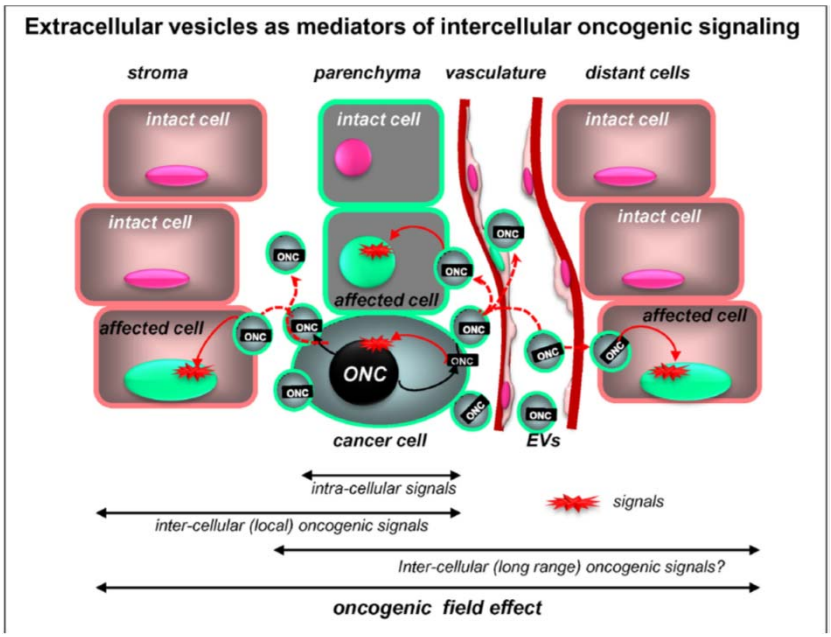
Kucharzewska P, Belting M. **Emerging roles of extracellular vesicles in the adaptive response of tumour cells to microenvironmental stress**. J Extracell Vesicles. 2013 Mar 5;2. doi: 10.3402/jev.v2i0.20304. eCollection 2013.



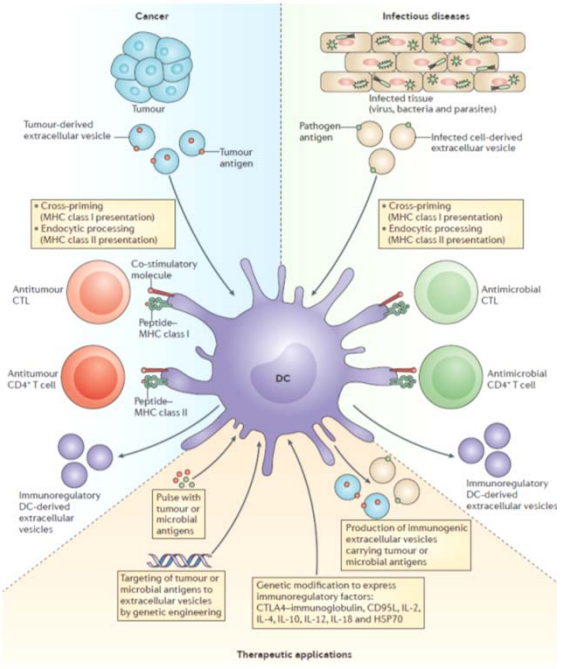
Extracellular vesicles (EVs) are potential conveyors of stress-mediated tumour progression.

EVs are shed from various cellular components of the tumour milieu to mediate exchange of signalling proteins and genetic material, which altogether may support tumour growth and progression. Diverse tumour microenvironmental stress conditions augment tumour-promoting activities of EVs by modulating their secretion and trafficking in the extracellular space, as well as altering their molecular content and functional activity. Upon release, EVs may also enter the circulation and mediate long-range exchange of EV-associated cargo that may support the process of pre-metastatic niche formation. In addition, circulating EVs carrying multifaceted, molecular stress signatures may offer unique, non-invasive biomarkers that can be used in the management of cancer patients.

Kucharzewska P, Belting M. **Emerging roles of extracellular vesicles in the adaptive response of tumour cells to microenvironmental stress**. J Extracell Vesicles. 2013 Mar 5;2. doi: 10.3402/jev.v2i0.20304. eCollection 2013.



D'Asti E, Garnier D, Lee TH, Montermini L, Meehan B, Rak J. **Oncogenic extracellular vesicles in brain tumor progression**. Front Physiol. 2012 Jul 24;3:294.



RUOLO DELLE VESCICOLE EXTRACELLULARI NELLA REGOLAZIONE DELL'IMMUNITA' DEI TUMORI E DEI MICROORGANISMI CHE PUO' ESSERE MODIFICATA PER APPLICAZIONI TERAPEUTICHE

Robbins PD, Morelli AE. Regulation of immune responses by extracellular vesicles. Nat Rev Immunol. 2014 Mar;14(3):195-208.

Contenuto e funzioni di vescicole extracellulari rilasciate da differenti tipi di cellule tumorali – 1

Tumor Type	Type of Vesicles	Content	Function
Lung carcinoma	Microvesicles	EMMPRIN	Tumor stroma interaction
Lung carcinoma	Microvesicles	None	Angiogenesis and metastasis
Lung carcinoma	Microvesicles	Lung specific RNAs	Phenotypic changes in marrow cells
Pancreatic adenocarcinoma, colorectal adenocarcinoma, lung carcinoma.	Microvesicles	mRNA for VEGF, HGF, IL-8 and surface determinants (CD44H)	Activation of tumor infiltrating monocytes
Prostate carcinoma	Microvesicles	Matrix metalloproteinases; Exchange of receptors (CX3CL1/fractalkine-CX3CR1)	Establishment of a favorable tumor niche
Prostate carcinoma	Microvesicles	Prostate specific RNAs	Prostate specific gene expression in human bone marrow cells.
Breast cancer	Exosomes	Hsp90alpha	Increase in cancer cell motility
Gliomas	Microvesicles	Oncogenic form of EGFRvIII	Tumor progression
Breast carcinoma and glioma cells	Microvesicles	Trans glutaminase, fibronectin	Transformation
Ovarian cancer	Microvesicles	CD147/extracellular matrix metalloproteinase inducer	Angiogenesis

Camussi G, Deregibus MC, Tetta C. **Tumor-derived microvesicles and the cancer microenvironment**. Curr Mol Med. 2013 Jan;13(1):58-67.

Contenuto e funzioni di vescicole extracellulari rilasciate da differenti tipi di cellule tumorali – 2

Tumor Type	Type of Vesicles	Content	Function
Human squamous carcinoma, alveolar basal epithelial adenocarcinoma and colon cancer	Microvesicles	Oncogenic EGFR	Angiogenesis by induction of autocrine VEGF production
Rat pancreatic adenocarcinoma	Exosomes	CD44v6	Lung metastasis
Human fibrosarcoma and prostate carcinoma	Microvesicles	Sphingomyelin	Angiogenesis
Glioblastoma	Microvesicles	mRNA, microRNA, proteins	Tumor growth and diagnostic bio markers
Colorectal carcinoma	Microvesicles	Cell cycle related mRNA	Angiogenesis
Glioblastoma, medulloblastoma, atypical teratoid rabdoid tumor and melanoma	Microvesicles	Retro-transposon elements, amplified oncogene sequences-	Tumor growth and progression
Renal cancer stem cells	Microvesicles	mRNA and microRNA	Angiogenesis, tumor invasion and metastasis
Glioblastoma	Exosomes	Mitochondrial DNA	Tumor progression

Camussi G, Deregibus MC, Tetta C. **Tumor-derived microvesicles and the cancer microenvironment**. Curr Mol Med. 2013 Jan;13(1):58-67.

Contenuto e funzioni di vescicole extracellulari rilasciate da differenti tipi di cellule tumorali – 3

Tumor Type	Type of Vesicles	Content	Function
Colorectal carcinoma	Microvesicles	Cell cycle related mRNA	Angiogenesis
Glioblastoma, medulloblastoma, atypical teratoid rabdoid tumor and melanoma	Microvesicles	Retro-transposon elements, amplified oncogene sequences-	Tumor growth and progression
Renal cancer stem cells	Microvesicles	mRNA and microRNA	Angiogenesis, tumor invasion and metastasis
Glioblastoma	Exosomes	Mitochondrial DNA	Tumor progression
Breast cancer	Exosomes	None	Conversion of MSCs in tumor associated myofibroblasts

Abbreviations: EMMPRIN, extracellular matrix metalloproteinase inducer also known as basigin and CD147; VEGF, vascular endothelial growth factor; HGF, hepatocyte growth factor; IL-8, interleukin-8; EGFR, epidermal growth factor receptor; MSCs, mesenchymal stem cells.

Camussi G, Deregibus MC, Tetta C. **Tumor-derived microvesicles and the cancer microenvironment**. Curr Mol Med. 2013 Jan;13(1):58-67.

SEMINARIO

Exosomi

Risposta immunitaria

Microvesicles: ubiquitous contributors to infection and immunity

Frances W. Lai, Brian D. Lichty, and Dawn M. E. Bowdish[1]

ABSTRACT

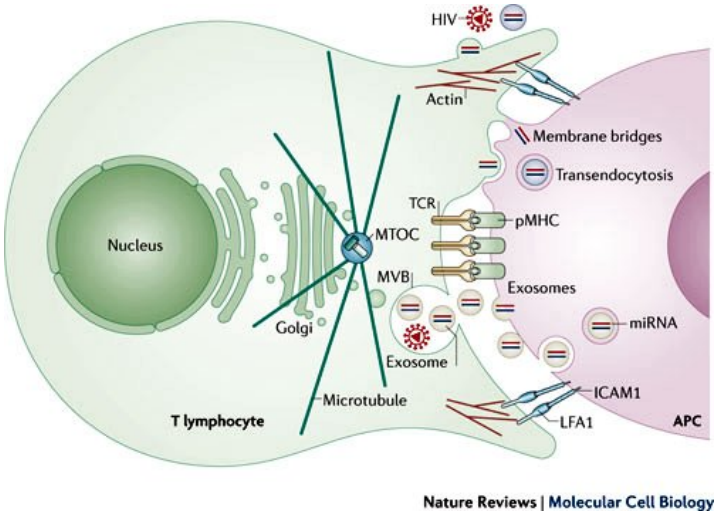
MVs, which can be subgrouped into exosomes, SVs, and OMVs, are secreted by eukaryotic and prokaryotic cells. Many previously inexplicable phenomena can be explained by the existence of these vesicles, as they appear to be important in a wide range of biologic processes, such as intercellular communication and transfer of functional genetic information. In this review, we discuss the immunologic roles of MVs during sterile insult and infectious disease. MVs contribute to clotting initiation, cell recruitment, and neovascularization during wound healing. In the context of pathogen infection, both the host and the pathogen use MVs for communication and defense. MVs are exploited by various viruses to evade the host immune response and contribute to viral spread. Bacteria produce MVs that contain virulence factors that contribute to disease pathology and antibiotic resistance. This review summarizes the role of MVs in the pathology and resolution of disease *J. Leukoc. Biol.* **97: 000–000; 2015.**

Vescicole di membrana come vettori di risposte immunitarie

- **Porzioni della membrana plasmatica** di cellule coinvolte nella risposta immunitaria possono essere **trasferite fra cellule**, sia tramite contatto diretto (mediante i processi recentemente descritti di «**nibbling**» (rosicchiamento), **trogocitosi** e **nanotubi**) che tramite la ***secrezione di vescicole di membrana***.
- Le conseguenze funzionali di tali trasferimenti includono **l'induzione, amplificazione e/o modulazione delle risposte immunitarie nonché l'acquisizione di nuove proprietà funzionali da parte delle cellule che le ricevono, quali capacità migratorie o metastatiche**.
- Inoltre, nelle vescicole di membrana secrete sono stati identificati **mRNAs** e **microRNAs**, e ciò ha sollevato l'eccitante ipotesi che il **trasferimento di materiale genetico** potesse influenzare il comportamento delle cellule riceventi.
- Complessivamente, tali dati portano all'ipotesi che il **trasferimento di membrane sia un modo comune di comunicazione intercellulare**.

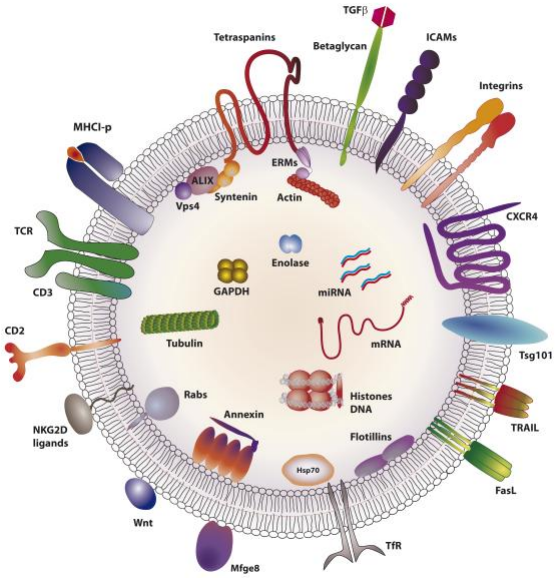
Théry C, Ostrowski M, Segura E. **Membrane vesicles as conveyors of immune responses**. Nat Rev Immunol. 2009 Aug;9(8):581-93.

La sinapsi immunologica funge da piattaforma per facilitare il passaggio di material genetico tra le cellule



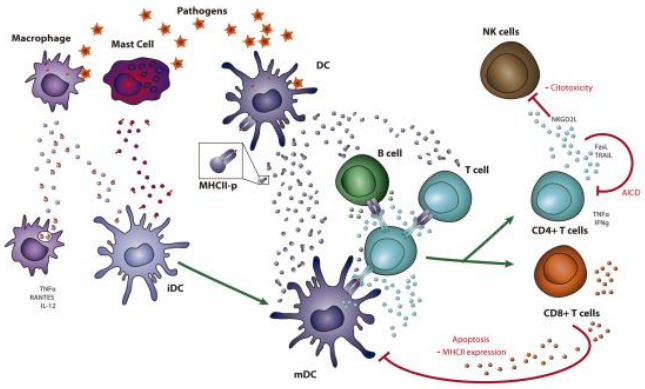
- Durante la formazione di una **sinapsi immunologica**, le molecole coinvolte nel riconoscimento dell'antigene (ad es. il "T cell receptor; TCR) e le molecole del "peptide-loaded major histocompatibility complex; pMHC) si muovono verso un aggregato centrale circondato da un anello periferico arricchito in molecole di adesione (ad es. l'integrina "leukocyte function-associated antigen 1" (LFA1) e le "intercellular cell adhesion molecules; (ICAMs) e di citoscheletro di actina.
- Il linfocito T orienta il suo "microtubule-organizing centre (MTOC) e i compartimenti di secrezione (ad es. l'apparato di Golgi e "i multivesicular bodies» (MVBs) verso la "antigen presenting cell" (APC).
- Noi proponiamo che la sinapsi immunologica fornisce una via di maggiore efficienza per lo scambio di materiale genetico mediante la combinazione di differenti meccanismi, incluso la secrezione polarizzata di exosomi carichi di microRNA (miRNA), transendocitosi e ponti di membrana. I patogeni, incluso batteri e virus, si appropriano delle sinapsi biologiche per propagrasi da cellula a cellula.

Mittelbrunn M, Sánchez-Madrid F. **Intercellular communication: diverse structures for exchange of genetic information**. Nat Rev Mol Cell Biol. 2012 Apr 18;13(5):328-35.



Typical molecular composition of T-cell exosomes Membrane and luminal distribution of molecules predicted to be found in a typical exosome produced by a T lymphocyte. TCR: T-cell receptor; TGFβ: transforming growth factor beta; ICAMs: intercellular adhesion molecule family; CXCR4: C-X-C chemokine receptor type 4 or CD184; Tsg101: tumor susceptibility gene 101; TRAIL: TNF-related apoptosis-inducing ligand; FasL: Fas ligand or CD95L; TfR: transferrin receptor; Mfge8: milk-fat globule-EGF factor 8; ALIX: ALG-2-interacting protein X; GAPDH: glyceraldehyde 3-phosphate dehydrogenase; ERMs: ezrin, radixin and moesin proteins. For more information about exosome composition see http://www.exocarta.org.

Gutiérrez-Vázquez C, Villarroya-Beltri C, Mittelbrunn M, Sánchez-Madrid F. **Transfer of extracellular vesicles during immune cell-cell interactions**. Immunol Rev. 2013 Jan;251(1):125-42.

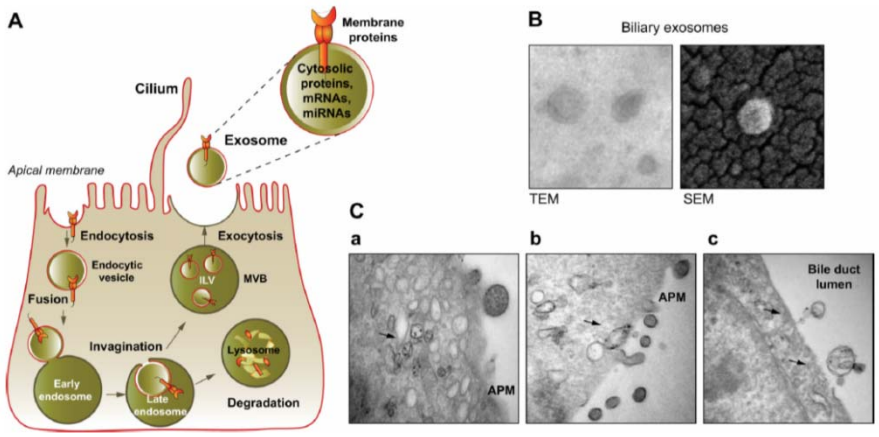


Role of immune-cell-derived EVs during infection During infection dendritic cells (DC) produce EVs that carry co-stimulatory molecules, antigens and Ag-MHC-II complexes. These EVs transfer Ag-presentation ability to other DCs and also to B cells and T cells (79, 82, 83), and might directly activate T cells (81, 83). Mast cells and macrophages can also transfer Ag-containing EVs to DCs and induce maturation and presentation of the acquired Ags (102, 152). EVs from macrophages also activate innate immune responses in uninfected macrophages (217). During Ag presentation, TCR and BCR triggering stimulate EV secretion (61, 70), and the formation of a functional immune synapse promotes the functional transfer of EVs (6). Activated T cells produce immune-regulatory EVs that inhibit NK cytotoxicity (65), promote apoptosis in T cells (38) and Ag-carrying DCs (64), and decrease DC antigen-presentation ability (64), thus contributing to homeostasis recovery.

Gutiérrez-Vázquez C, Villarroya-Beltri C, Mittelbrunn M, Sánchez-Madrid F. **Transfer of extracellular vesicles during immune cell-cell interactions**. Immunol Rev. 2013 Jan;251(1):125-42.

Vescicole extracellulari

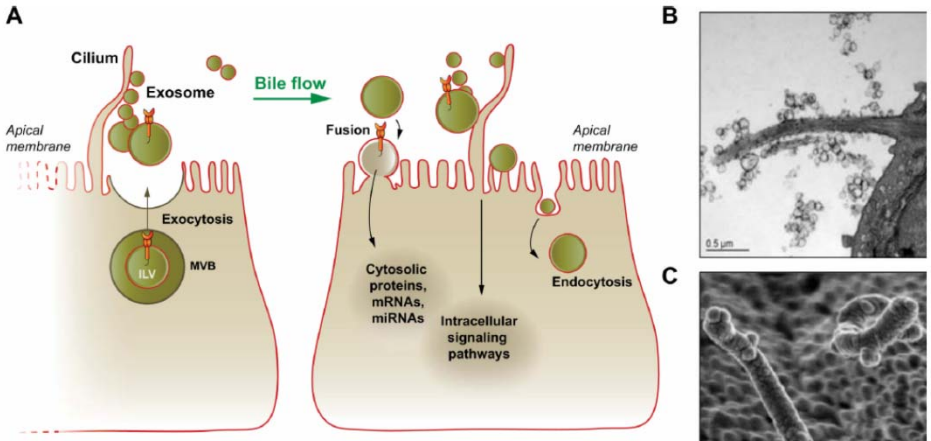
FEGATO



Exosome release

(A) **Exosomes** containing membrane and cytosolic proteins, mRNAs, and miRNAs, are **derived from the multivesicular body (MVB) sorting pathway**. Membrane proteins are oriented in a fashion (extracellular region out) that permits profound biological autocrine and paracrine effects. (B) Exosomes isolated from rat bile have a cup- or "deflated football"- shaped morphology by transmission electron microscopy (TEM), but they have a perfectly round shape by scanning electron microscopy (SEM). (C) In cholangiocytes of mouse liver, MVBs containing exosomes (arrows) (a) move to the apical plasma membrane (APM) (b), and release exosomes into the bile duct lumen by exocytosis (c).

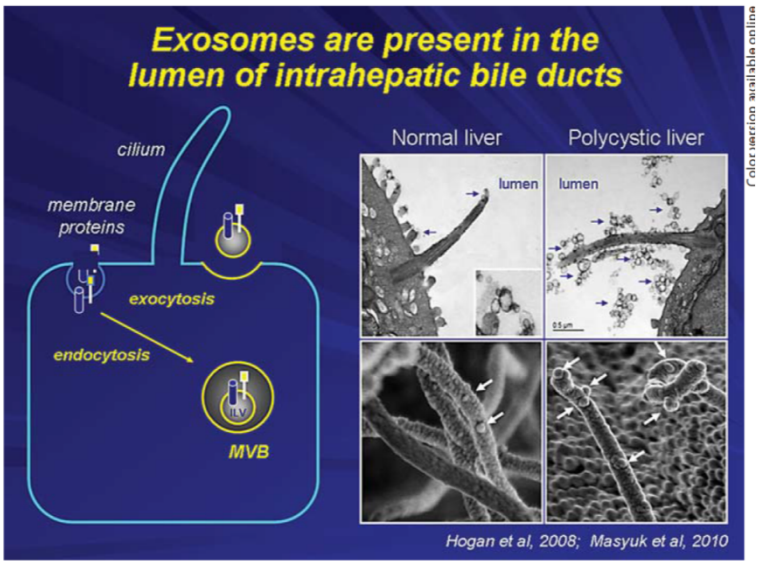
Masyuk AI, Masyuk TV, Larusso NF. Exosomes in the pathogenesis, diagnostics and therapeutics of liver diseases. J Hepatol. 2013 Sep;59(3):621-5.



Exosomes in intercellular signaling

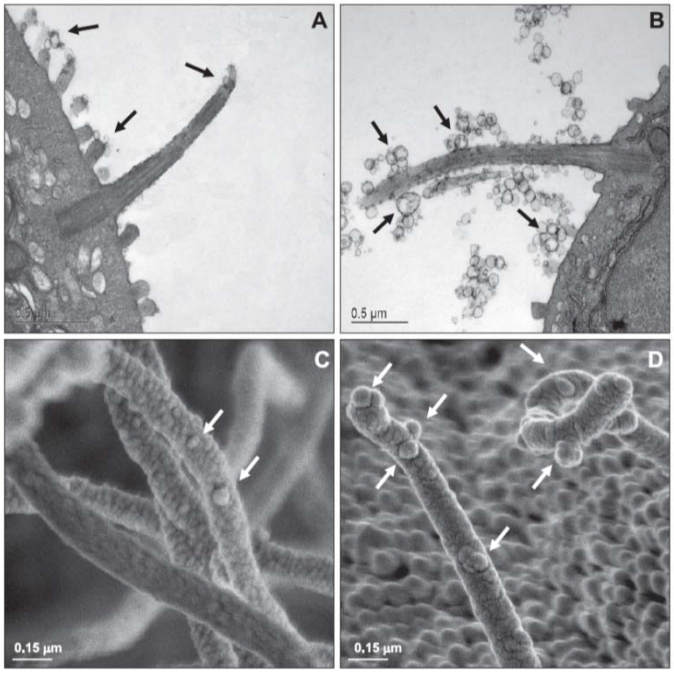
(A) In the liver, **exosomes derived from hepatocytes and cholangiocytes are transported by bile flow to target cholangiocytes with which they may interact via several mechanisms depending on their cargo and biological properties**. **They can fuse with the plasma membrane and deliver their content into the cytoplasm of a target cell**; **interact with receptors on the apical plasma and ciliary membrane inducing intracellular signaling**; and **endocytosed for recycling**. (B and C) Biliary exosomes surround and attach to cholangiocyte cilia in mouse liver as viewed by TEM (B) and SEM (C), supporting the involvement of exosomes and cilia in mechanisms of intercellular signaling.

Masyuk AI, Masyuk TV, Larusso NF. Exosomes in the pathogenesis, diagnostics and therapeutics of liver diseases. J Hepatol. 2013 Sep;59(3):621-5.



Larusso NF, Masyuk TV. The role of cilia in the regulation of bile flow. Dig Dis. 2011;29(1):6-12.

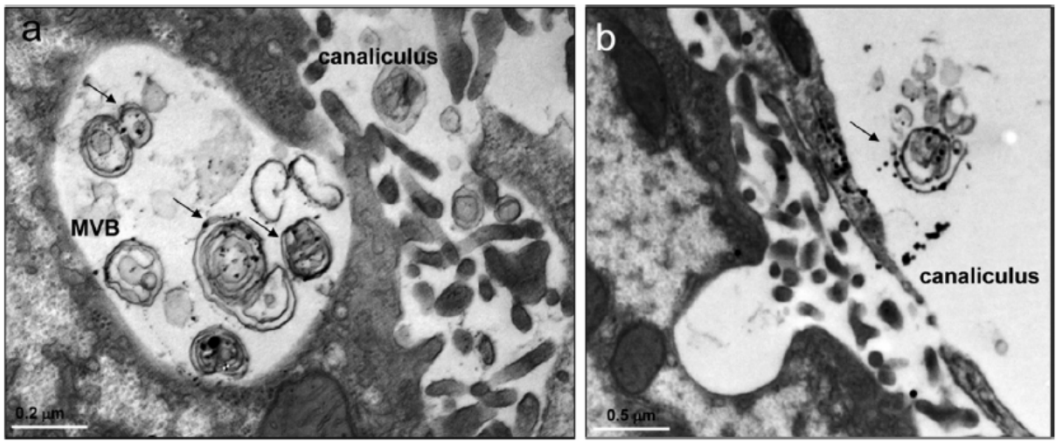
Gli **exosomi** sono **coinvolti nella funzione chemosensoriale delle cilia primarie dei colangiociti** (cellule dei dotti biliari). Gli exosomi sono piccole (30 -100 nm di diametro) vescicole extracellulari rivestite da membrana. Sono derivati da vescicole interne di corpi multivescicolari (MVBs) che si fondono con la membrana plasmatica in una modalità simile all'esocitosi e rilasciano il loro contenuto nello spazio extracellulare (schema). La presenza di vescicole tipo exosomi di 50-80 nm di diametro nel lume dei dotti intraepatici di topi «wild-type» e policistici è stata confermata da microscopia elettronica a trasmissione (destra, panelli di sopra). Queste vescicole circondono cilia dei colangiociti ed alcune sembrano attaccarsi alla membrana ciliare e dei microvilli. L'immagine del microscopio elettronico a scansione (SEM) (destra, panello di sotto) suggerisce che vescicole simili ad exosomi di fatto si leghino alle cilia.



Exosome-like vesicles surround and attach to mouse cholangiocyte [primary] cilia in vivo.

By transmission (TEM; A and B) and scanning (SEM; C and D) electron microscopy, exosome-like vesicles (black and white arrows) are present in the lumen of intrahepatic bile ducts in the wild-type (A and C) and Pkhd1del2/del2 (B and D) mice. The vesicles surround the cilium (B) and attach to this organelle (A–D) and microvilli (A) of the cholangiocyte apical plasma membrane.

Masyuk AI, Huang BQ, Ward CJ, Gradilone SA, Banales JM, Masyuk TV, Radtke B, Splinter PL, LaRusso NF. Biliary exosomes influence cholangiocyte regulatory mechanisms and proliferation through interaction with primary cilia. Am J Physiol Gastrointest Liver Physiol. 2010 Oct;299(4):G990-9.



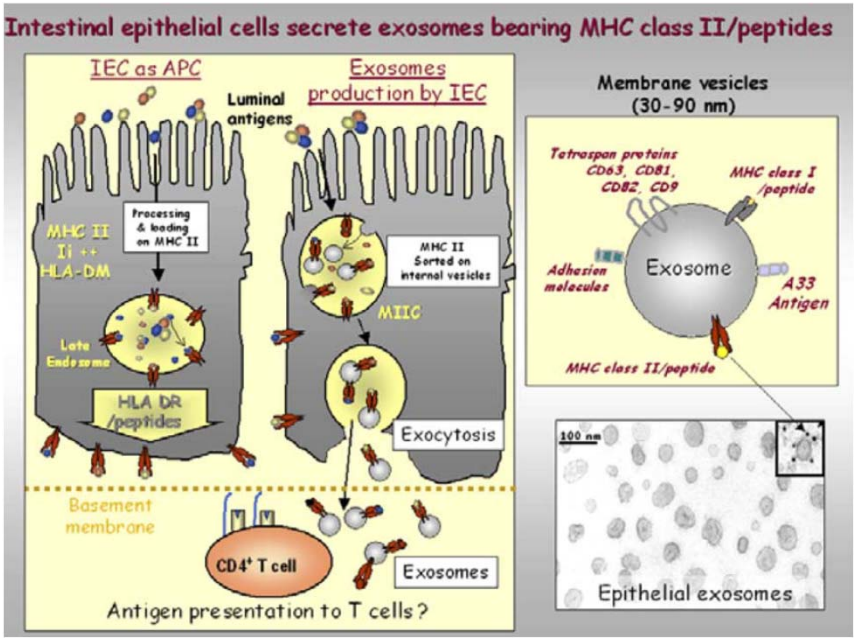
Hepatocyte multivesicular bodies (MVBs) and **luminal vesicles are positive for an exosomal marker**, CD63 [tetraspanin].

MVBs and intraluminal vesicles positive for an exosomal marker, CD63, (black arrows) were observed in normal rat hepatocytes. MVBs are seen in a proximity to the hepatic canaliculus (a). CD63-positive vesicles are also seen in the canalicular lumen (b), suggesting that hepatocytes release exosomes in vivo.

Masyuk AI, Huang BQ, Ward CJ, Gradilone SA, Banales JM, Masyuk TV, Radtke B, Splinter PL, LaRusso NF. Biliary exosomes influence cholangiocyte regulatory mechanisms and proliferation through interaction with primary cilia. Am J Physiol Gastrointest Liver Physiol. 2010 Oct;299(4):G990-9.

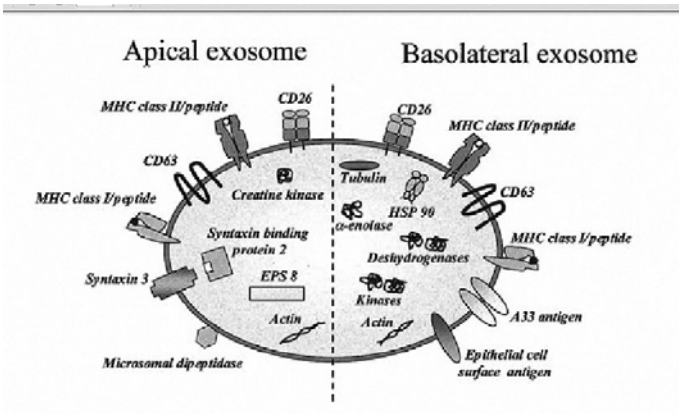
Vescicole extracellulari

Intestino



Intestinal epithelial cells (IEC) secrete exosomes. IEC express accessory molecules (MHC class II, invariant chain, HLA-DM) and are considered as non-professional antigen presenting cells. The lack of direct contact between IEC and CD4+ T cells limits direct antigen presentation in vivo. However, IEC secrete exosomes which are small membrane vesicles originating from the MHC class II-enriched compartment (MIIC) and are released by exocytosis of these compartments in the external medium. Such epithelial exosomes bear class II/peptide complexes and molecules potentially involved in cell– cell or cell –matrix interactions.

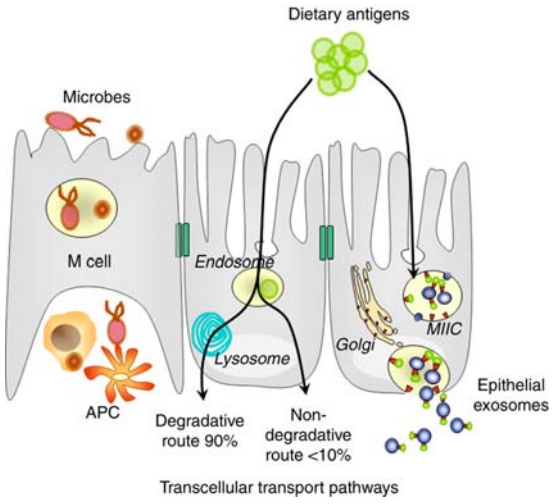
Mallegol J, van Niel G, Heyman M. **Phenotypic and functional characterization of intestinal epithelial exosomes**. Blood Cells Mol Dis. 2005 Jul-Aug;35(1):11-6.



A model for the molecular structure of epithelial-derived exosomes. Ubiquitously expressed molecules such as enzymes of the intracellular metabolism (pyruvate kinase M2, creatine kinase, a-enolase, phosphoglycerate kinase, glyceraldehyde-3-phosphate dehydrogenase, L-lactate dehydrogenase) and cytoskeleton proteins (actin, tubulin), as well as molecules possibly involved in antigen presentation (MHC class I, MHC class II, CD63), were found in both apical and basolateral exosomes. Apical exosomes also carried molecules involved in apical addressing of endosomes (syntaxin 3, syntaxin-binding protein 2), whereas basolateral exosomes had molecules that might act as adhesion or costimulatory molecules (A33 antigen and epithelial cell surface antigen).

van Niel G, Raposo G, Candalh C, Boussac M, Hershberg R, Cerf-Bensussan N, Heyman M. **Intestinal epithelial cells secrete exosome-like vesicles**. Gastroenterology. 2001 Aug;121(2):337-49.

INTESTINO
VIE DI TRASPORTO PARACELLULARE



Under steady-state condition, molecules of molecular weight (MW) > 600 Da (such as food antigens, peptides) are sampled by the epithelial cells by **endocytosis** at the apical membrane and **transcytosis** toward the lamina propria.

During transcytosis, full-length peptides or proteins are partly degraded in acidic and lysosomal compartments and released in the form of amino acids (total degradation) or breakdown products (partial degradation) at the basolateral pole of enterocytes. Early endosomes containing partially degraded food antigens meet the major histocompatibility complex (MHC) class II-enriched compartment (MIIC) where exogenous peptides are loaded on MHC class II molecules. Inward invagination of MIIC compartment lead to the formation of **exosomes**, which are small membrane vesicles (40 – 90 nm) bearing MHC class II / peptide complexes at their surface. **Exosomes can diffuse in the basement membrane and interact with local immune cells**. Exosome-bound peptides are much more potent than free peptides to interact with dendritic cells and stimulate peptide presentation to T cells.

Ménard S, Cerf-Bensussan N, Heyman M. **Multiple facets of intestinal permeability and epithelial handling of dietary antigens**. Mucosal Immunol. 2010 May;3(3):247-59.

Vescicole extracellulari

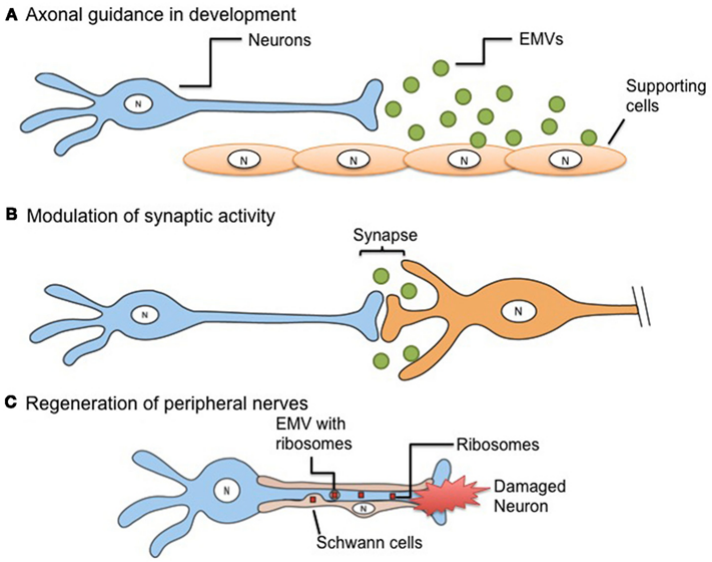
Cervello

Table 1 | Cellular origins of extracellular vesicles (EVs) in multiple sclerosis research.

EV origin	Marker	Sample	Technique
Endothelial	CD31+/CD42−	PPP and MVEC	FC
		WB and MVEC	FC
	CD51	PPP and MVEC	FC
	CD54	WB and MVEC	FC
	CD106	WB and MVEC	FC
	CD62E	WB and MVEC	FC
	CD146	PPP	FC
Platelet	CD61	PFP	FC
	CD41	PPP	FC
Leukocyte	CD45	PFP	FC
Monocyte	CD14	PFP	FC
Astrocyte	GFAP	CSF	FM/WestB
Neuronal	SNAP-25	CSF	FM/WestB
Oligodendrocyte	MBP	CSF	FM/WestB
Microglia/macrophage	IB4	CSF	FM/FC/EM
GENERAL MARKERS			
Exosomes	CD63	PFP	WestB
Microvesicles	AnV	CSF	FC

EM, electron microscopy (immunogold); PPP, platelet poor plasma; PFP, platelet free plasma; WB, whole blood; WestB, Western blot; CSF, cerebrospinal fluid; FC, flow cytometry; FM, fluorescence microscopy; MVEC, microvascular endothelial cell culture.

Sáenz-Cuesta M, Osorio-Querejeta I, Otaegui D. **Extracellular Vesicles in Multiple Sclerosis: What are They Telling Us?** Front Cell Neurosci. 2014 Mar 28;8:100. doi: 10.3389/fncel.2014.00100. eCollection 2014.



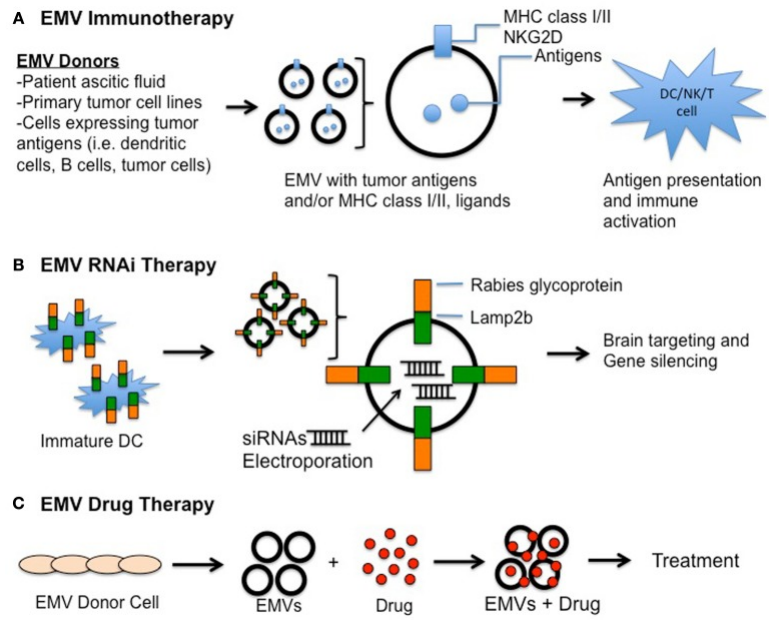
Extracellular membrane vesicles-mediated mechanisms in neurons.

(A) A gradient of EMVs in the developing nervous system can serve as a directional guide to axonal growth.

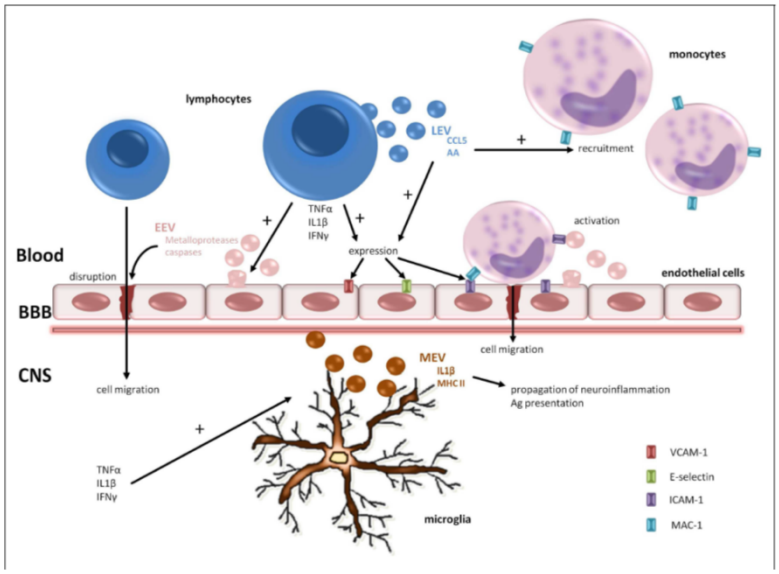
(B) EMVs released from presynaptic nerve terminals and taken up by their postsynaptic partners can carry informational content which can modulate the strength of synaptic activity.

(C) Regeneration of peripheral nerves is enhanced by the EMV transfer of ribosomes and mRNA directly from surrounding Schwann cells into the injured nerve to promote protein synthesis.

Lai CP, Breakefield XO. Role of exosomes/microvesicles in the nervous system and use in emerging therapies. Front Physiol. 2012 Jun 27;3:228. doi: 10.3389/fphys.2012.00228. eCollection 2012.



Lai CP, Breakefield XO. **Role of exosomes/microvesicles in the nervous system and use in emerging therapies**. Front Physiol. 2012 Jun 27;3:228. doi: 10.3389/fphys.2012.00228. eCollection 2012.



Extracellular membrane vesicles-based therapies.

(A) EMV immunotherapy. EMVs containing tumor-antigen within and/or on the membrane surface are isolated from different sources and introduced in vivo to elicit targeted immuneresponses.

(B) EMV RNAi therapy. EMVs derived from immature dendritic cells (DCs) expressing Rabies glycoprotein-Lamp2b fusion protein were electroporated with siRNAs for targeting against neurons, microglia, and oligodendrocytes for subsequent gene silencing.

(C) EMV drug therapy. Therapeutic compounds can be packaged into/onto EMVs isolated from donor cells to minimize degradation and increase delivery to intended sites.

EMV: extracellular membrane vesicles

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