

EXOSOMES: NEW TECHNOLOGY FOR NEW CANCER HOPE

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PUTTING EXOSOMES IN HISTORICAL PERSPECTIVE

- Since ancient times, healers tried to cure cancer
- Mid-to-late 19th century – surgery became predominant
- Early-mid 20th century – radiation therapy added to armamentarium
- Late 20th century – exosomes identified as cellular “trash bags”
- 21st century breakthrough – harness intercellular communication resources
- Virtually every cell in the body produces exosomes

EXOSOMES ARE
CELLULAR
PRODUCTS
THAT ACT AS
TELEGRAMS

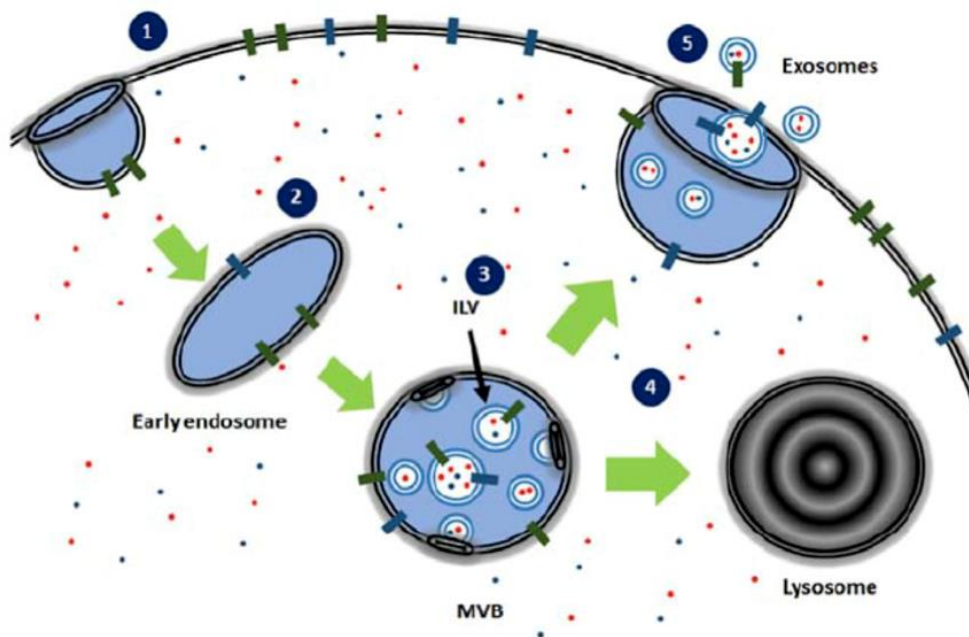


WESTERN UNION GENERATES A TELEGRAM

- Efficient compact communication
- Inbound signals translated into words on paper
- Packaging – paste verbal units on paper (cargo) and put in envelope
- Delivered to locations near and far
- Recipient is changed by good or bad news
- This is basically what exosomes do in the body

CELLS GENERATE EXOSOMES

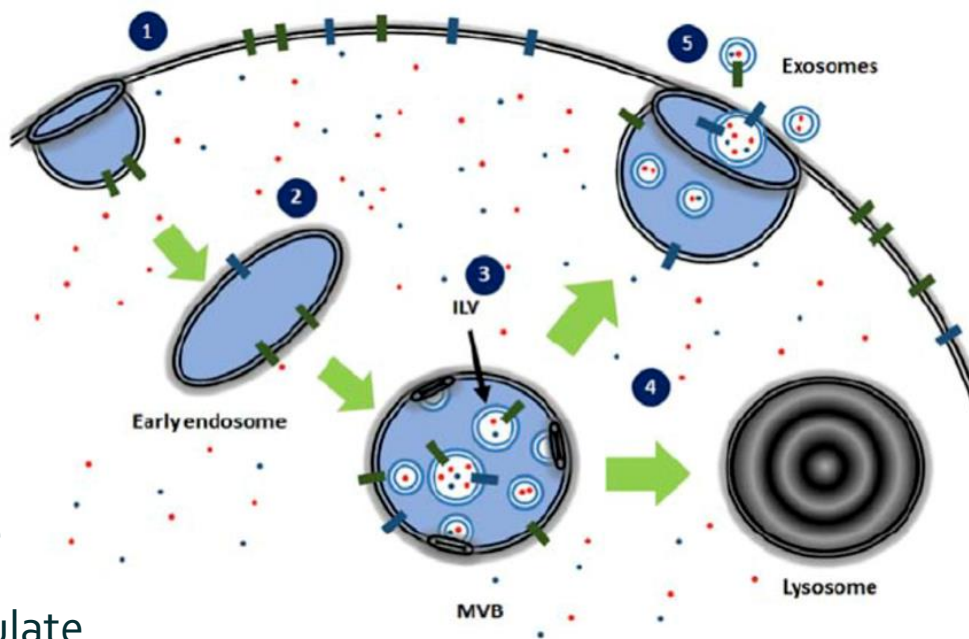
- Incoming “signal” accepted by cell receptor on membrane
- Triggers invagination
- Invagination causes inward budding of plasma
- Bud forms endocytic vesicle (**early endosome**)



Source: https://www.researchgate.net/publication/287971352_The_role_of_exosomes_in_tumor_progression_and_metastasis_Review/figures?lo=1 (permission requested)

PACKAGING IT

- Early endosomes bud inward to form nano-sized **intraluminal vesicles (ILVs)**
- ILVs contain cargo (bioactive molecules including mRNA, microRNA, genomic DNA, etc.)
- Now called a **late endosome** or **multi-vesicular body (MVB)**
- MVB fuses with cell's membrane and secreted into extracellular space
- ILVs (now called **exosomes**) will circulate throughout the body in fluids



SIMILAR TO TELEGRAMS

- Efficient compact communication
- Inbound biochemical messages translated into bioactive molecules
- Packaging – molecules (cargo) put in plasma membrane
- Delivered to cells near and far via bodily fluids
- Recipient cells changed by helpful or harmful exosomes

EXOSOME PROPERTIES

- Released by virtually cell type including cancer
- Nanoparticles 30-100 nanometers (nm)
- Roughly 1000x smaller than parent cell
- Surface proteins characterize and distinguish them from other entitiesⁱ
- Communicate with cells everywhere throughout the body

EXTRACELLULAR PATHWAYS = ALL BODILY FLUIDS

- Blood
- Urine
- Amniotic fluid
- Saliva
- Breast milk
- Cerebrospinal fluid
- Able to cross the blood brain barrier

ADDITIONAL FEATURES

- Contain particular membrane transport and fusion proteins per type of parent cell
- Engage receptors of recipient cells that “recognize” themⁱⁱ
- Transfer cargo into preferential recipient cells
- Potential to alter recipient cell activity

EXOSOME CARGO

- Content depends on and reflects the cell of origin
- Enriched in endosomal-derived components
- Bioactive molecules either on their surface or within their lumen
 - ✓ *Proteins*
 - ✓ *Lipids*
 - ✓ *Messenger RNAs*
 - ✓ *Micro RNAs*
 - ✓ *Genomic DNA*

RESEARCH POINTS TO NUMEROUS EXOSOME PROCESSES

Most widely studies subtype of extracellular vesicles in health-related research that points to several important processes in which they functionⁱⁱⁱ

- Organism development (helpful)
- Epigenetic regulation (helpful)
- Wound healing (helpful)
- Immuno-regulation (helpful)
- Tumorigenesis (harmful)
- Tumor progression (harmful)

CANCER CELL EXOSOMES: HARMFUL PROCESSES

- Till recently, cancer cell communication linked with communication/adherent junctions and cytokine interactions
- Now known that cancer cell exosomes can also mediate cell communication with neighbor and/or distant cells.^{iv}
- Contain enzymes and other cell adhesion-related molecules to help tumor progression^v
- Transfer cancer cell genetic material into a healthy recipient cell
- Recipient cell activity altered » cancer cell like the exosome's parent cell
- Enlarges our understanding of metastasis processes
- Holds potential for new approaches to treating cancer

POTENTIAL EXOSOME USES IN CLINICAL PRACTICE

- Exosome biomarkers useful for early diagnosis (e.g. PCa urine test)
- Therapeutic tissue repair and regeneration
- Deliver growth factors to stimulate neurogenesis and angiogenesis
- Promote anti-inflammatory action
- Promising vehicle for strategic drug delivery, especially across the blood brain barrier
- Target neurodegenerative diseases,
- Target brain cancer as well as other cancers
- Promising vehicle to be loaded with antibodies or RNA to manipulate gene expression within cancer cells to disable them
- Potential to control and prevent disease processes

ADVANTAGES OF EXOSOMES

- Avoids most problems associated with stem cell-based therapies
 - Expensive to produce
 - Hard to generate a significant amount
 - Source can be controversial
- Offers the therapeutic efficacy of stem cells
- Can be sterilized by filtration
- Longer shelf life than stem cells
- Thanks to nano size, they circulate easily to reach target sites/conditions
- Cross the blood brain barrier

ADDITIONAL ADVANTAGES

- Long-term use does not trigger toxicity
- Highly stable thanks to membrane composition
- Biocompatible and biodegradable
- Can be produced in vitro
- Can be engineered to target cancer cells more efficiently

REGENERATIVE EXOSOME USE (ANIMAL MODELS)

Promising alternative to stem-cell therapies

- Accelerate hepatic regeneration in hepatectomized rats^{vi}
- Preserve/support cardiac function in myocardial animals^{vii}
- Ischemic wound healing in rats^{ix} and mice^{ix}
- Ameliorate renal injury, prevent fibrosis, preserve remnant renal function in mice^x

Evidence of exosome-induced regeneration in vivo supports potential for accelerated healing following surgery, radiotherapy, ablation or other cancer treatments.

EXOSOMES AND POTENTIAL APPLICATION TO FOCAL THERAPY FOR PROSTATE TUMORS

- My interest began with the therapeutic use of platelet-rich plasma (PRP)
 - Platelets - fragments in blood, assist with coagulation and tissue repair
 - PRP used in orthopedics (injury recovery, arthritis treatment, bone repair, etc.)
 - Prepared from a patient's own blood
- Platelets Debate: true cells or not?
 - No nucleus or genes, but have many cell properties
 - They produce exosomes
- In certain cases, I administer PRP after FLA to support erectile function recovery.^{xi}

PRP MOTIVATED ME TO LOOK MORE DEEPLY AT POSSIBLE EXOSOME USE AFTER FLA

- Support regeneration of healthy tissues and nerves outside ablation zone
- Promote anti-inflammatory activity
- Potentially one day load exosomes with therapeutic agents to target microscopic cancer outside ablation zone or even more widely in the body (drugs or genetic manipulation) to reduce recurrence and metastasis rates

CHALLENGES AHEAD: EXOSOME THERAPY IS NOT YET READY FOR PRIME TIME

Producing exosomes

- How to produce clinical-grade exosomes in quantity
- Will isolation or cargo-loading methods impact durability/potency of engineered exosomes?
- More understanding needed regarding circulation and distribution
- Safety and purity – no inadvertent administration of cancer cell-derived exosomes

PLATELET-DERIVED EXOSOMES TO OVERCOME SOME PRODUCTION CHALLENGES?

- Easily obtained and less expensive than harvesting from stem cells or progenitor cells
- Able to be released locally into the body
- Travel easily through the body
- Low immunogenicity
- Natural participation in modulating signal transduction

CONCLUSION

- Exosomes are compatible with and support existing cancer treatments
 - ✓ Facilitate recovery
 - ✓ Nerve/healthy tissue regeneration
 - ✓ Delivery of chemotherapeutic drugs, antibodies, and RNA/genetics
- They already perform such functions in the body
- In cancer treatment and elsewhere, harnessing exosomes may be the next revolution in medicine

SPERLING

PROSTATE CENTER

THANK YOU.

File: F.L.Wright
Folder: ~~General Correspondence~~
1206

DOMESTIC SERVICE	
Check the class of service desired; otherwise this message will be sent as a full rate telegram	
FULL RATE TELEGRAM	SERIAL
DAY LETTER	NIGHT LETTER

WESTERN UNION

W. P. MARSHALL, PRESIDENT

INTERNATIONAL SERVICE	
Check the class of service desired; otherwise this message will be sent at the full rate	
FULL RATE	LETTER TELEGRAM
VICTORY LETTER	SHIP RADIOGRAM

NO. WDS.-CL. OF SVC.	PD. OR COLL.	CASH NO.	CHARGE TO THE ACCOUNT OF	TIME FILED
			THE SOLOMON R. GUGGENHEIM FOUNDATION	2:55

Send the following message, subject to the terms on back hereof, which are hereby agreed to.

120 Broadway, New York, N.Y.
December 14, 1953

Mr. Frank Lloyd Wright
Taliesin West
Phoenix, Arizona

MANY THANKS YOUR INVITATION WHICH I HAVE ON MY RETURN WRITING AFFECTIONATE
REGARDS.

HARRY

HFG:mks

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- ⁱⁱ [Bastos N, Ruivo CF, da Silva S, Melo SA](#). Exosomes in cancer: Use them or target them? [Semin Cell Dev Biol](#). 2018 Jun;78:13-21.
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- ^{iv} [Bastos N, Ruivo CF, da Silva S, Melo SA](#). Exosomes in cancer: Use them or target them? [Semin Cell Dev Biol](#). 2018 Jun;78:13-21.
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