WIE-biotech

立效生物

外泌体与自噬

干货版

方案组

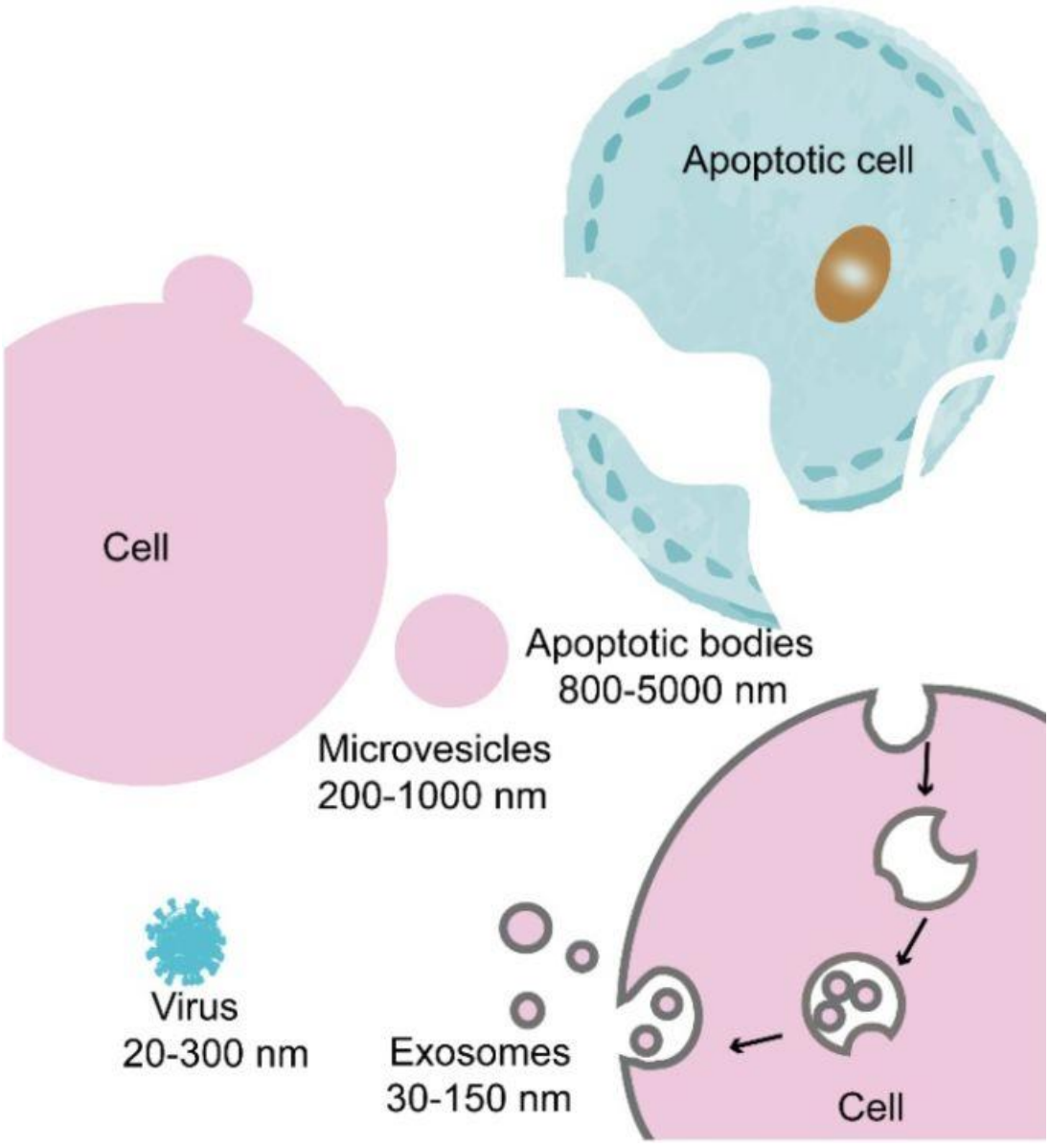
2022/8/8

目录

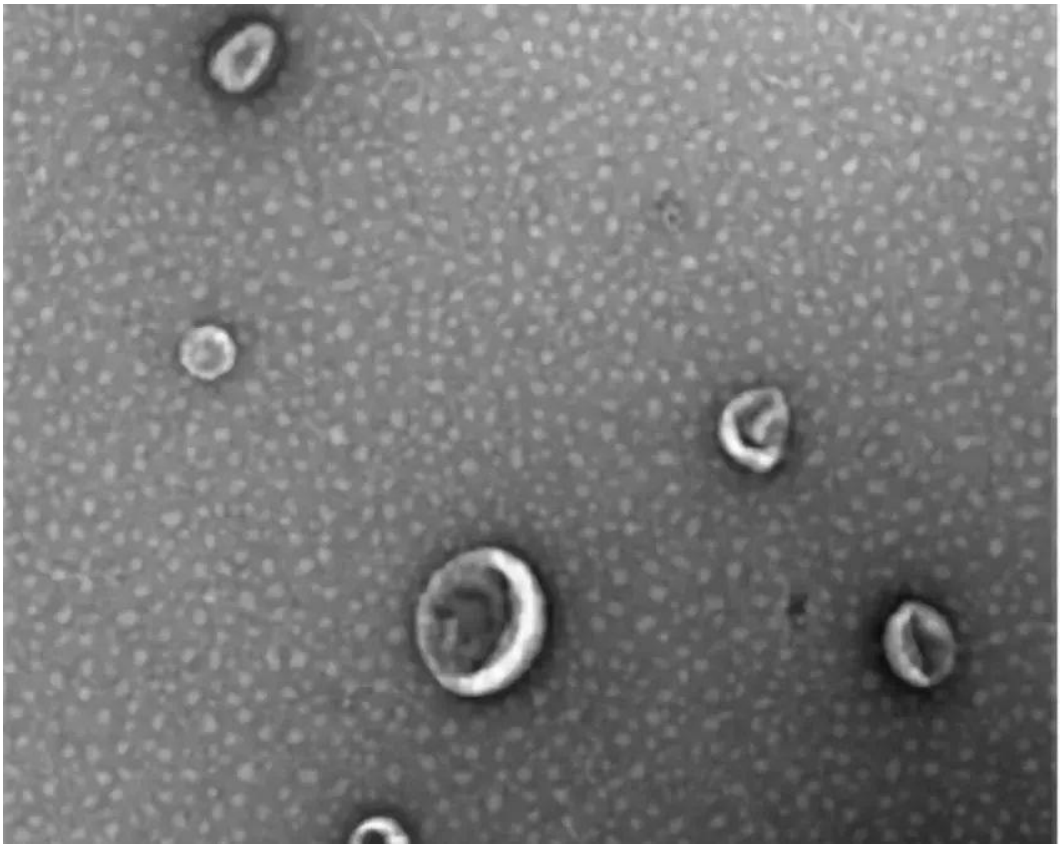
一、外泌体简介

（内容物、释放途径及标志物等）

细胞外囊泡主要分为：凋亡小体、微囊泡和外泌体等。



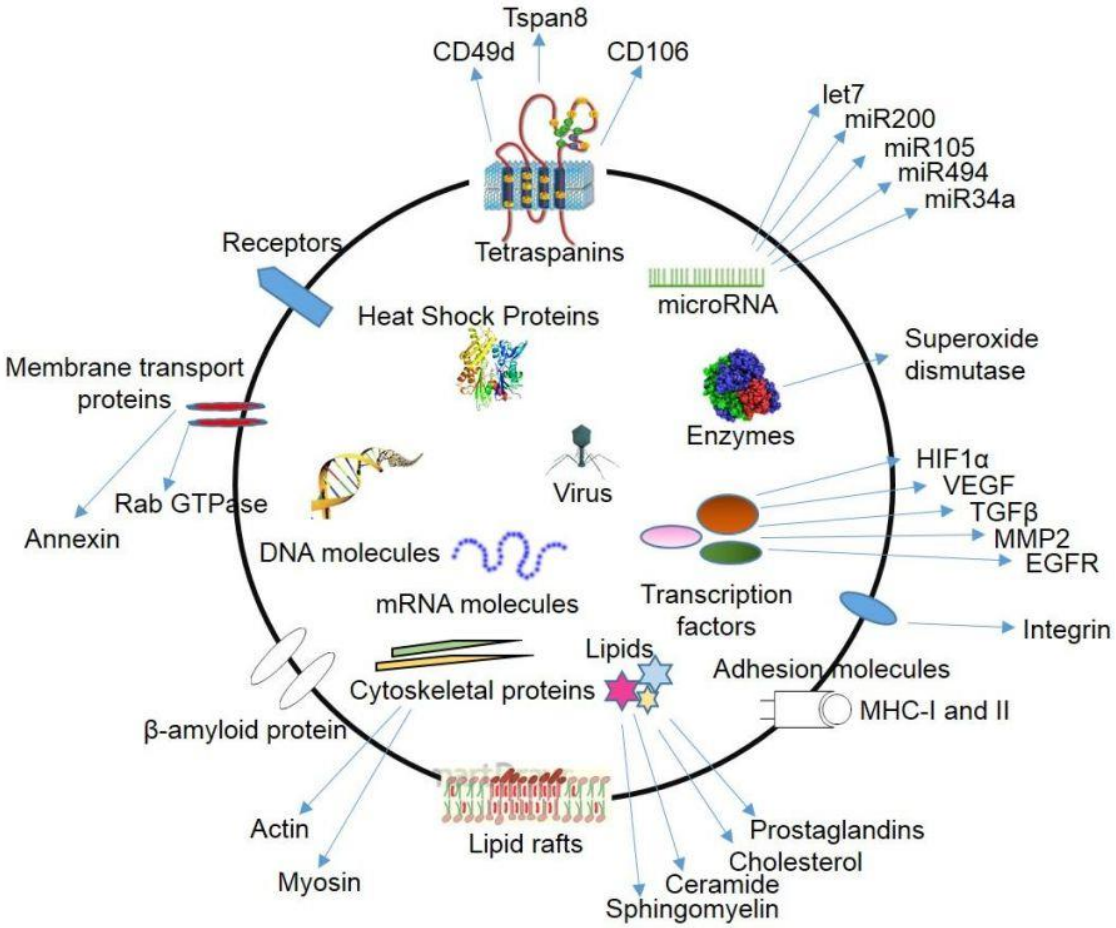
不同类型的细胞外囊泡（EVs）



来源于尿液的外泌体透射电镜图

Ref: Theranostics. 2018 Jan 1;8(1):237-255. IF:8.537.

1、外泌体内容物



a. 四分子交联体家族成员9（CD49d, CD106）

b. microRNA (miR200, miR105)

c. 酶类（ATPase, pgk1）

d. 转录因子

e. 黏附分子（integrin: 整合素）

f. 脂质筏（cholesterol: 胆固醇）

g. 细胞骨架蛋白（Actin）

h. mRNA and DNA

i. 膜转运蛋白（Annexin, Rab GTPase）

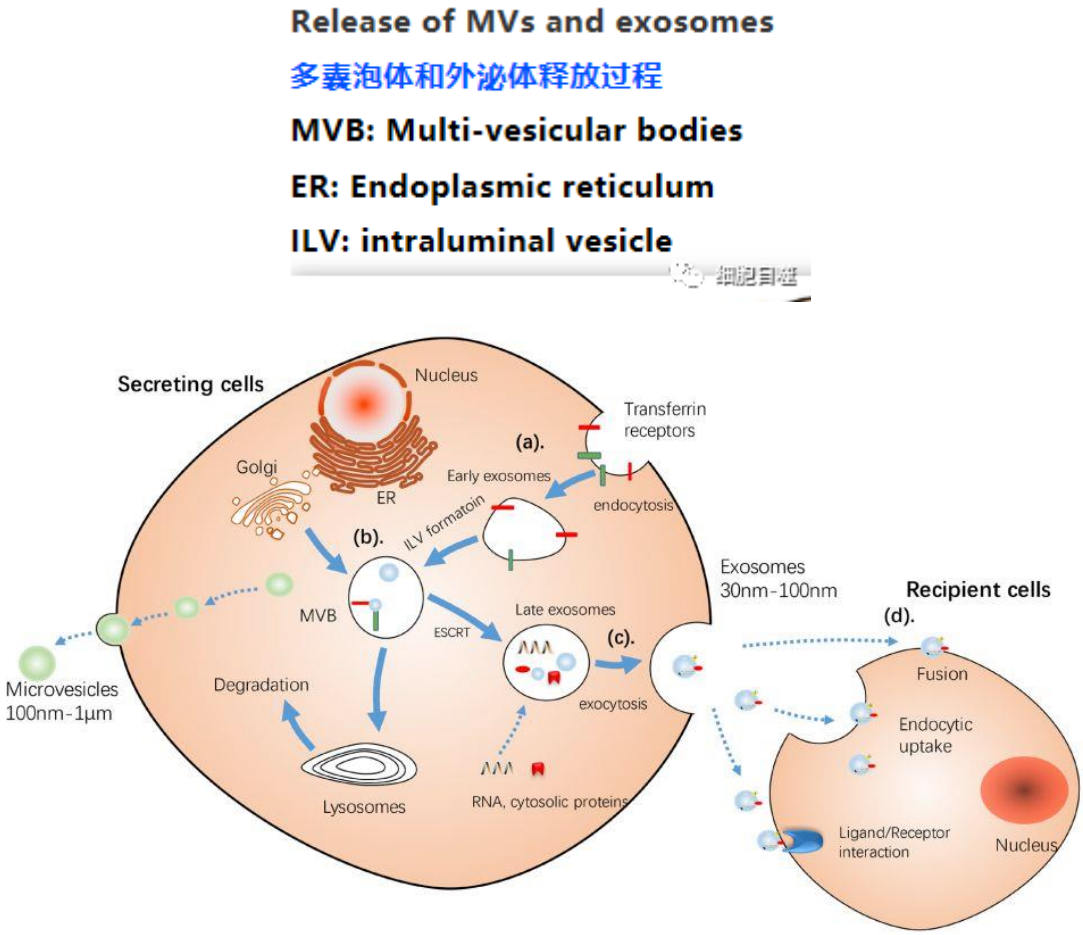
j. 受体

k. 热休克蛋白（HSP90）

l. 病毒

Ref: J Control Release. 2015 Dec 10;219:278-294. IF: 7.877.

2、外泌体释放途径



a. 细胞膜内吞作用-最初内涵体出现（包含膜上受体和跨膜蛋白）；

b. 成熟晚期内涵体-内生微囊泡-多囊泡体（外泌体内容物被装载入囊泡中）

c. 外泌体通过多囊泡体与质膜融合分泌到细胞外；

d. 外泌体能够通过生物体液（如血清和淋巴）在体内传播。

Ref: Oncotarget. 2017 Jun 20;8(25):41717-41733.

3、外泌体生物标志物

Biomarkers of exosomes isolated from cells and clinical samples

Biomarker	Type	Source	Analysis	Disease
PDCD6IP, FASN, XPO1, and ENO1	Protein	细胞	LC-MS/MS	前列腺癌
PCA-3, TMPRSS2:ERG	mRNA	尿	RT-PCR	
MiR-141, MiR-375	mRNA	血清	RT-PCR	
EGFR, EGFRvIII, TGF-β	Protein	血清	SDS-PAGE	胶质母细胞瘤
EGFRvIII	mRNA	血清	RT-PCR	
EGFR, EGFRvIII, PDPN, IDH1 R132H	Protein	血液	μ-NMR, ELISA	
MiR-21	micro-RNA	CSF	RT-PCR	
MiR-21	micro-RNA	血液	RT-PCR	ESCC
MiR-155, MiR-210, MiR-21	micro-RNA	血清	RT-PCR	淋巴瘤
MiR-21, MiR-141, MiR-200a, MiR-200c, MiR-200b, MiR-203, MiR-205, MiR-214	micro-RNA	血清	Microarray	卵巢癌
EpCAM, CD24	Protein	腹水	nPLEX	
MiR-718	micro-RNA	血清	Microarray	肝细胞癌

CSF: Colony stimulating factor，集落刺激因子；ESCC：食管鳞状细胞癌

Biomarkers of exosomes isolated from cells and clinical samples

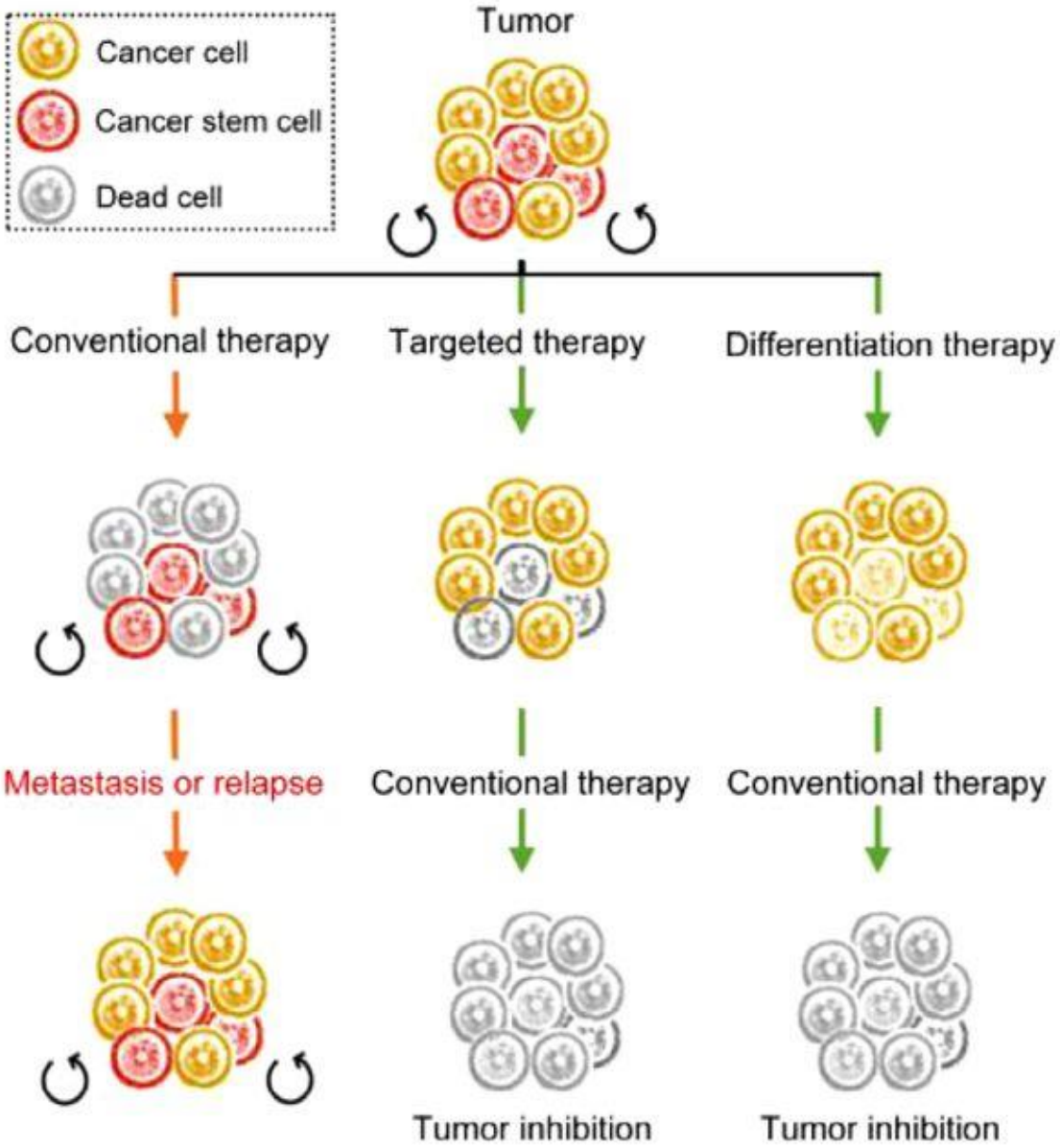
Biomarker	Type	Source	Analysis	Disease
MiR-17-3p, MiR-21, MiR-106a, MiR-146, MiR-155, MiR-191, MiR-192, MiR-203, MiR-205, MiR-210, MiR-212, MiR-214	micro-RNA	血浆	Microarray	肺癌
EpCAM	Protein	血浆	Magnetic cell sorting	
LRG1	Protein	尿	LC-MS/MS	
Apbb1ip, Daf2, Foxp1, Incenp, Aspn, BC031781, Gng2	mRNA	唾液	Microarray	胰腺癌
NT5E/CD73	Protein	腹水	MS/MS	
NT5E/CD73	Protein	细胞	MS/MS	结直肠癌
CD63, Caveolin-1	Protein	血浆	Exotest (ELISA)	黑色素瘤

Ref: J Control Release. 2015 Dec 10;219:278-294. IF: 7.877.

二、外泌体研究分析

1、外泌体和肿瘤干细胞

肿瘤干细胞（CSCs），又叫肿瘤起始细胞，能够介导肿瘤的复发和转移。



CSCs特性：

自我更新能力；

无限增殖能力；

对肿瘤治疗（如化疗）耐受。

Ref: Cancer Treat Rev. 2018 Jul 17;69:152-163. IF: 8.122.

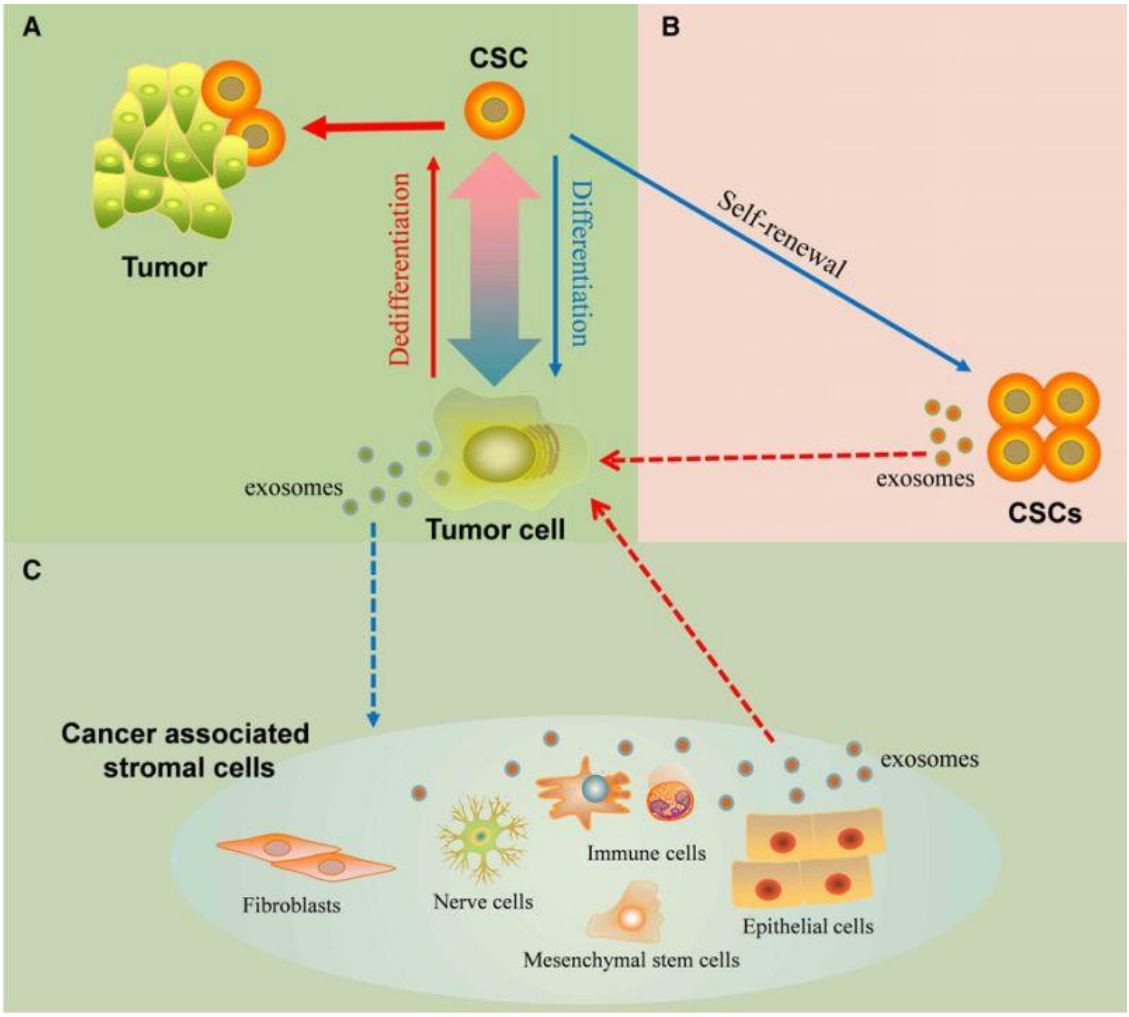
外泌体在维持CSCs动态平衡中的作用：

A. CSCs分化为肿瘤细胞，肿瘤细胞去分化为CSCs；

B&C. 外泌体在non-CSCs和CSCs相互转换中的作用。

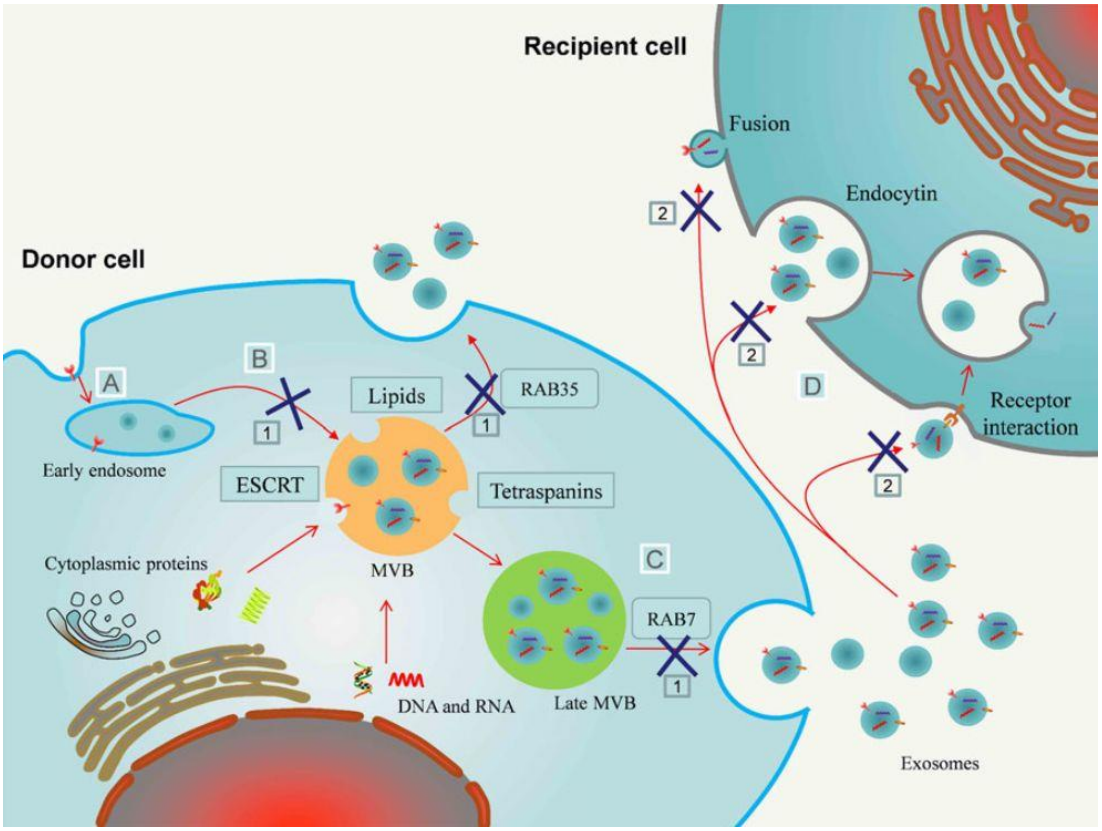
外泌体通过传递干性相关分子诱导肿瘤细胞去分化获得干性表型；

肿瘤来源外泌体也会影响肿瘤微环境中周围细胞，且这些非肿瘤细胞能够通过释放外泌体来促进肿瘤的发生和发展。



Ref: J Cell Mol Med. 2018 May 25. PMID: 29799161. IF: 4.302.

靶向外泌体信号通路可能打破这一动态平衡，相比于靶向 CSCs 和 non-CSCs 治疗，这可能会是新的、更好的治疗策略。



Ref: J Cell Mol Med. 2018 May 25. PMID: 29799161. IF: 4.302.

×1 通过干扰多囊泡体（MVB）形成和/或释放，抑制外泌体生物形成过程；

×2 通过阻断参与外泌体结合或内化的外泌体配体或细胞表面受体来打断受体细胞的外泌体吸收。

2、外泌体和自噬

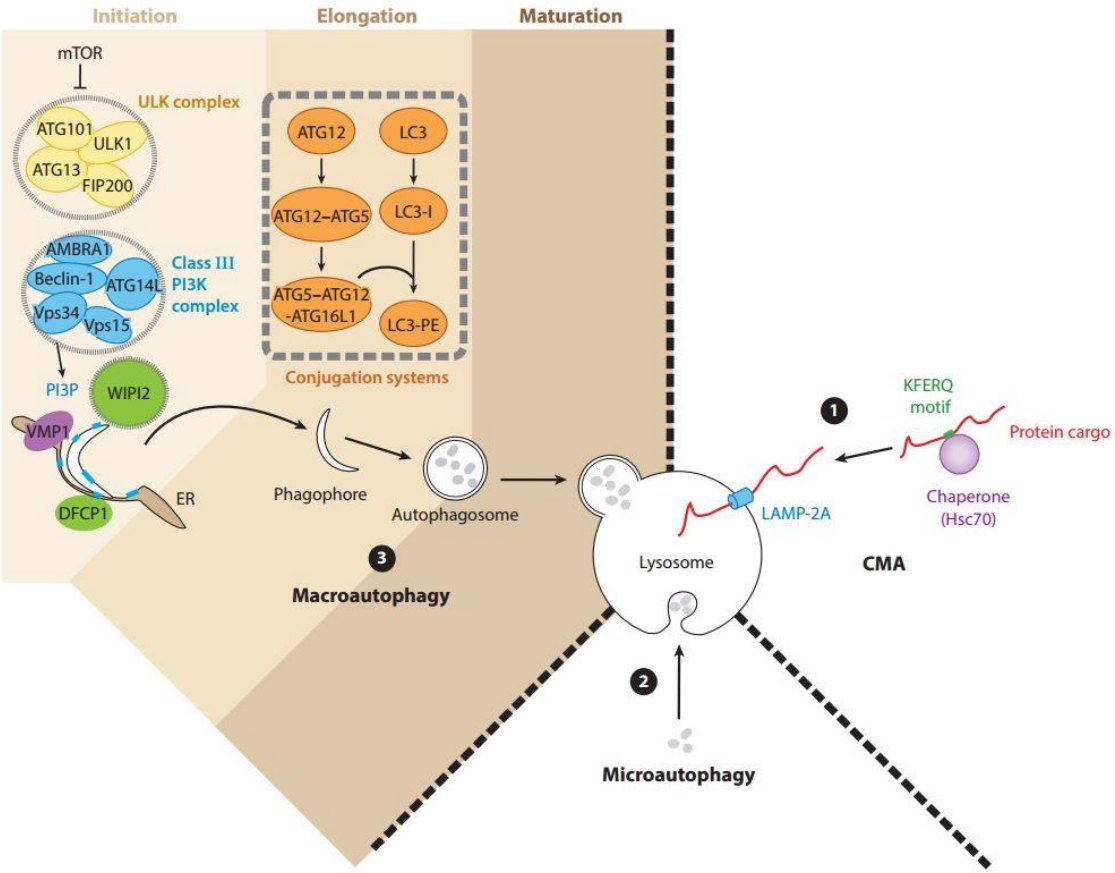
自噬是一个动态、保守的细胞分解代谢过程，由溶酶体介导的细胞降解系统来降解细胞内过剩或受损的细胞器和蛋白聚集体，从而实现能量的再循环。

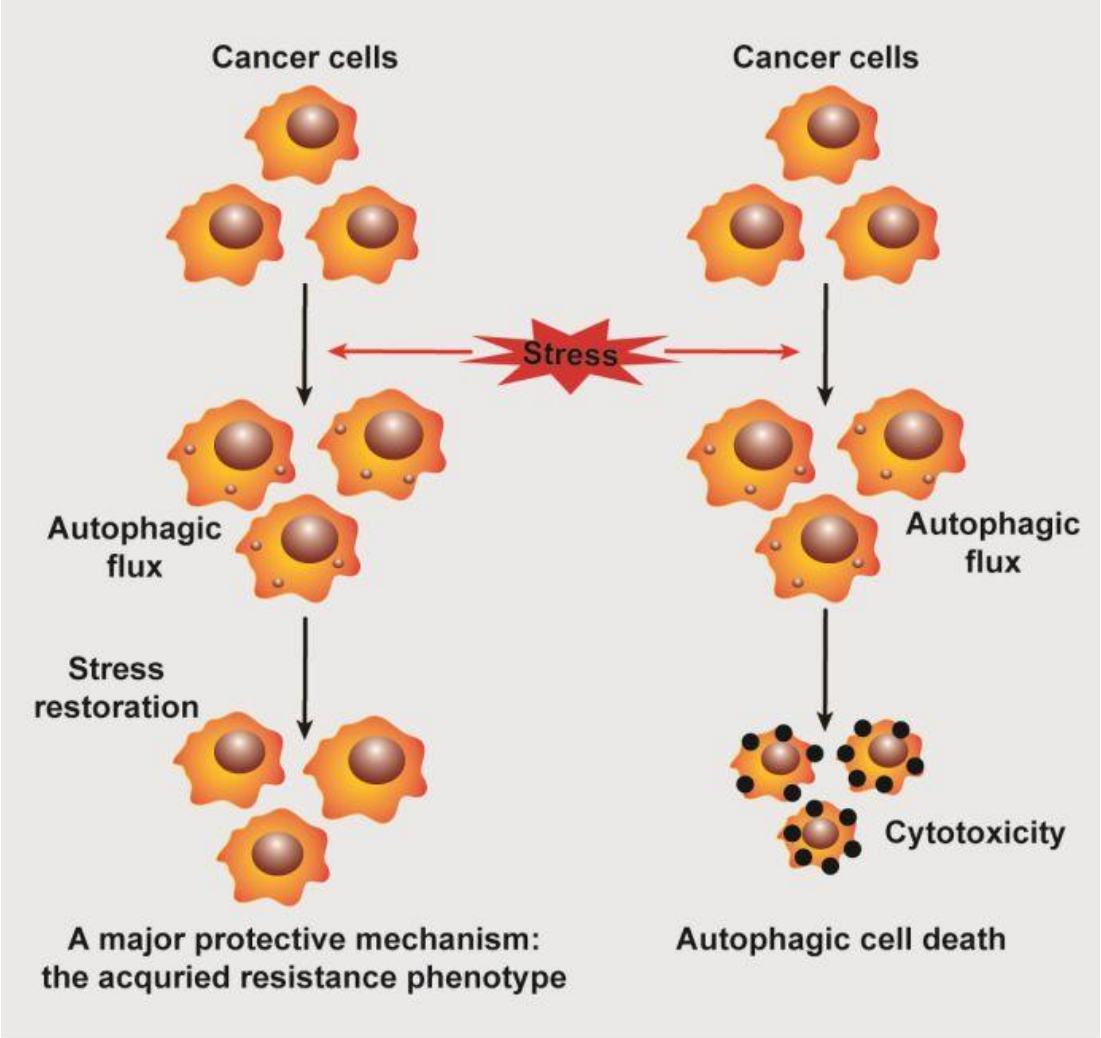
自噬在肿瘤中有着双重作用且被分为:

巨自噬；

微自噬；

分子伴侣蛋白介导自噬（CMA）。


Initiation
Elongation
Maturation
mTOR
ULK complex
ATG101
ULK1
ATG13
FIP200
AMBRA1
Beclin-1
ATG14L
Vps34
Vps15
Class III PI3K complex
PI3P
WIPI2
VMP1
DFCP1
ER
ATG12
LC3
ATG12–ATG5
LC3-I
ATG5–ATG12 -ATG16L1
LC3-PE
Conjugation systems
Phagophore
Autophagosome
3
Macroautophagy
1
KFERQ motif
Protein cargo
Chaperone (Hsc70)
LAMP-2A
Lysosome
CMA
2
Microautophagy

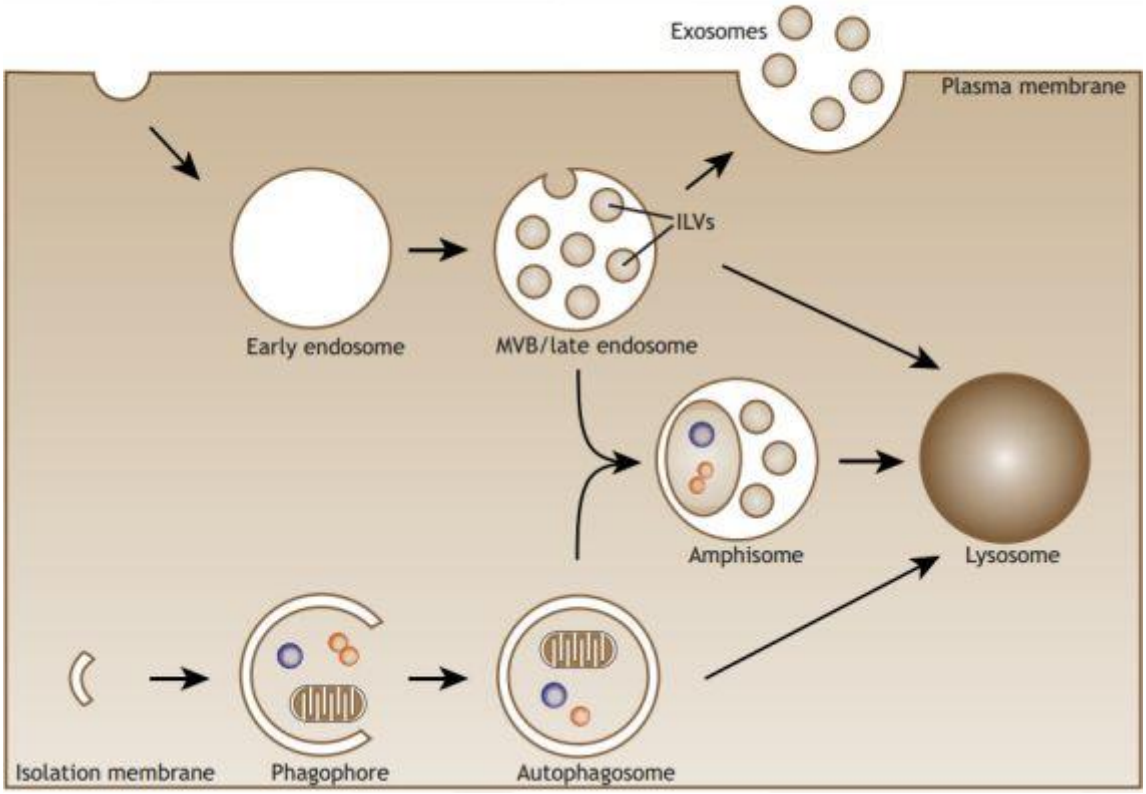


Ref: Annu Rev Pharmacol Toxicol. 2017 Jan 6;57:375-398. IF: 13.295.

MVB: Multi-vesicular bodies

ILVs: intraluminal vesicles

自噬和外泌体生物形成



a. 早期内涵体-多囊泡体/晚期内涵体-管腔内囊泡（ILV）-外泌体/溶酶体；

b. 起始-吞噬泡-自噬小体-自噬溶酶体-降解和回收；

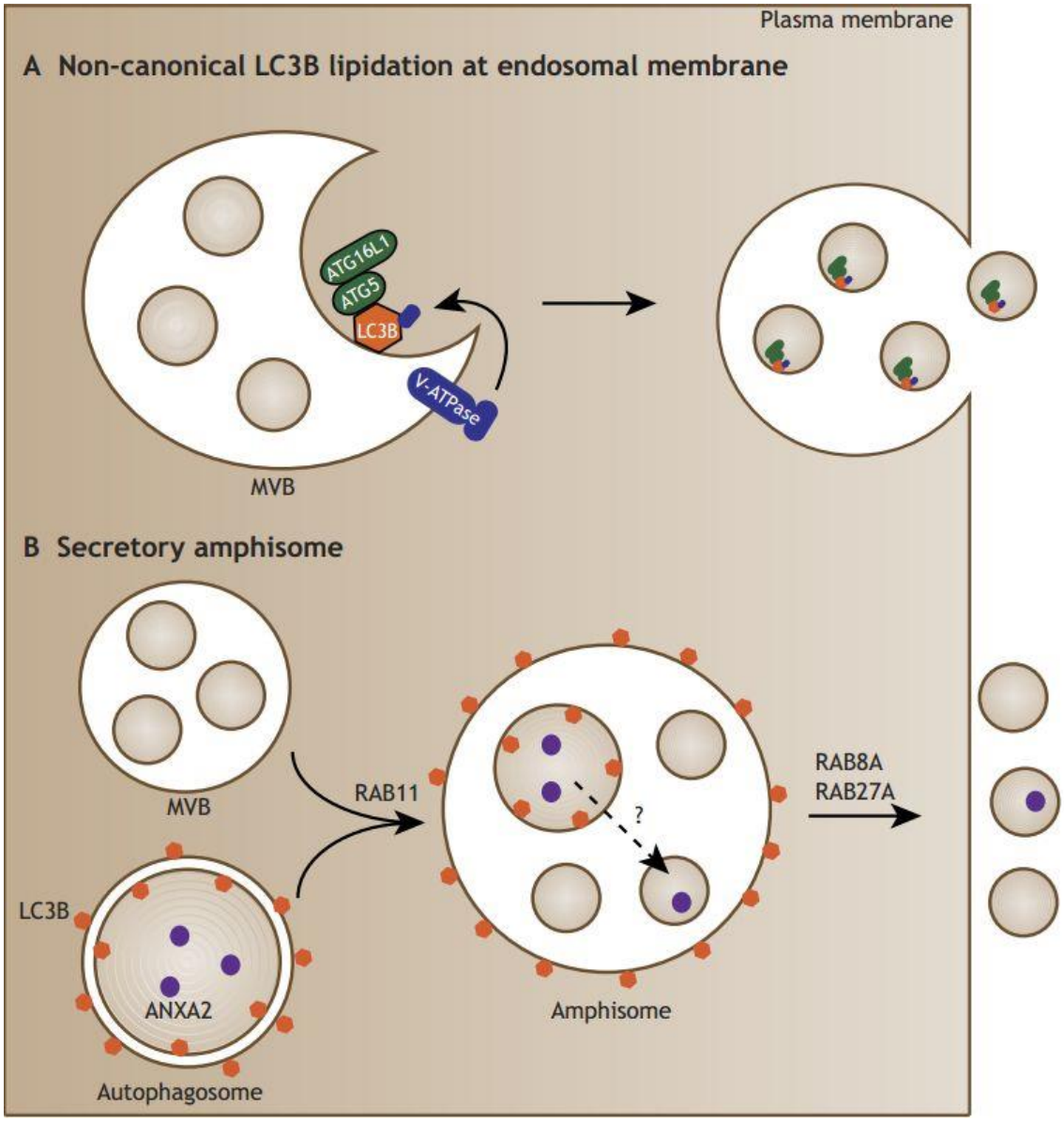
c. 自噬小体+内涵体=自噬内涵体。

Ref: J Cell Sci. 2018 Aug 3;131(15). PMID: 30076239. IF: 4.401.

自噬和外泌体相互影响

A.ATG5-ATG16复合物介导非经典LC3B脂化，并促进V-ATP酶的分离，从而抑制多囊泡体（MVBs）的酸化及随后的溶酶体降解;

B.自噬依赖的膜联蛋白（Annexin）A2（ANXA2）分泌：需要自噬内涵体中间介导释放外泌体从而释放胞质ANXA2。



Ref:

Dev Cell. 2017 Dec 18;43(6):716-730.e7. IF: 9.616.

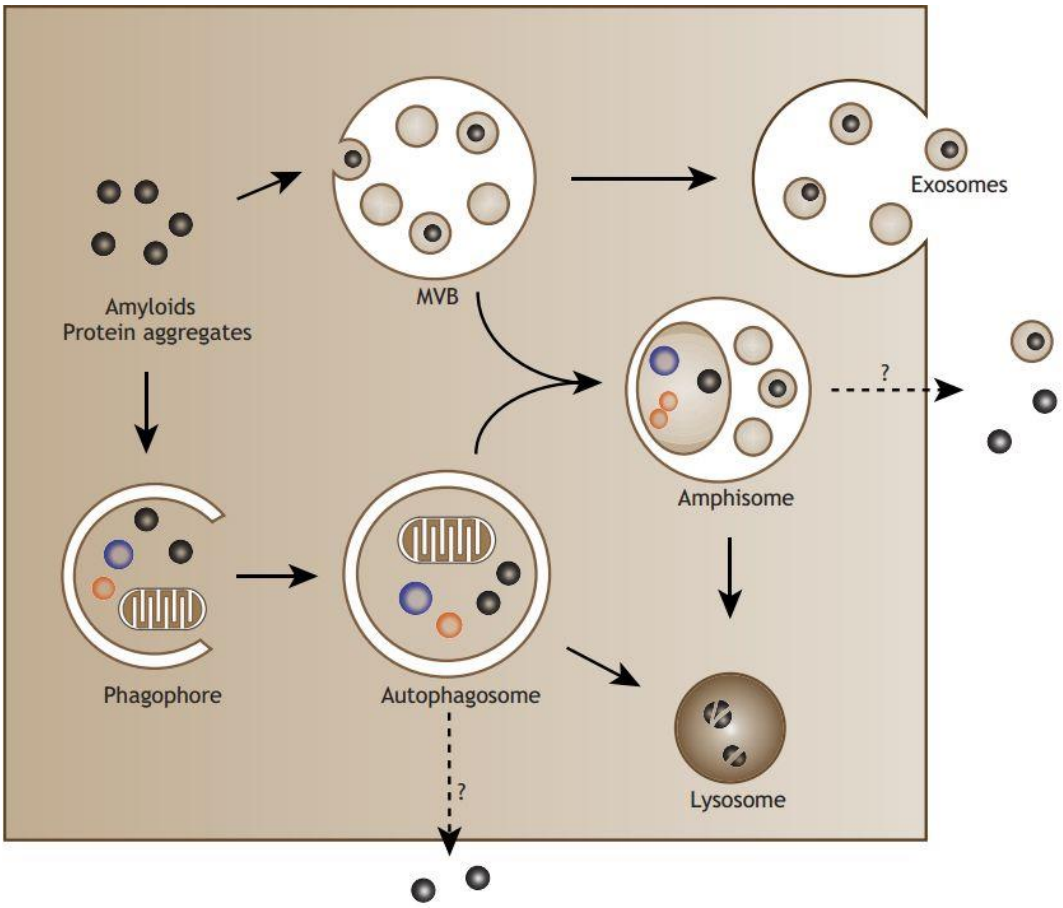
J Cell Sci. 2018 Aug 3;131(15). PMID: 30076239. IF: 4.401.

自噬和外泌体在神经退行性疾病中串扰

A.蛋白的异常积累和聚集是多种神经退行性疾病的标志；

B.外泌体释放和自噬降解是消除淀粉样蛋白和蛋白聚集物的两种协同途径；

C.在溶酶体或自噬功能障碍时，多囊泡体（MVBs）可能以外泌体的形式释放含有蛋白聚集物或淀粉样蛋白的管腔内囊泡（ILVs），从而减少细胞中蛋白毒性应急。



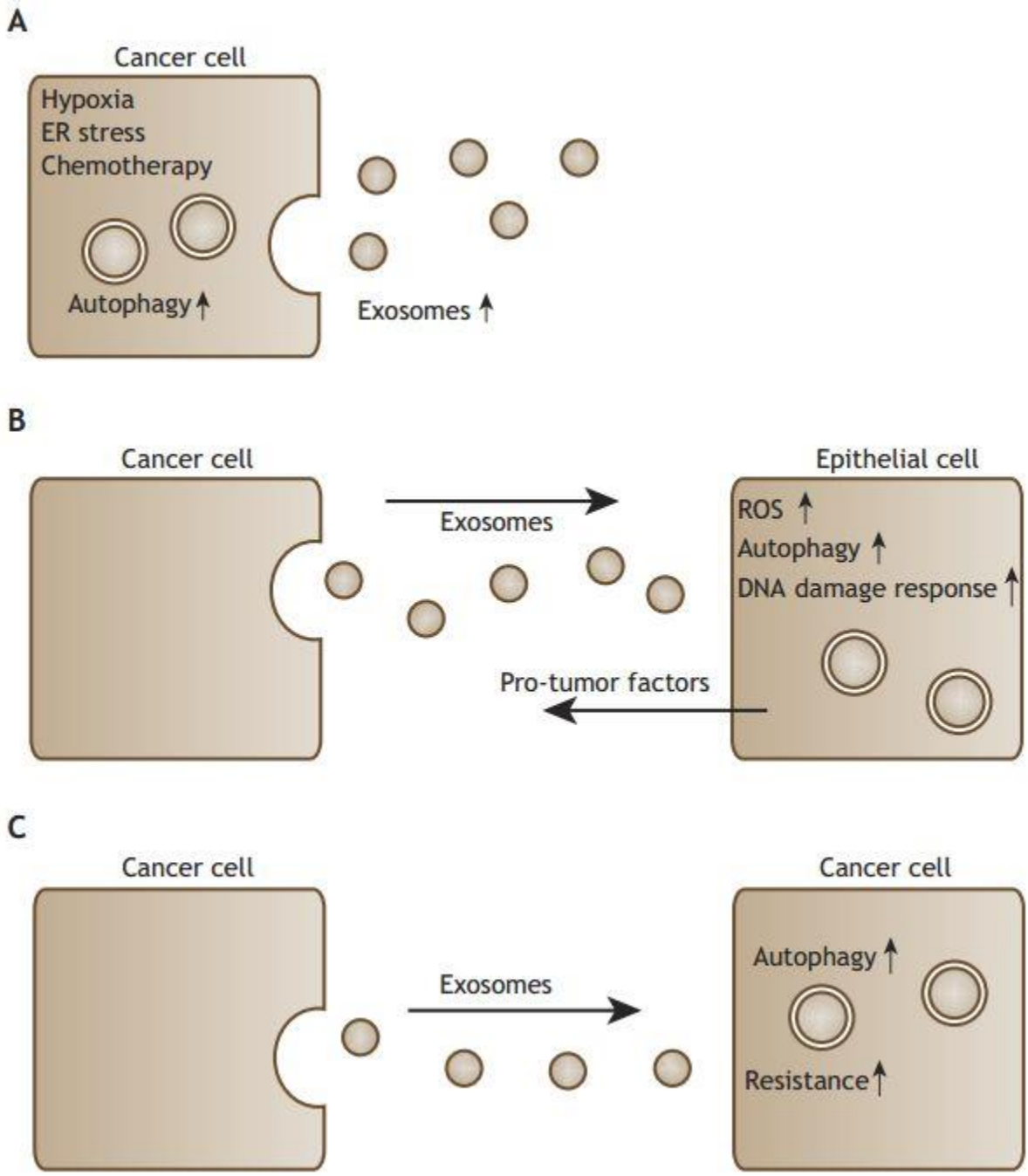
Ref: J Cell Sci. 2018 Aug 3;131(15). PMID: 30076239. IF: 4.401.

自噬和外泌体在肿瘤中串扰

A. 细胞应激（缺氧、内质网应激和化疗等）时，自噬和外泌体释放同时上调，具体分子机制尚待研究；

B. 肿瘤细胞释放外泌体增加上皮细胞内ROS水平，诱导上皮细胞DNA损伤，并通过未知机制增加自噬和促肿瘤因子释放；

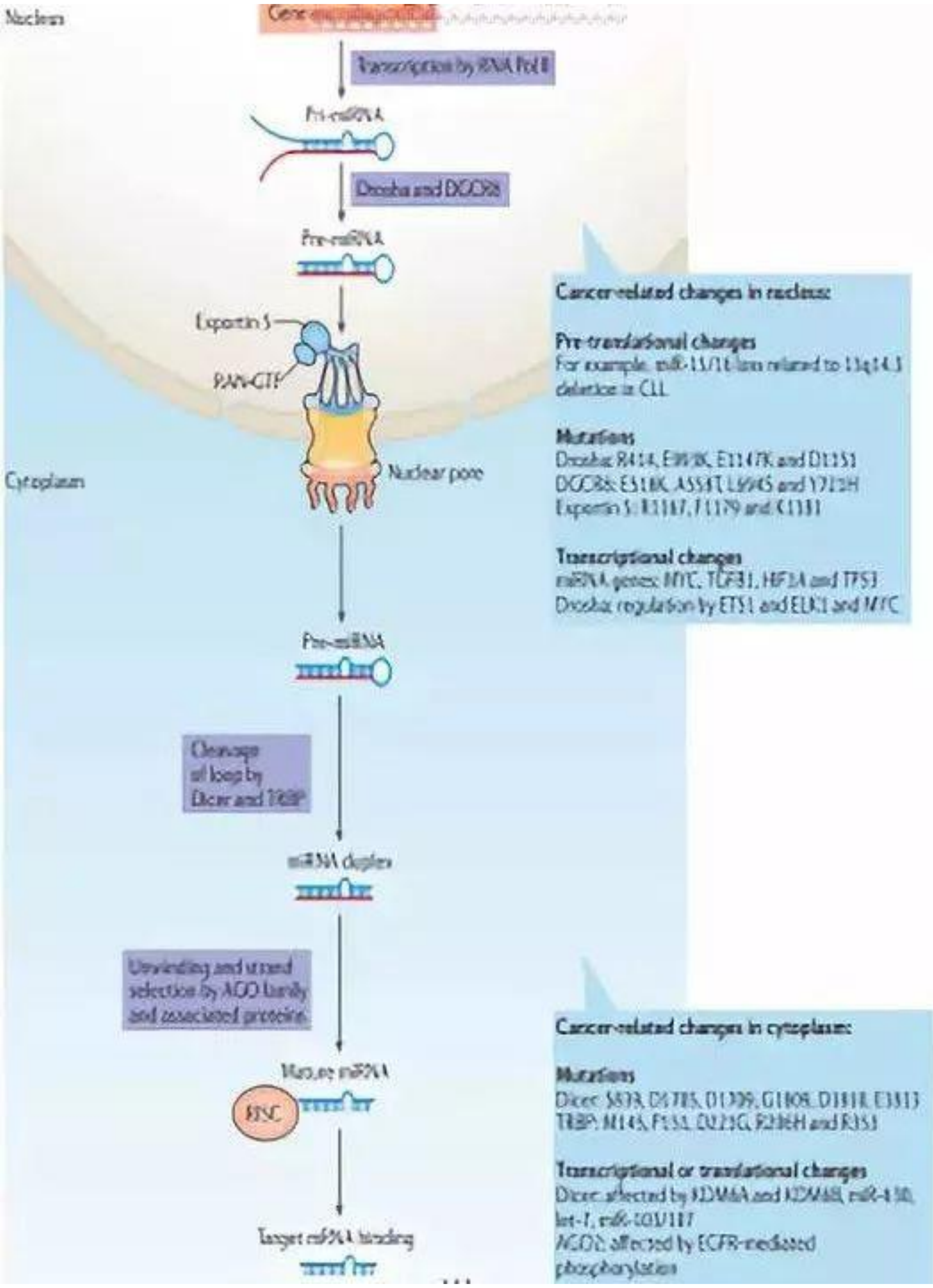
C. 抗癌药物治疗的肿瘤细胞能够诱导外泌体释放，使得受体细胞保护性自噬上调，从而调节其对抗癌药物的敏感性。



Ref: J Cell Sci. 2018 Aug 3;131(15). PMID: 30076239. IF: 4.401.

3、外泌体和 miRNA

miRNA 生物合成



Nucleus
Transcription by RNA Pol II
Pri-miRNA
Drosha and DGCR8
Pre-miRNA
Exportin 5
RAN-GTP
Nuclear pore
Cytoplasm
Pre-miRNA
Cleavage of loop by Dicer and TRBP
miRNA duplex
Unwinding and strand selection by AGO family and associated proteins
Mature miRNA
RISC
Target mRNA binding
Cancer-related changes in nucleus:
Pre-translational changes
For example, miR-15/16 loss related to 13q14.3 deletion in CLL
Mutations
Transcriptional changes
miRNA genes: MYC, TGFB1, HIF1A and TP53
Drosha regulation by ETS1 and ELK1 and MYC
Cancer-related changes in cytoplasm:
Mutations
Transcriptional or translational changes
AGO2: affected by EGFR-mediated phosphorylation

miRNAs是一类非编码RNA分子，通过与互补的靶mRNA结合，在细胞分化、增殖和生存过程中发挥着重要作用，最终导致mRNA翻译抑制或降解。

上图中为miRNA生物合成的概述，强调了与miRNA改变有关疾病的关键突变和下调因素。

Ref: Nat Rev Drug Discov. 2017 Mar；16(3)：203-222.IF：50.167.

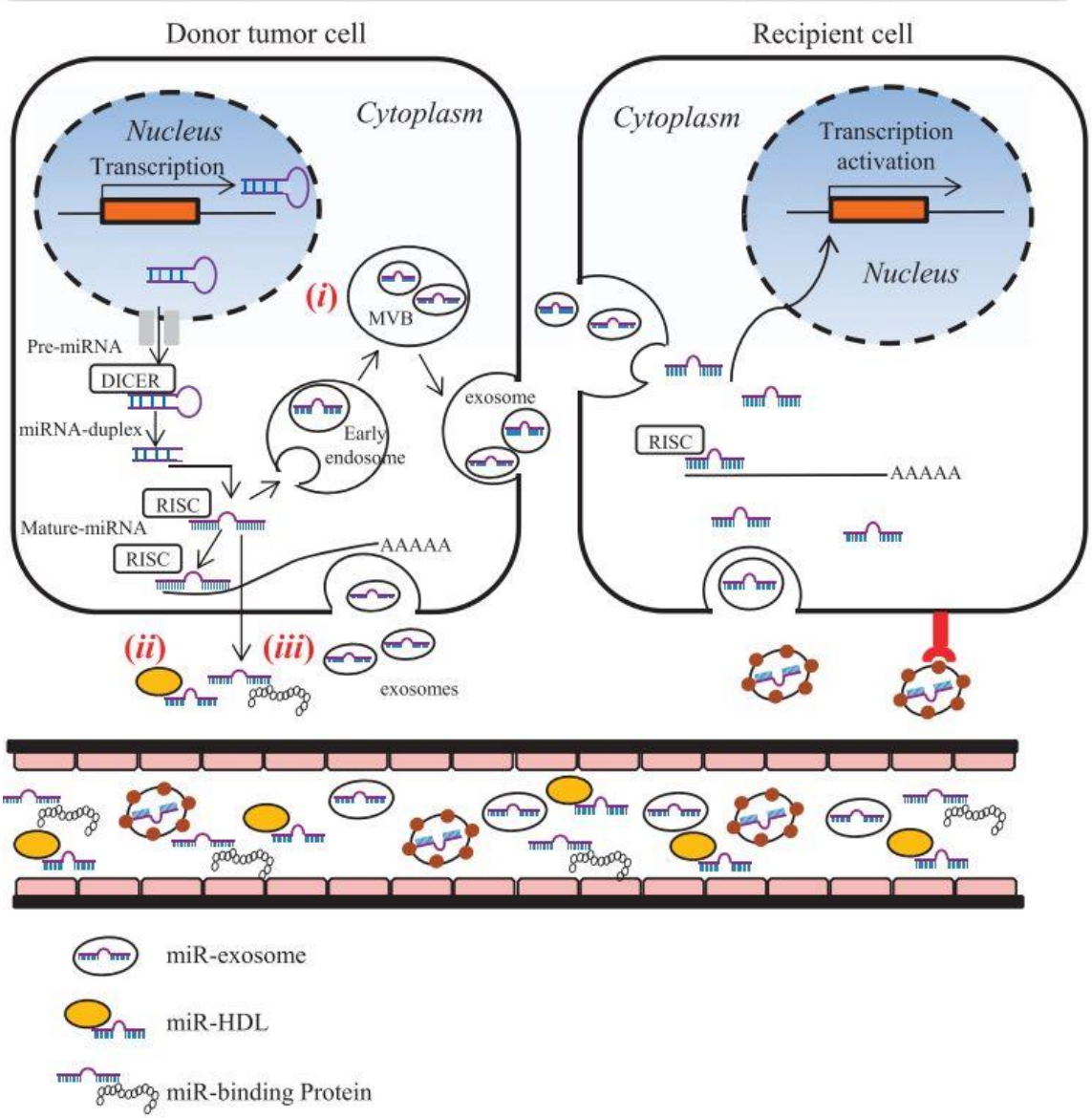
miRNA生物合成和释放机制

一小部分miRNAs从细胞内释放到细胞外环境中：

(i) 包载入多囊泡体（MVB）并通过外泌体释放；

(ii) 合并入高密度脂蛋白（HDL）颗粒；

(iii) 与RNA结合蛋白结合，如：AGO2，从而释放miRNA–AGO复合物。

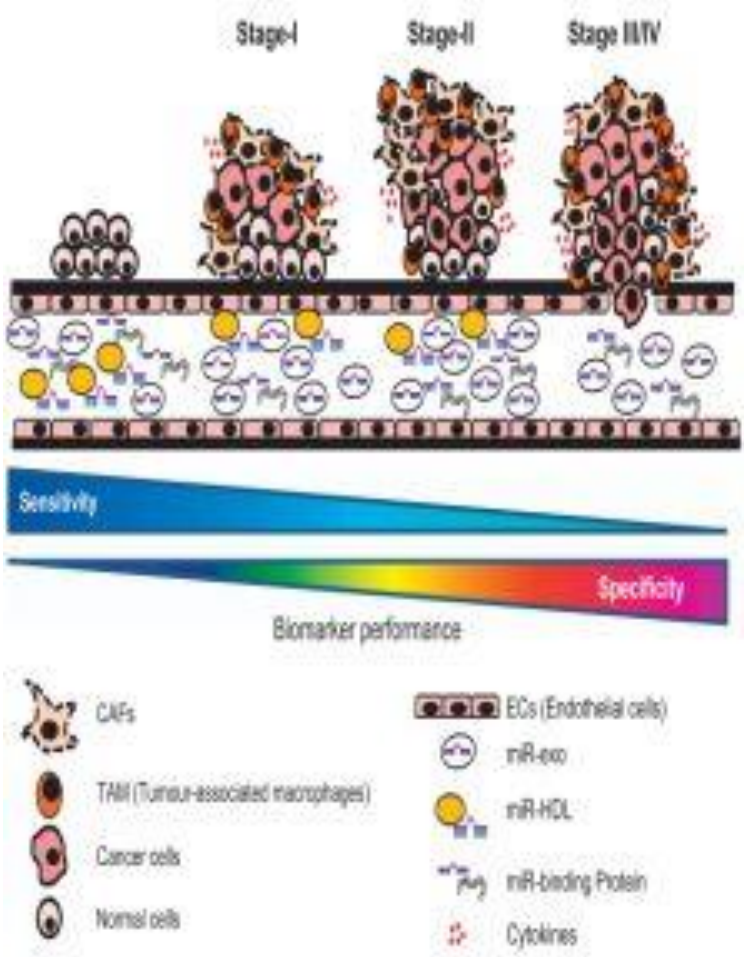


AGO2, a protein associated with the RNA-induced silenced complex (RISC)

Ref: Exp Mol Med. 2017 Jan 20;49(1):e285. PMID: 28104913. IF: 5.584.

Exo-miRs 从发生恶性转化和进展肿瘤组织中释放

在肿瘤进展过程中，细胞向血液中释放 exo-miRs，可作为循环生物标志物用于肿瘤的早期发现和预后评估。



Exo-miRs作为标志物优势：

A.稳定性高；

B.与非肿瘤细胞来源外泌体差异显著；

C.比血液中miRs更能提供信息。

Cancer associated fibroblast, CAF;

High-density lipoproteins, HDL;

Ref: Exp Mol Med. 2017 Jan 20;49(1):e285. PMID: 28104913. IF: 5.584.

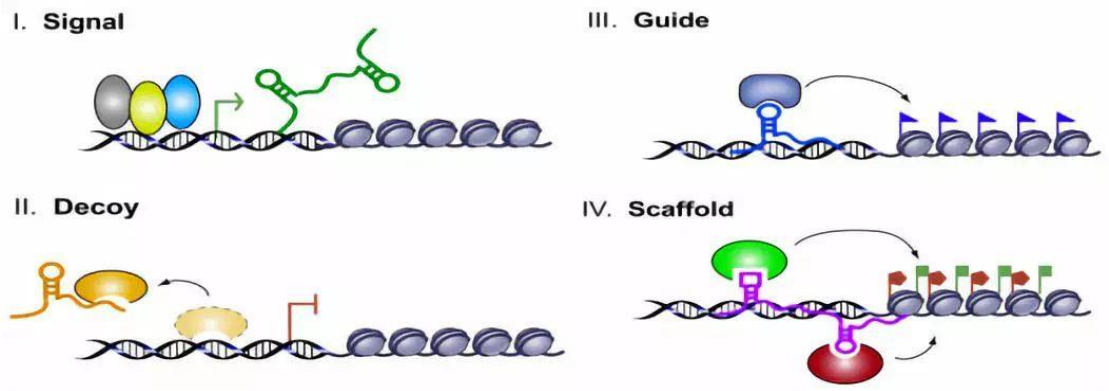
Exo-miRs 能够区分患者的不同病理状况

Sample description	Quantification method	Findings
Tumor cells from glioblastoma patients at passage 1-15; serum from glioblastoma patients and controls	Quantitative PCR	11 miRNAs (miR-15b, miR-16, miR-196, miR-21, miR-26a, miR-27a, miR-92, miR-93, miR-320, and let-7a) were known to be abundant in gliomas, able to be detected in their derived microvesicles; the level of exosomal miR-21 was elevated serum microvesicles compared with controls
Plasma from NSCLC patients and controls	Quantitative PCR	The levels of exosomal let-7f and/or miR-30e-3p in NSCLC patients can distinguish patients with resectable tumors from those with non-resectable tumors
Serum from malignant tumor patients, benign tumor patients, and controls	Microarray	The levels of 8 exosomal miRNAs (miR-21, miR-141, miR-200a, miR-200b, miR-200c, miR-203, miR-205, and miR-214) from malignant tumor are significantly distinct from those observed in benign tumor; exosomal miRNAs could not be detected in normal controls
Plasma from lung adenocarcinoma and controls	Microarray	The levels of 12 exosomal miRNAs (miR-17-3p, miR-21, miR-106a, miR-146, miR-155, miR-191, miR-192, miR-203, miR-205, miR-210, miR-212, and miR-214) are significantly different between patients and controls

Ref: Genomics Proteomics Bioinformatics. 2015 Feb;13(1):17-24. IF: 6.615.

lncRNAs 是一个转录 RNA 分子大家族，长度超过 200nt，很少或没有已知的蛋白编码潜能。

lncRNA 机制的四种模型



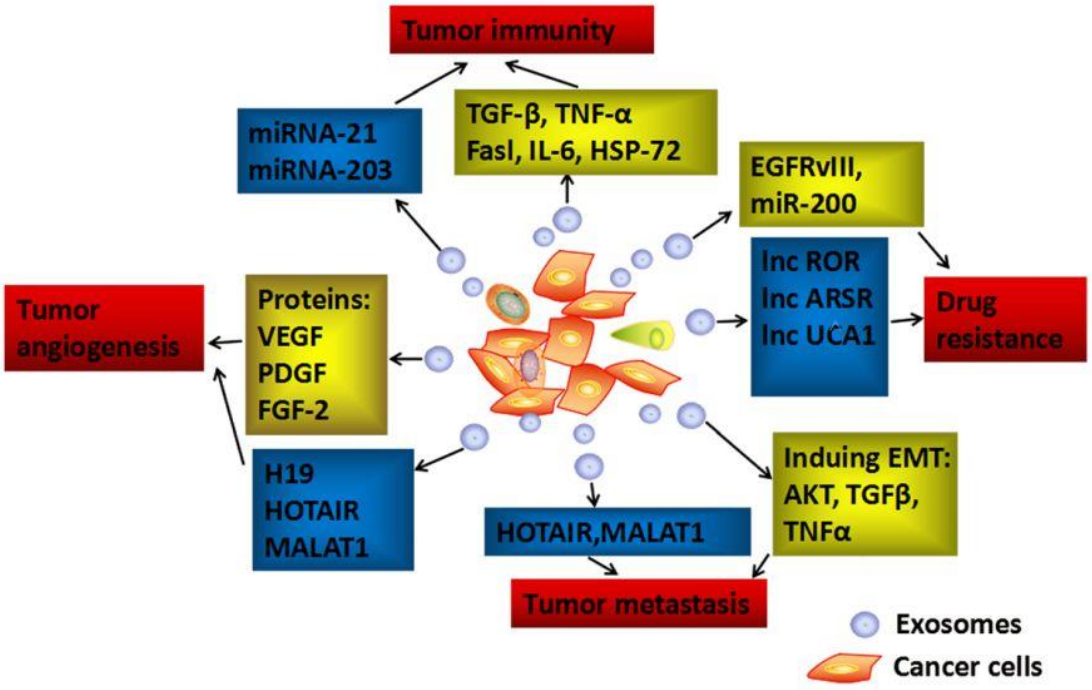
Ref:

Clin Pharmacol Ther. 2016 May;99(5):494-50. IF: 6.544.

Mol Cell. 2011 Sep 16;43(6):904-14. IF: 14.248.

4、外泌体和 lncRNA

外泌体在肿瘤微环境中的功能作用



肿瘤细胞和基质细胞利用外泌体转运lncRNA和蛋白来修饰肿瘤微环境中的周围细胞。

Ref: Mol Cancer. 2018 Apr 20;17(1):82. PMID:29678180. IF: 7.776.

外泌体lncRNA和肿瘤耐药

RCC:

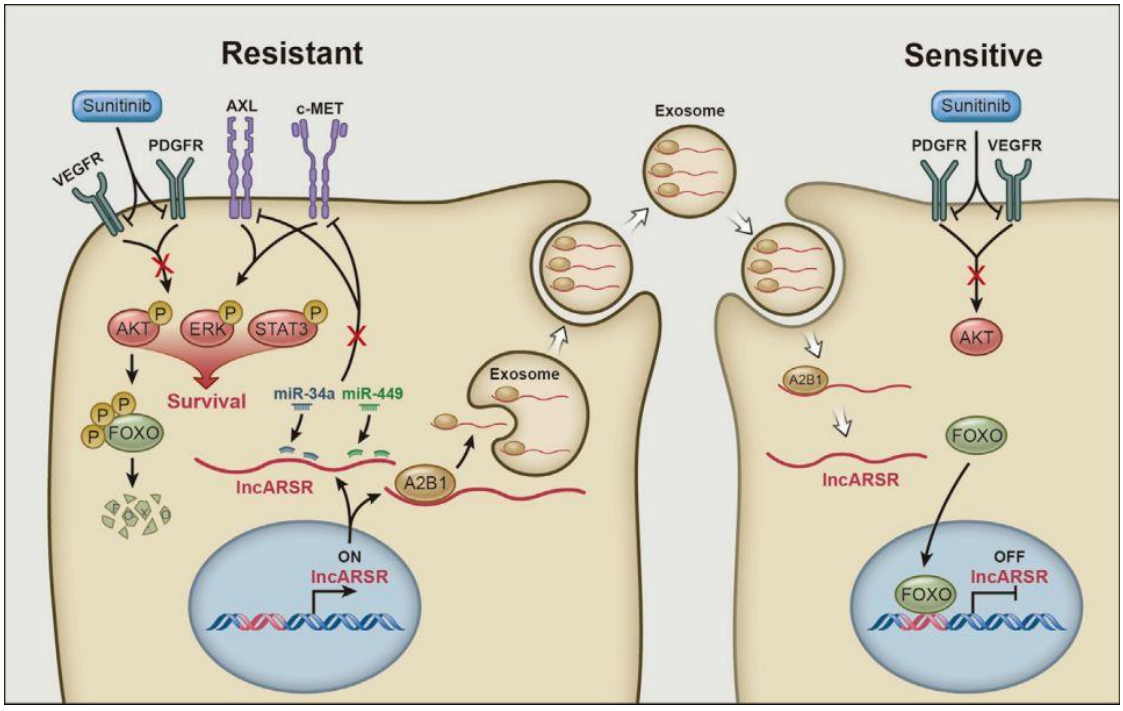
Renal cell carcinoma

PDGF:

Platelet-derived growth factor

VEGF:

Vascular endothelial growth factor



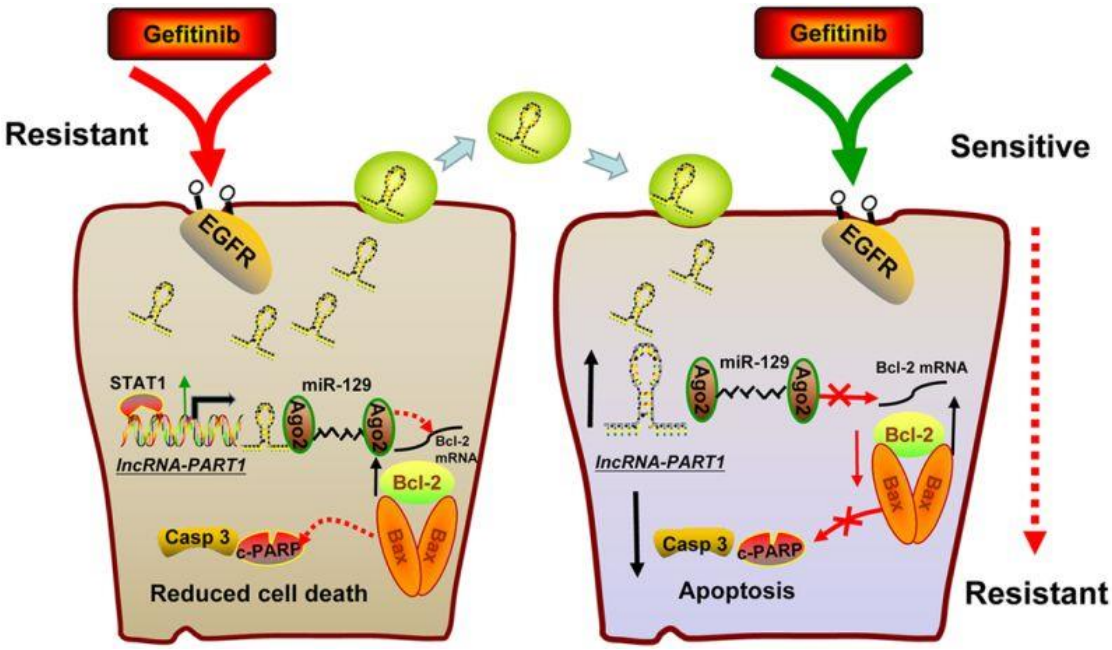
LncARSR 能被包装进外泌体，从抗舒尼替尼的肾细胞癌细胞中分泌出来，将耐药性传递给受体敏感的细胞。

Ref: Cancer Cell. 2016 May 9;29(5):653-668.IF: 22.844.

外泌体 lncRNA 和肿瘤耐药

ESCC:

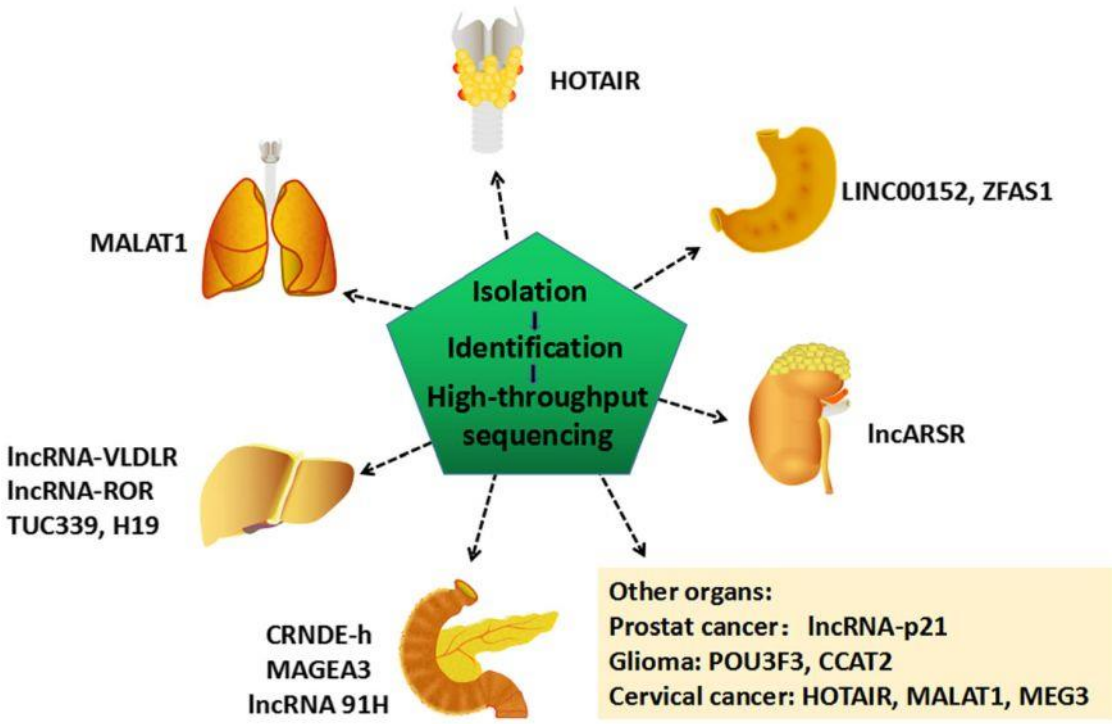
Esophageal squamous cell carcinoma



LncRNA-PART1 被包装入外泌体，从吉非替尼耐药的食管鳞状细胞癌细胞中分泌出来，将抗性传递给受体敏感的细胞。

Ref: J Exp Clin Cancer Res. 2018 Jul 27;37(1):171,PMID: 30049286. IF: 6.217

外泌体 lncRNA 作为新的肿瘤生物标志物



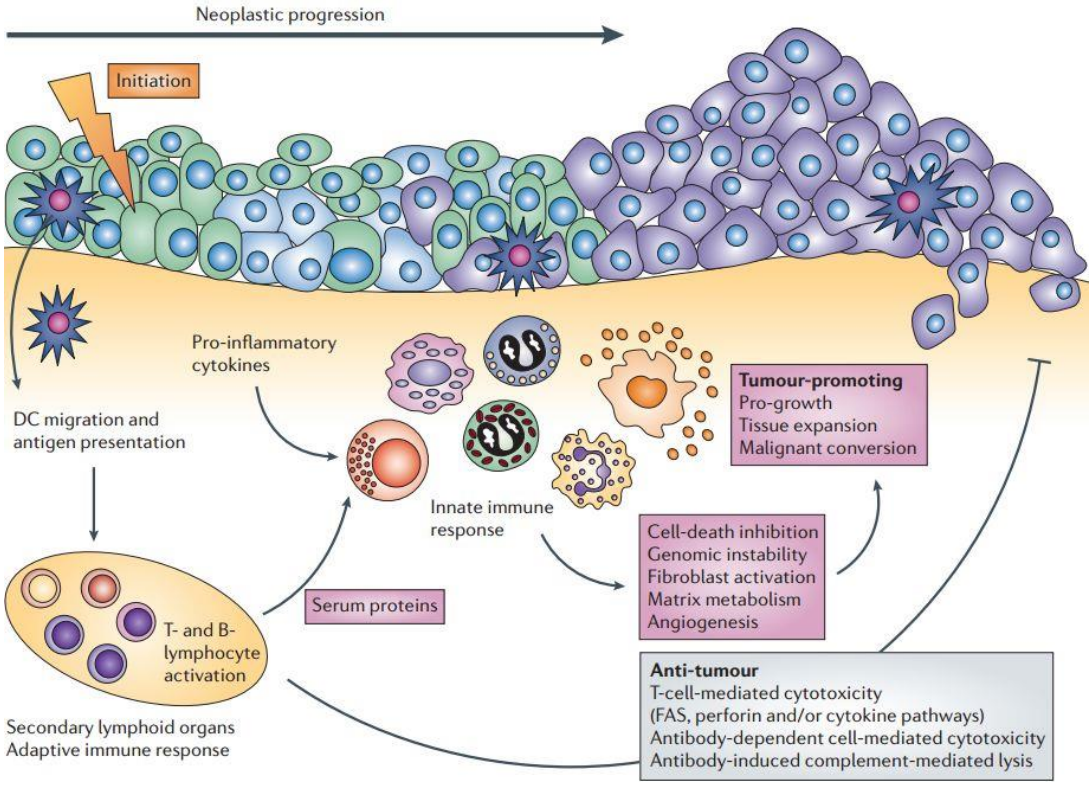
越来越多的外泌体 lncRNAs 已经被报道在人类肿瘤中异常表达；

外泌体 lncRNAs 可能成为肿瘤潜在的生物标志物。

Ref: Mol Cancer. 2018 Apr 20;17(1):82. PMID:29678180. IF: 7.776.

5、 外泌体和免疫系统

在炎症相关肿瘤发展中先天性和适应性免疫细胞功能。



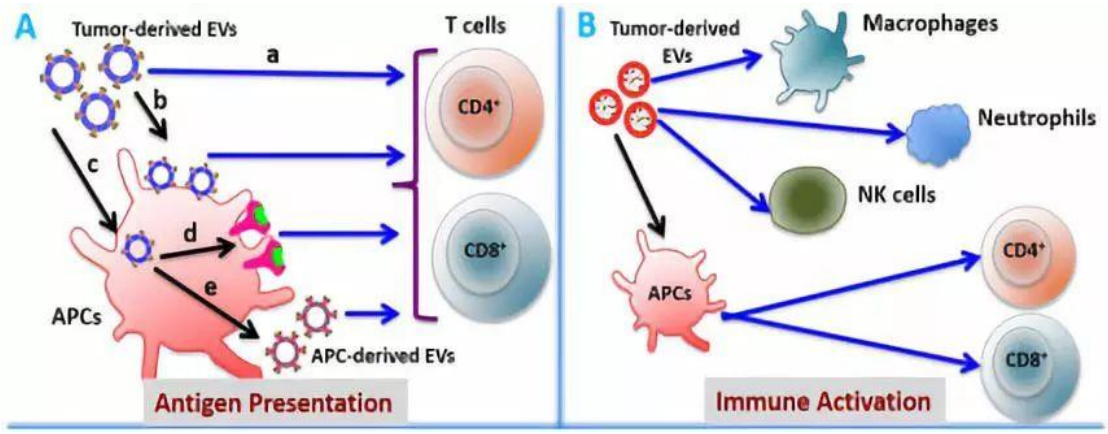
抗原–树突状细胞（DCs）-淋巴器官（适应性免疫反应）：

B细胞活化和体液免疫激活-先天性免疫慢性激活-改变细胞周期进程，提高肿瘤细胞存活率，促进组织重构和血管生成系统发展-促进肿瘤发展；

激活适应性免疫（T细胞介导细胞毒性等）-抗肿瘤反应。

Ref: Nat Rev Cancer. 2006 Jan;6(1):24-37. IF:42.784.

肿瘤中外泌体调节免疫系统



Panel A:

a. 直接通路：外泌体上MHC-肽复合物与T细胞上受体直接相互作用；

b&c.间接通路：外泌体与抗原呈递细胞（APCs）相互作用，b（变装）：外泌体表面被装饰；

c.被APCs内化；

d.被APCs降解，随后抗原呈递在APCs表面；

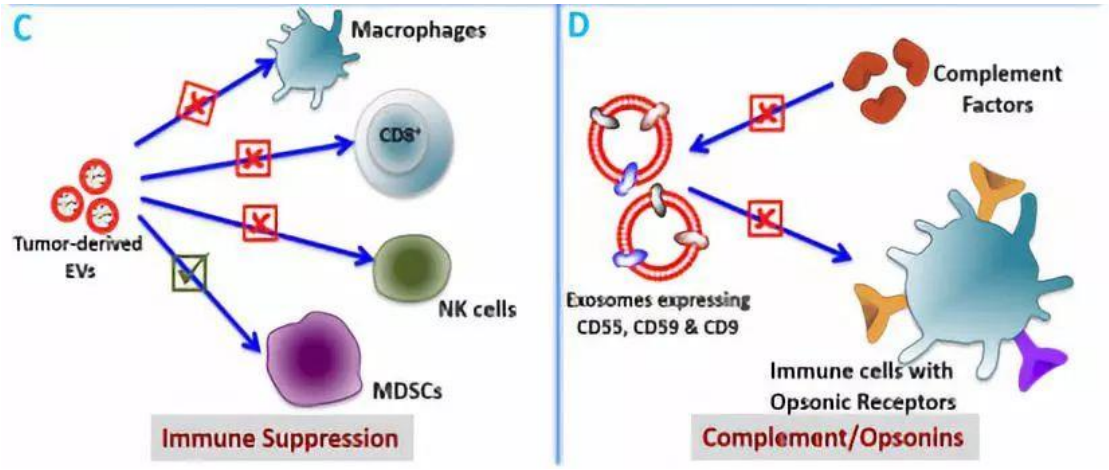
e.分泌APCs来源外泌体与T细胞相互作用。

Panel B:

外泌体能够直接活化巨噬细胞、中性粒细胞、NK细胞和APCs。

Ref: J Control Release. 2015 Dec 10;219:278-294.IF: 7.877.

肿瘤中外泌体调节免疫系统



Panel C:

外泌体还能抑制免疫反应，保护肿瘤细胞不被免疫细胞识别和破坏；

外泌体能够诱导T细胞凋亡，减少NK细胞和巨噬细胞活力。增加骨髓来源抑制细胞（MDSCs，具有显著抑制免疫应答能力）数量。

Panel D:

外泌体通过表达表面分子来逃避免疫识别，从而抑制补体系统的激活。

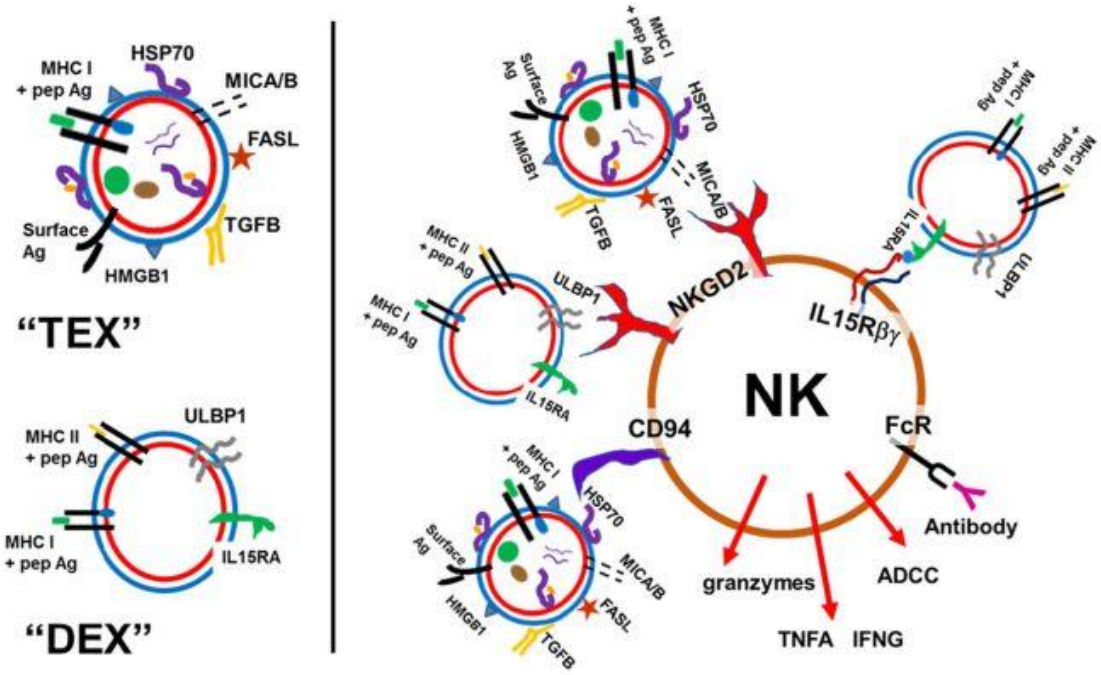
Ref: J Control Release. 2015 Dec 10;219:278-294.IF: 7.877.

外泌体与 NK 细胞相互作用，刺激和抑制

TEX: Tumor cell exosome;

DEX: Dendritic cell exosome;

NK: Natural killer cell.



激活：

A.肿瘤细胞来源外泌体 MICA/B 刺激 NKG2D、HSP70 与 CD94 相互作用；

B.树突状细胞来源外泌体 ULBP1 引发 NKG2D；

C.树突状细胞来源外泌体 IL15RA 传递 IL15 到 NK 细胞 IL15Rβ（和 γ)上。

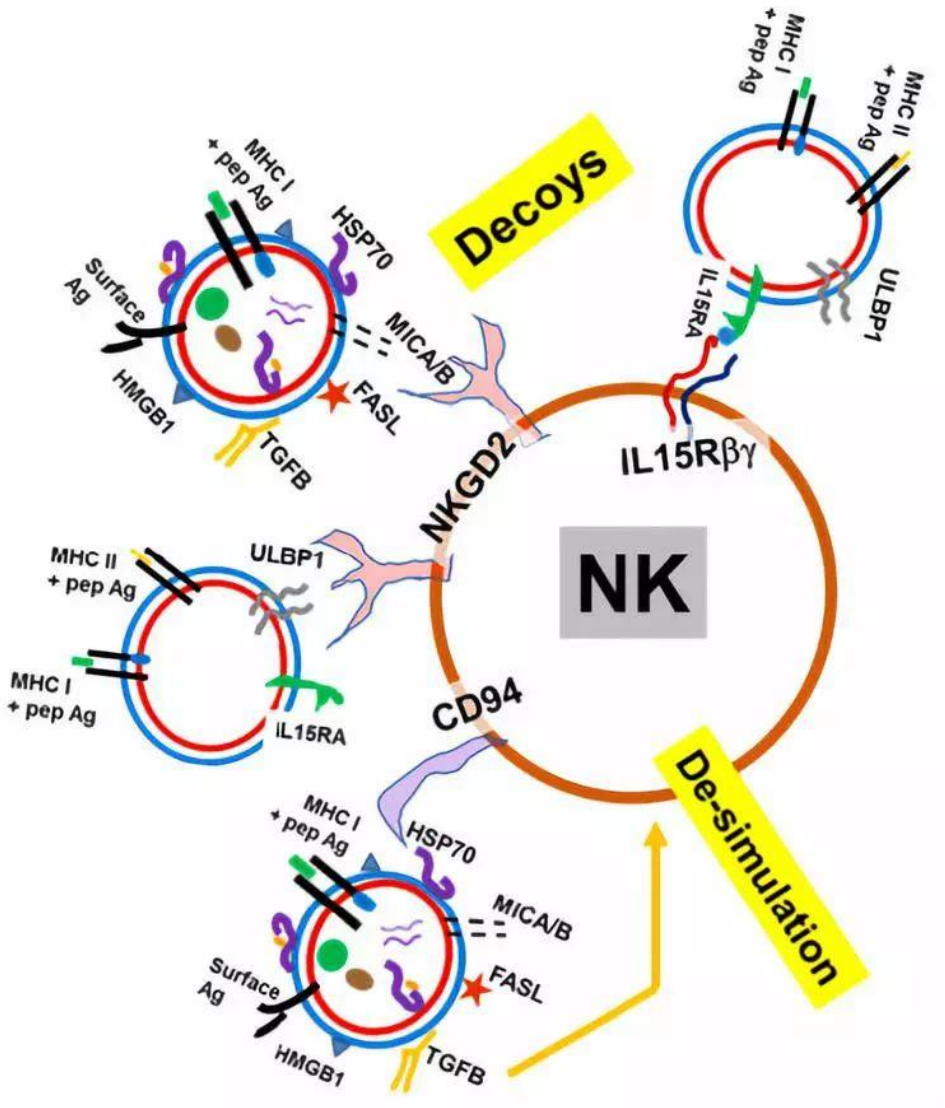
Ref: Semin Immunopathol. 2018 Jun 4. PMID: 29869058. IF: 6.437.

外泌体与 NK 细胞相互作用，刺激和抑制

NKGD2: Activating natural killer group 2 member D;

MIC: MHC class I polypeptide related sequence;

ULBP1: UL16 binding protein 1.



抑制：

A.MICA/B或ULBPs对NKDG2的长期刺激，能够下调NK细胞受体，HSP70与CD94的相互作用也能够起到相同作用（Semin Cancer Biol. 2014 Oct;28:24-30. IF: 10.198, PLoS One. 2011 Feb 25;6(2):e16899. PMID: 21364924）；

B.肿瘤细胞来源外泌体TGFB能够使NK细胞失活，从而导致NK细胞抗肿瘤活性的全面抑制（Haematologica. 2011 Sep;96(9):1302-9. IF: 9.09）。

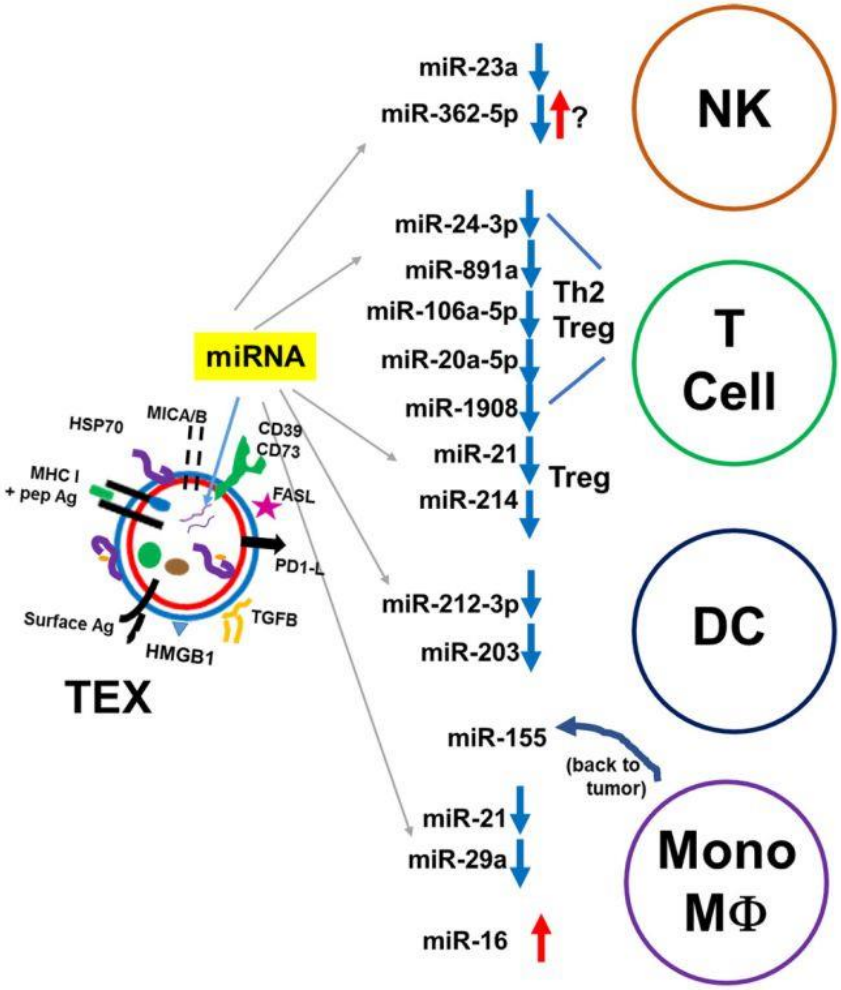
Ref: Semin Immunopathol. 2018 Jun 4. PMID: 29869058. IF: 6.437.

T 细胞和 TEX 诱导免疫抑制

FASL (R): Fas ligand (Receptor);

PDL1: PD1 ligand;

Tregs: Regulatory T cells.



Ref: Semin Immunopathol. 2018 Jun 4. PMID: 29869058. IF: 6.437.

A.外核苷酸酶CD39通过"ATP-ADP-AMP"过程产生腺苷，随后，CD73通过"AMP-腺苷"产生胞外腺苷，最终导致T细胞失活；

B.肿瘤来源外泌体FASL能够通过结合T细胞FASR直接促进T细胞凋亡；

C.肿瘤来源外泌体PD-L1能够去活表达PD-1受体的T细胞；

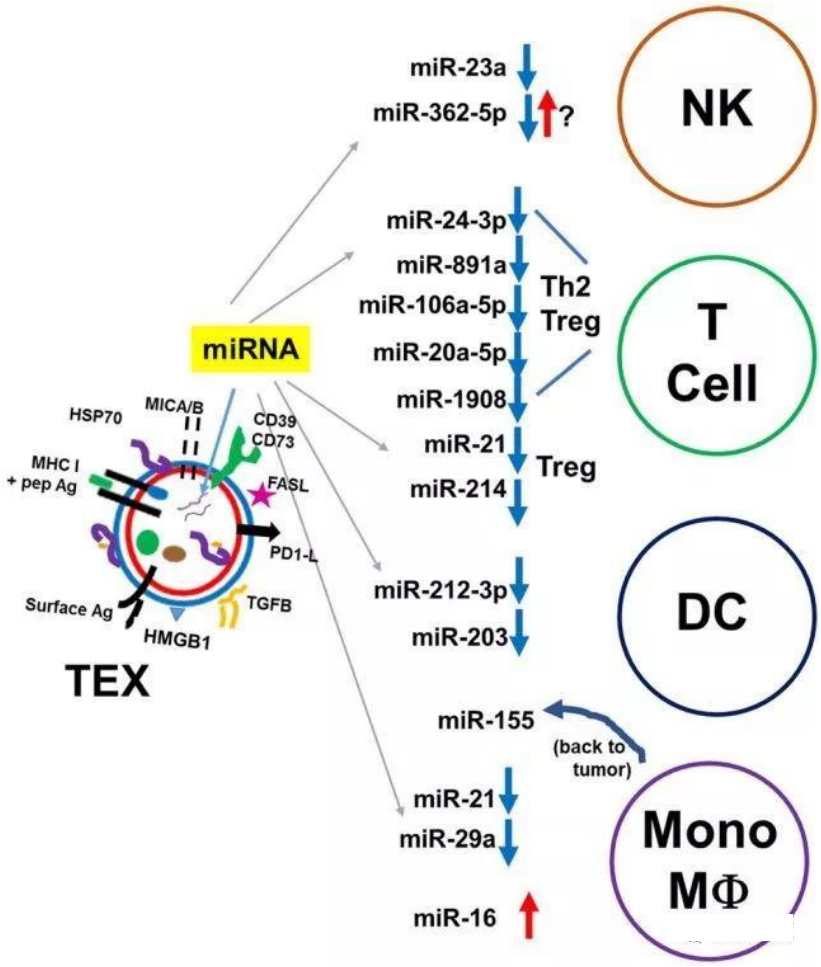
D.肿瘤来源外泌体TGFB能够促进Tregs的形成，通过Tregs有效的调节/抑制能力导致进一步的免疫抑制。

TEX miRNA 和免疫系统

Mono/MΦ: monocytes/macrophage;

DC: dendriticcells;

TERF1: telomericrepeat binding factor 1



TEX-miRNA下调NK细胞、T细胞、DCs和单核细胞/巨噬细胞免疫活性。

值得注意的是，来源于受TEX影响的巨噬细胞miRNA-155，通过外泌体被传递回肿瘤细胞，最终导致肿瘤化疗耐药；

其具体机制为：miR-155靶基因TERF1被下调，TERF1是一种端粒酶抑制剂，端粒酶上调从而促进肿瘤细胞对顺铂的耐药性（Oncol Rep. 2009 Sep;22(3):549-56）。

Ref: Semin Immunopathol. 2018 Jun 4. PMID: 29869058. IF: 6.437.

Exosome Therapies

Investigational Exosome Therapies

Disease	Origin of exosome	Conclusion
Melanoma	TEX (Tumor cell derived exosome)	Exosomes promote metastatic niche at distant sites
	TEX	Exosomes augmented metastatic potential of primary tumors
	TEX	Exosomes accumulate at sentinel lymph nodes for promoting metastatic niche
Mouse breast cancer	TEX	Inhibition of Rab27a inhibited TEX secretion, primary tumor growth and metastatic potential
Cervical Cancer	TEX	Inhibition of Rab27a and b, inhibited exosome production
Mouse colon cancer	TEX	Inhibition of Na^{+}/Ca^{2+} channels and exosome secretion using dimethyl amiloride. Improved anticancer efficacy for cyclophosphamide treatment
Prostate cancer	TEX	Exosomes transferred drug resistance from resistant cells to non-resistant cells
Breast cancer	TEX	Curcumin modified the ubiquintinated protein content of the TEX, inhibiting their immunosuppressive properties
Mouse Plasmacytoma	TEX	Exosomes carrying surface HSP caused more efficient dendritic cell maturation

Disease	Origin of exosome	Conclusion
Leukemia	DEX (Dendritic cell derived exosome)	Exosomes pulsed with tumor specific antigen induced spleen cell proliferation and activated them against tumor cells, inhibiting tumor growth
	TEX	Exosome immunization caused partial tumor growth inhibition
Mouse Mastocytoma	DEX	Exosomes pulsed with acid-eluted peptide immunized mice and caused tumor regression
	TEX	Exosomes carried native tumor specific antigens to dendritic cells for potent T-cell-dependent antitumor effect
Glioma	TEX	Exosomes carried antigen presenting molecules and tumor antigen, capable of causing dendritic cells to activate T lymphocytes against glioma cells
Lymphoma	TEX	Exosomes by heat-shocked tumor cells contained higher number of HSP proteins and were able to induce dendritic cell maturation and potent T cell responses
Melanoma	DEX	Exosomes carried Mart-1 tumor antigen to dendritic cells for specific lymphocyte stimulation

Ref: J Control Release. 2015 Dec 10;219:278-294, IF: 7.877.

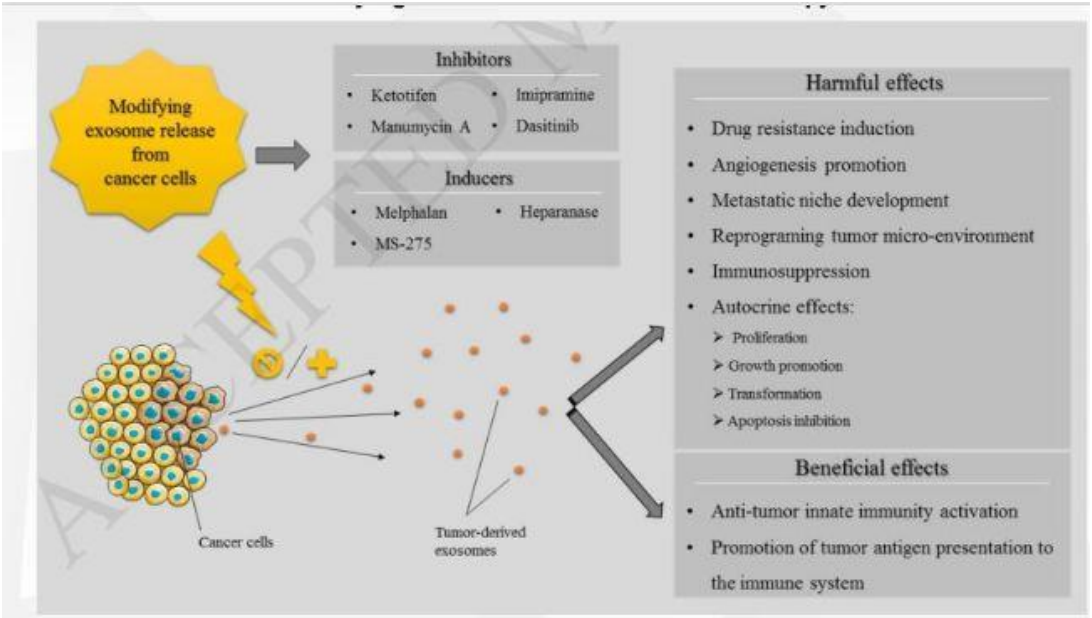
Exosome based clinical trials

Condition	Role	Source	Active ingredient	Trial	Status
Melanoma	Vaccine	DCs	MAGE A3 peptide	Phase I	Completed
NSCLC	Vaccine	DCs	MAGE A3, MAGE A4, MAGE A10, MAGE-3DPO4		
Colorectal	Vaccine	Ascites-derived	GM-CSF		
Malignant Glioma	Vaccine	Tumor-derived	-		
Oral mucositis in Head & Neck chemotherapy	Drug delivery	Grape-derived	Lortab	Phase I	Recruiting
Colon	Drug delivery	Grape-derived	Curcumin		
Pancreatic	Vaccine	-	-		
NSCLC	Vaccine	DCs	-	Phase II	Not known
Type I Diabetes	-	-	-	Phase I	Recruiting by invitation
Parkinson's	-	-	-	Phase I	Recruiting

DCs: Dendritic cells; MAGE: melanoma antigen gene.

Ref: J Control Release. 2015 Dec 10;219:278-294, IF: 7.877.

Modifying exosome release in cancer therapy



TDE: Tumor-derived exosome

Ref: Pharmacol Res. 2018 Aug;134:246-256, IF: 4.897.

Targeting exosomes release from cancer cells

Agent	Target cancer cell(s)	outcome	Suggested mechanism of action
Manumycin A	Castration-resistant prostate cancer cells	Suppression of exosome biogenesis and synthesis	Inhibition of Ras/Raf/MEK/ERK1/2 signaling ERK-dependent inhibition of hnRNP H1
Ketotifen	MCF-7 Hela BT-549	Modulation of exosome release Inhibition of exosome-mediated doxorubicin efflux (↑ drug sensitivity)	Blockade of calcium influx to the cell
Chloramidine	Human prostate cancer (PC3) MCF-7	↓ EMV release	Inhibition of peptidylarginine deiminase (PAD)
Bisindolylmaleimide-1	Human prostate cancer (PC3) MCF-7	↓ EMV release	Acting as a PKC (protein kinase C) inhibitor to prevent externalization of phosphatidylserine (PS)
Imipramine	NM (not mentioned)	↓ MV release	Inhibition of acid sphingomyelinase (aSMase)

Ref: Pharmacol Res. 2018 Aug;134:246-256, IF: 4.897.

EMV: Extracellular Microvesicle

Targeting exosomes release from cancer cells

Agent	Target cancer cell(s)	outcome	Suggested mechanism of action
D-pantethine	NM	↓ MV release	Blockade of PS translocation
Y27632	NM	↓ Apoptosis-induced EMV	Rho A inhibition → GTPase-Rho kinase inhibition → Actin-cytoskeletal changes
Calpeptin	Human prostate cancer (PC3)	NM	Calpain inhibition
Chlorpromazine	Human prostate cancer (PC3) MCF-7	Exclusive inhibition of exosome-sized vesicles	Endocytosis inhibition
MβCD			
Calcium chelators like EGTA	NM	↓ EMV release	Calcium chelation
Dasitinib	Imatinib-resistant K562	↓ exosome release	Inhibition of beclin-1 and Vps34

Targeting exosomes release from cancer cells

Agent	Target cancer cell(s)	outcome	Suggested mechanism of action
Melphalan	Primary human multiple myeloma cells and cell lines: SKO007(J3) and ARK	↑ release of exosome containing NK cell stimulating DAMPs (damage associated molecular patterns)	NM
Dimethyl amiloride	3 mouse models of cancer	Increasing cyclophosphamide therapeutic efficacy via ↑ exosome release	NM
MS-275	Human HepG2 cells	↑ exosome-mediated release of immunostimulatory molecules	NM
PEG-SMR-Clu peptide	MCF-7 MDA-MB-231	↓ exosome release	Mortalin blockade vanished the effects of PEG-SMR-Clu peptide on exosome release
Heparanase	MCF-7 B16-F10	↑ exosome-release	Trimming their heparin sulphate residues

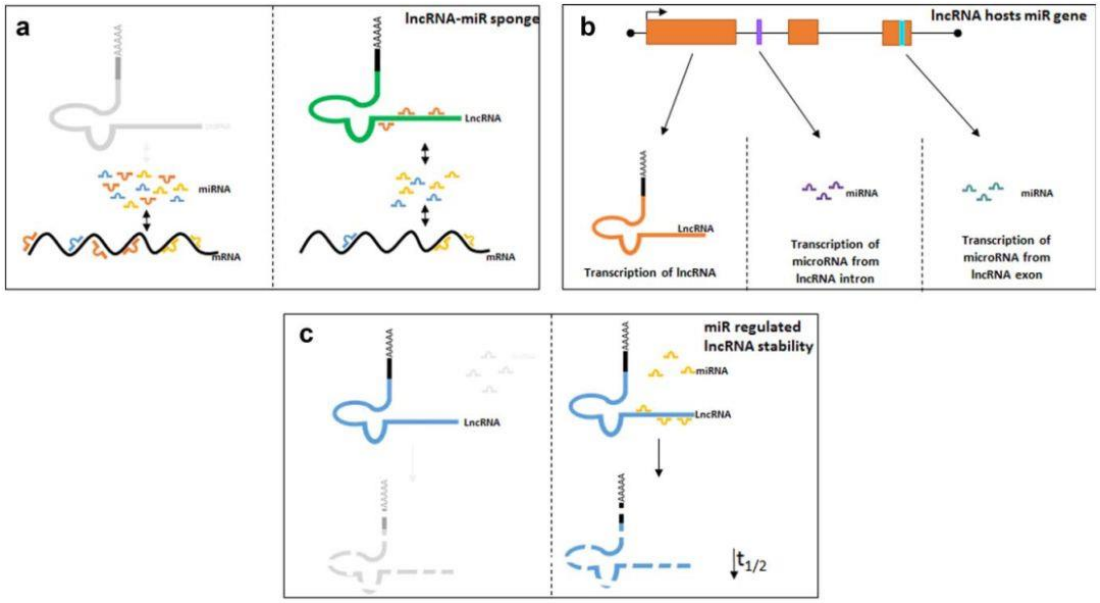
Recommended targets of exosome biogenesis to control TDE release

Cell type	Suggested targeting methods/agents	Possible mechanism(s) of interference with EX biogenesis/release
Breast cancer	Introduction of exogenous exosomes to culture	Negative feedback regulation (Involvement of invadopodia formation)
PC-3	Addition of: DL-threo-1-phenyl-2-decanoylamino-3-morpholino-1-propanol	Inhibition of glucosylceramide synthase
Lung cancer	siRNAs for silencing of YKT6	Inhibition of SNARE-mediated EX release
MDA-MB-231, HKCs, MLE15	siRNAs for silencing of PRAS40	Inhibition of EX release in a ER/Golgi-independent pathway
Hepatocellular carcinoma	Inhibition of Vsp4A upregulation	Modifying cargo sorting of TDE to hinder tumor progression
AsPC-1 and PANC-1	Increasing EX release by GIPC inhibition (Induction of chemo-sensitivity)	NM
Breast cancer or any other cancer cell	Altering EX release and content using EPA/DHA	Changing lipid raft composition and formation

DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; EX: exosome; NM: not mentioned; SNARE: soluble N-ethylene maleimide-sensitive factor attachment protein receptors.

miRNA and lncRNA

lncRNA: miRNA-mediated interactions.



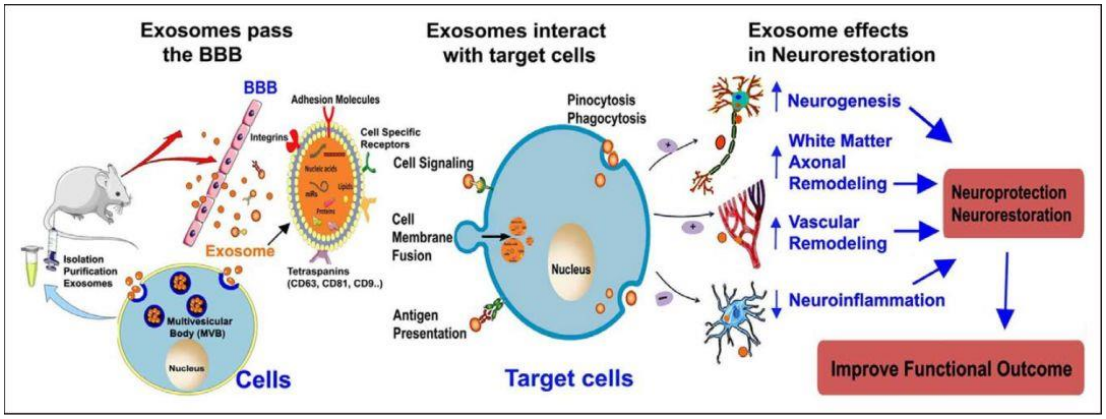
(a) lncRNA-miRNA sponge: binds and sequesters miRNA away from their site of action, thus reducing their function within the cell.

(b) lncRNA generating miRNA. lncRNA may host miRNA both within their exons and introns.

(c) Some lncRNA are degraded by miRNA.

Ref: Clin Pharmacol Ther. 2016 May;99(5):494-501, IF: 6.544.

Therapeutic effects of exosome in stroke



BBB: blood-brain barrier;

Intravenous injection of exosomes can pass the BBB and are taken up by brain cells;

Exosomes interact with target cells and transfer their cargo by: i) the endocytosis route, ii) fusion with plasma membrane, iii) ligand–receptor interactions;

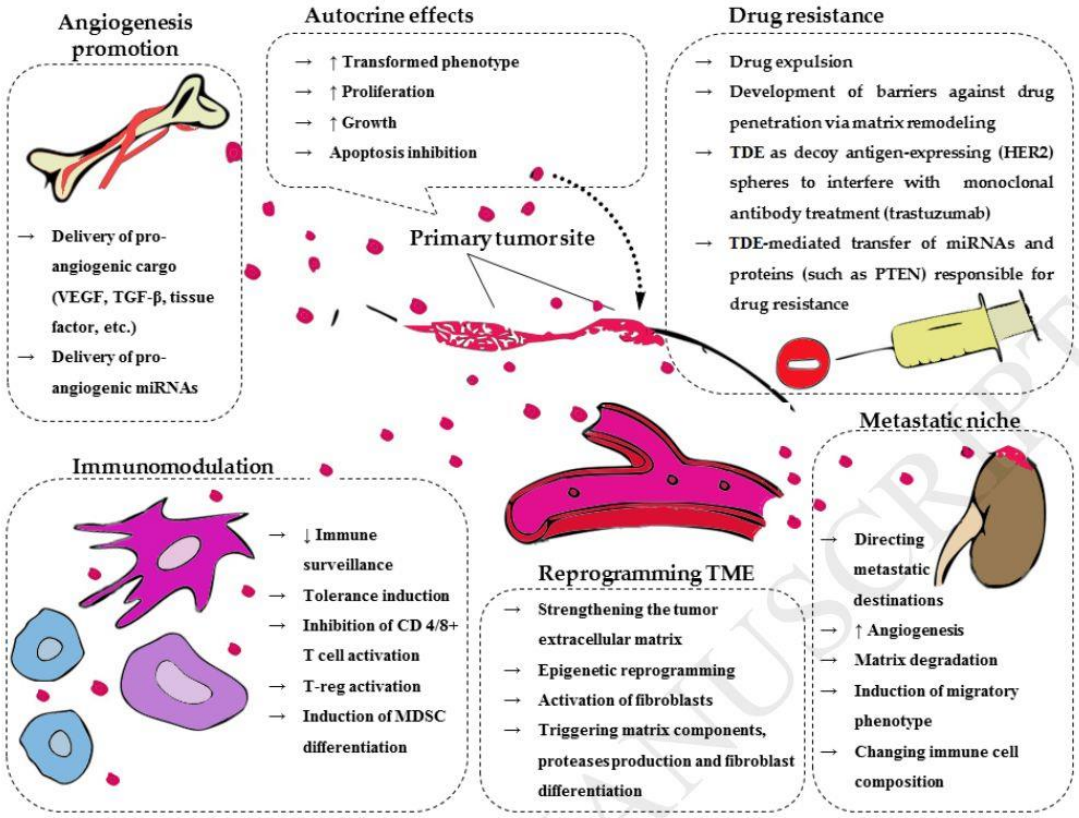
Exosomes induce neurogenesis and white matter/axonal and vascular remodeling, as well as inhibit neuroinflammation.

Ref: Stroke. 2018 May;49(5):1083-1090. IF: 6.239.

The function of MSC-derived exosomes

Source of exosomes	Function	Target/pathway
Human bone marrow-derived MSCs	↑Breast cancer growth in vivo	miRNA-21 and 34a
Mouse bone marrow-derived MSCs	↓Suppress angiogenesis in vitro and in vivo	miRNA-16,VEGF
Human bone marrow-derived MSCs	↑Promote tumor growth in vivo	VEGF, ERK1/2
Mesenchymal stromal cell	↑Conferred temozolomide chemosensitivity to tumor cells in vitro	anti-miRNA-9
Mesenchymal stromal cell exosomes	↓Reduced intracranial tumor volume in vivo	miRNA-146b
Multiple myeloma-derived MSCs	↑MM cells growth in vitro; ↑Tumor growth in vivo; ↑BM homing	MM BM-MSC-derived exosomes
Human umbilical cord Wharton's jelly MSC	↓Significantly tumor size; ↑Apoptosis	hWJMSC-Evs + hWJMSCs
Human adult liver stem cell	↓Significantly tumor size; ↑Apoptosis	HLSC-derived exosomes
BM MSC	↓Proliferation; ↓Tumor formation	BM-MSC-derived Exosome-treated cells
Glioma Associated human MSC	↑increase the tumorigenicity of glioma stem-like cells; ↑enhance the aggressiveness of glioblastoma	miRNA-1587
MSC	↓induce drug resistance in gastric cancer cells	CaM-Ks/Raf/MEK/ERK
Murine or human marrow MSC	↓reverse radiation injury to murine bone marrow in vivo and in vitro; ↓apoptosis	FDC-P1

Multifaceted effects of TDE on different body compartments in health and disease



Pharmacol Res. 2018 Aug;134:246-256, IF: 4.897.