

# The role of exosomes in the metastatic cascade and the pre-metastatic niche formation

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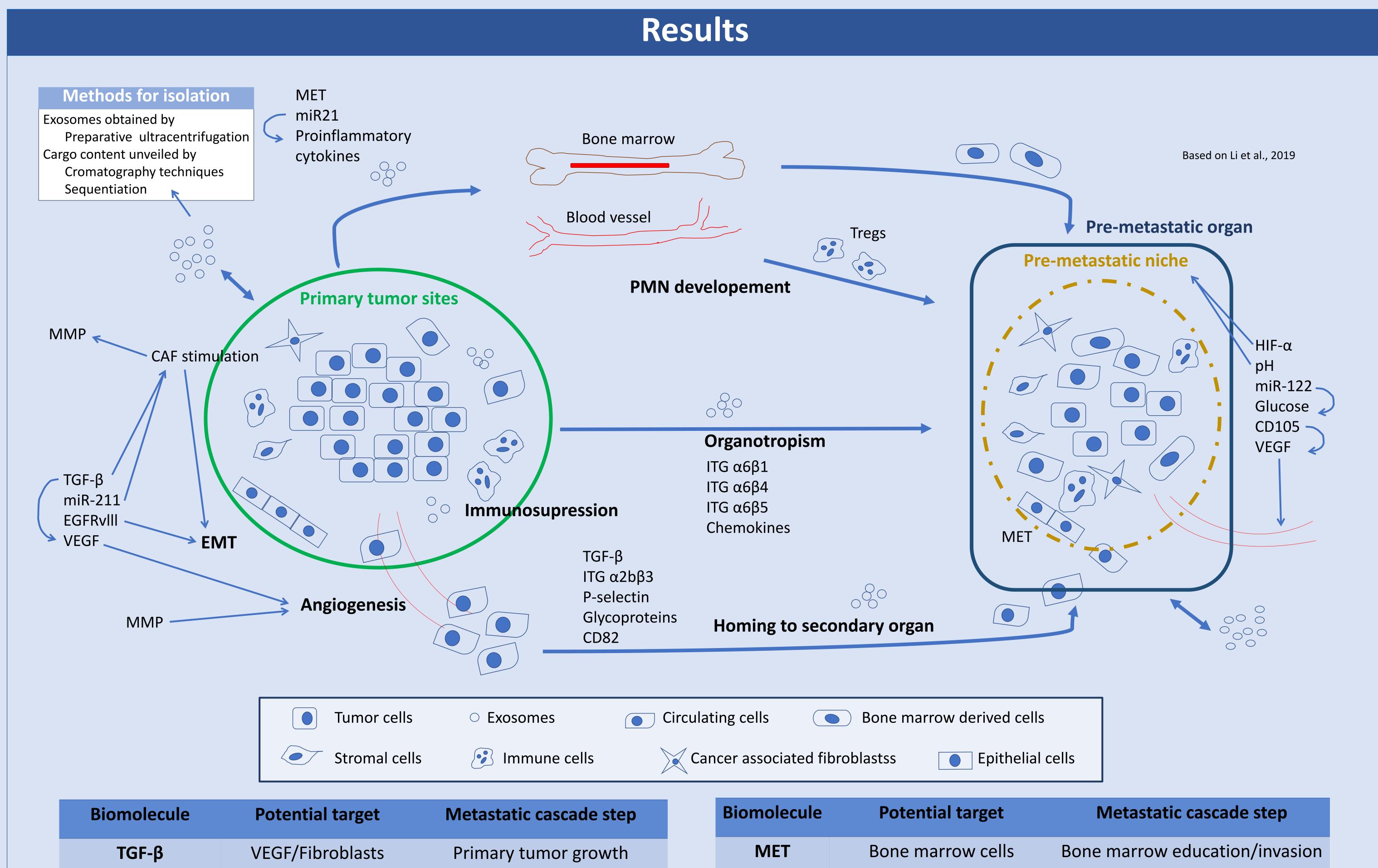
# Background

- ➤ Cancer is one the most incident diseases in our society that contributes to 9 million fatalities a year in the world, being metastasis the key stage that accounts for 90% of all cancer-associated deaths.
- Many efforts have been put in finding the mechanisms and processes underlying cancer metastasis to design new approaches in diagnosis and therapies.
- > Tumor derived exosomes have been described as important regulatory components in every single step of the metastatic cascade.
- > Specific biomolecules contained within these exosomes modify local environments and are believed to ease the pre-metastatic niche formation.
- Current therapies are already studying them as potential biomarkers for a better diagnosis, but also as effective drug delivers and targets.

### Goals

This project aims to review and clarify:

- The specific role these exosomes play in each step of the complex metastatic cascade.
- The importance of the pre-metastatic niche formation in cancer metastasis and the underlying drivers involved on it.
- > The complex interaction between tumor derived exosomes and the particular environment at metastatic sites.
- ➤ New tumor derived exosomes-based therapies that are currently being studied and analyze them as possible and feasible future alternatives in cancer's treatment.



Biomolecule	Potential target	Metastatic cascade step
TGF-β	VEGF/Fibroblasts	Primary tumor growth
EGFRvIII	Epithelial cells	EMT
VEGF	Endothelium	Angiogenesis
miR-21	Innate immune cells	Immune evasion/progression

Biomolecule	Potential target	Metastatic cascade step
MET	Bone marrow cells	Bone marrow education/invasion
ITG	Organ-specific cells	Organotropism
CD82	Epithelial cells	Homing to tissue/MET
HIF-α mi-R122	Stromal cells at PMN	PMN formation

### Conclusions

- > Tumor derived exosomes are involved in every step of the metastatic cascade: primary tumor formation, dispersion and colonization into secondary tissues.
- The development of the pre-metastatic niche is closely linked with the content of these exosomes, which widely vary among nucleic acids, proteins or lipids.
- Tumor derived exosomes-based therapies are being studied for their potential as biomarkers, drug delivers and targets, with promising results that need further research for an effective clinical application.

## References

- 1. Fabbri, M., Paone, A., Calore, F., Galli, R., Gaudio, E., and Santhanam, R. (2012). MicroRNAs bind to Toll-like receptors to
- induce prometastatic in flammatory response, *PNAS*, 109 (31), 110-116. https://doi.org/10.1073/pnas.1209414109

  2. Hoshino, A., Costa-silva, B., Shen, T., Rodrigues, G., Hashimoto, A., Mark, M. T., ... Wexler, L. H. (2015). Tumour exosome integrins determine organotropic metastasis. *Nature*, 527 (7578), 329–335. https://doi.org/10.1038/nature15756
- 3. Li, K, Chen, Y., Li, A., Tan, C., and Liu, X. (2019). Exosomes play roles in sequential processes of tumor metastasis.
- International Journal of Cancer, 144, 1486–1495. https://doi.org/10.1002/ijc.31774

  4. Lyden, D. (2016). Perspective Extracellular Vesicles in Cancer: Cell-to-Cell Mediators of Metastasis. Cell, 30, 836-848.
- https://doi.org/10.1016/j.ccell.2016.10.009
  5. Peinado, H., Alec, M., Lavotshkin, S., Matei, I., Costa-silva, B., G., ... Kang, Y. (2016). Melanoma exosomes educate bone marrow progenitor cells toward a pro-metastatic phenotype through MET. *Seminars in Cancer Biology*. 18 (6), 139-146.
- https://doi.org/10.1038/nm.2753
  6. Zhou, W., Fong, M. Y., Min, Y., Somlo, G., Liu, L., ... Boldin, M. P. (2014). Cancer-Secreted miR-105 Destroys Vascular Endothelial Barriers to Promote Metastasis. *Cancer Cell, 25* (4), 501–515. https://doi.org/10.1016/j.ccr.2014.03.007