Dark side of Exosome

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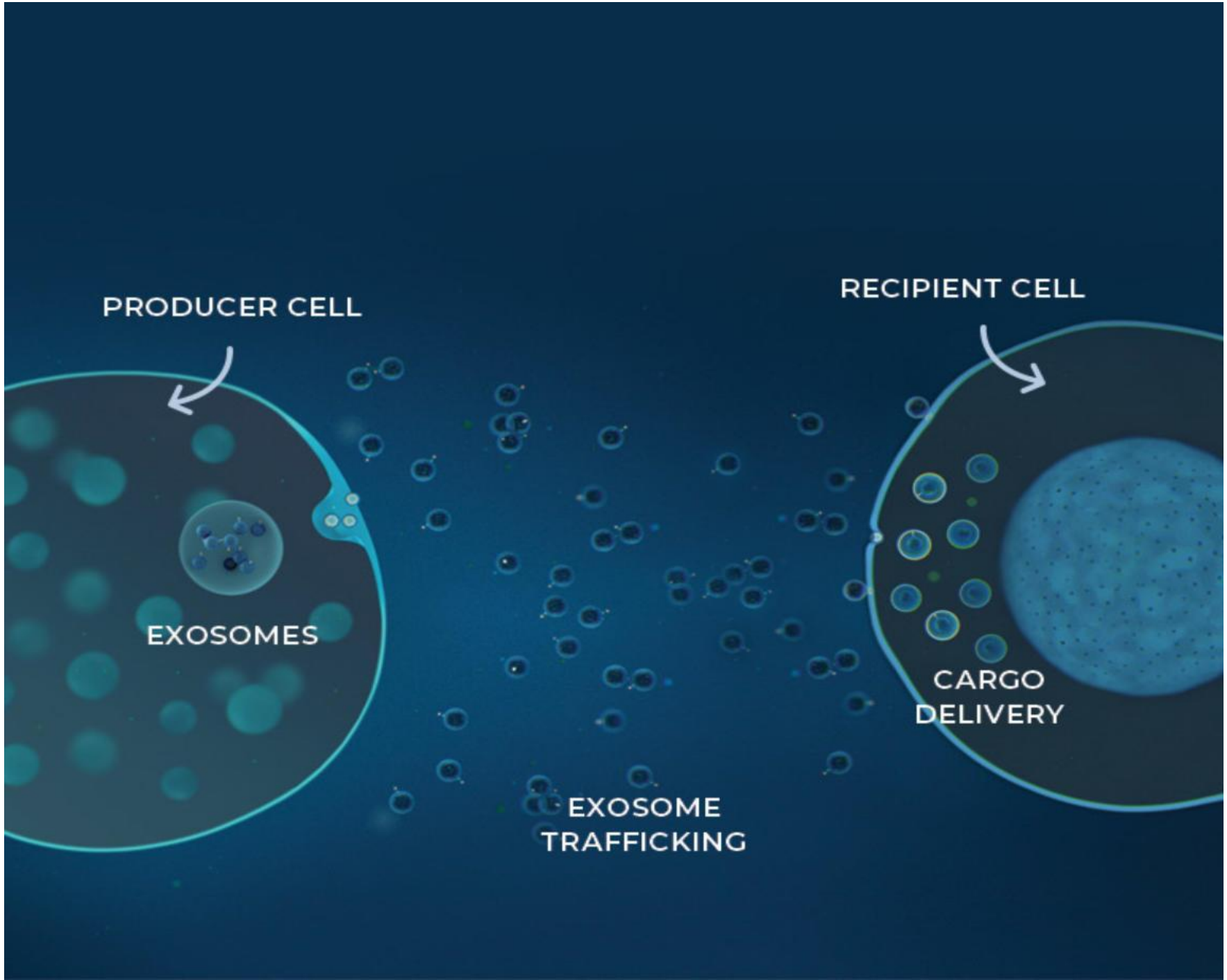
Fellowship of surgical oncology

SBMU

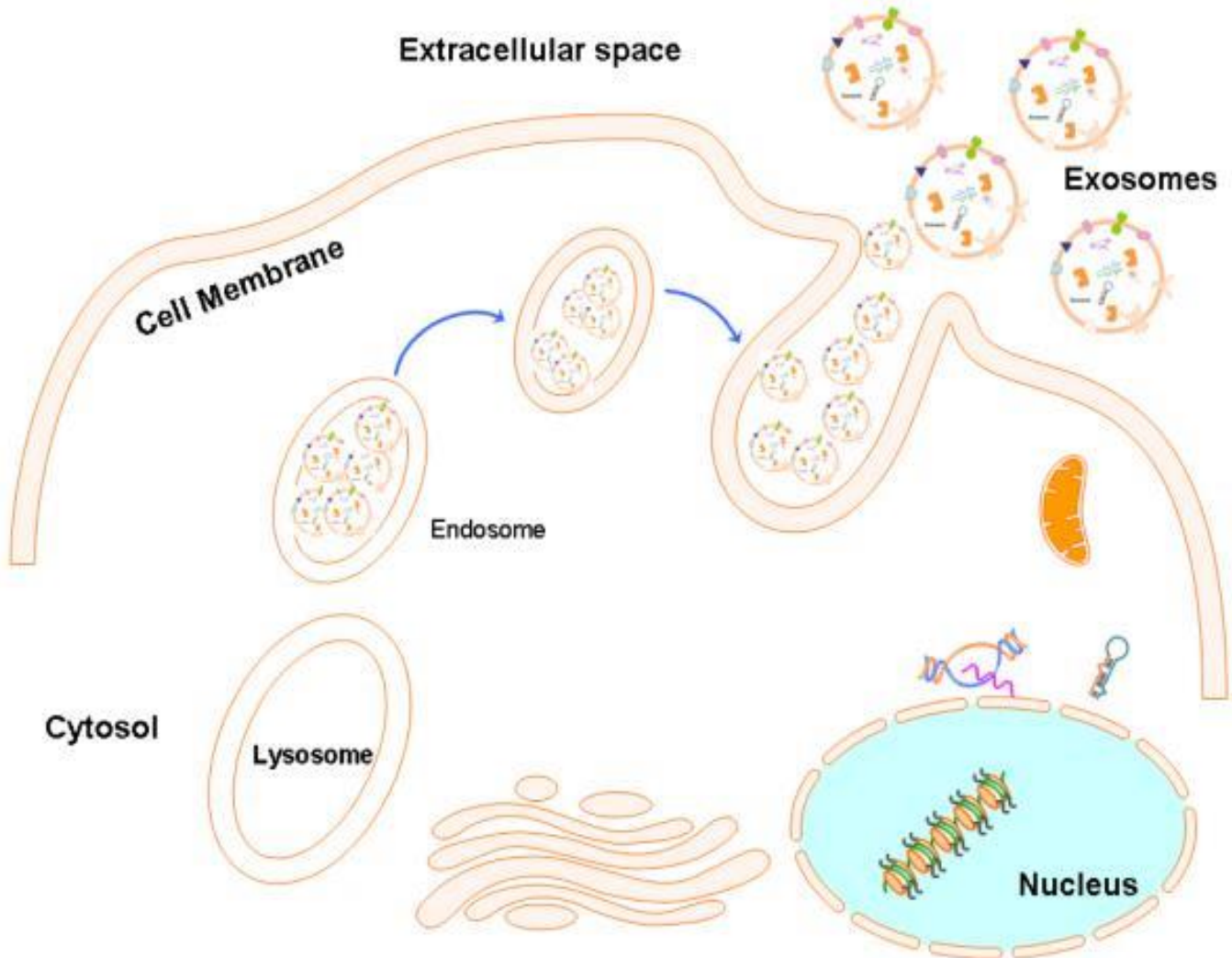

PRODUCER CELL
RECIPIENT CELL
EXOSOMES
CARGO
DELIVERY
EXOSOME
TRAFFICKING

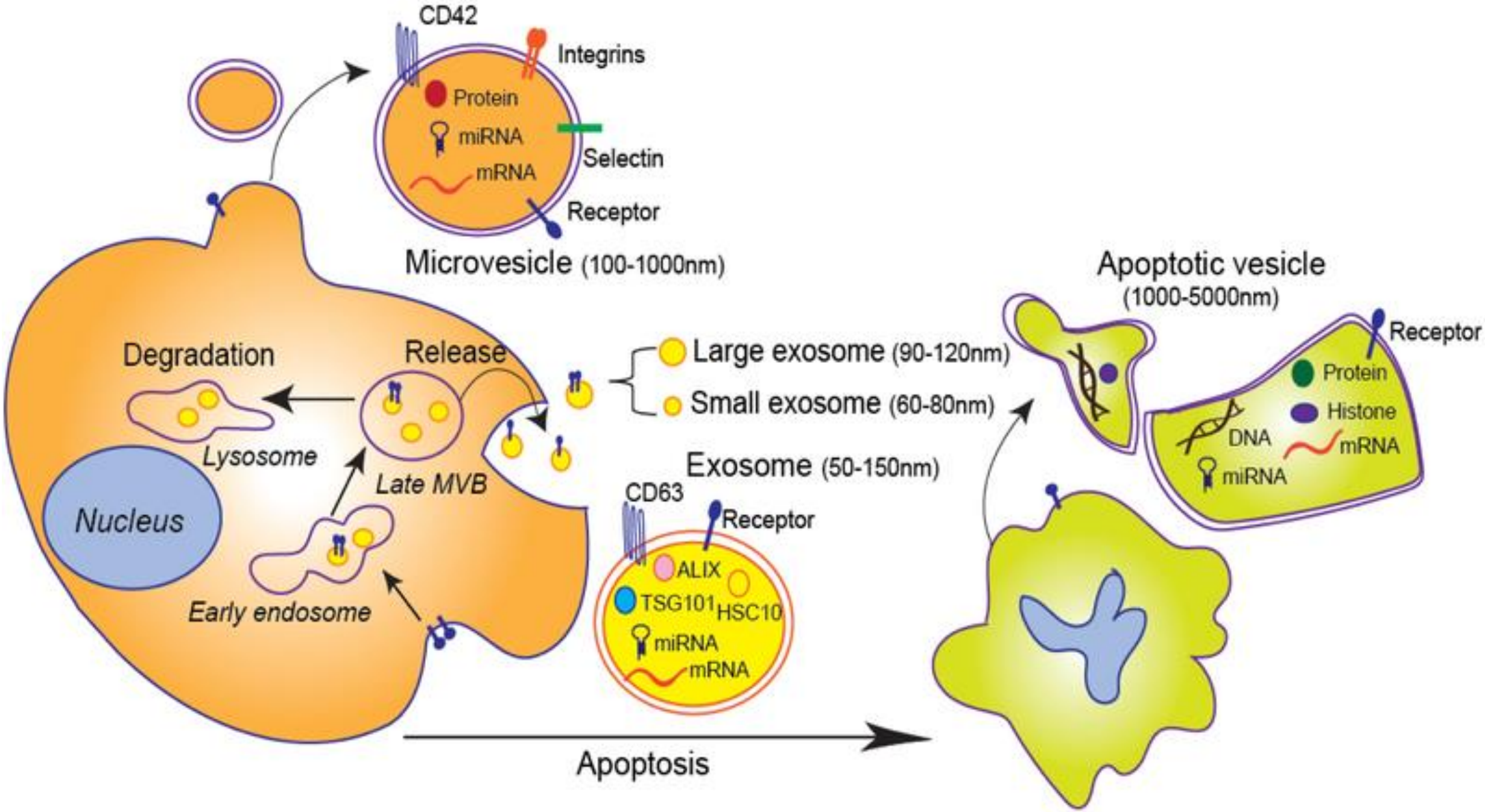
- **The "next cell hypothesis" supports the notion that exosomes constitute communication vehicles between neighboring cells.**

- **Exosomes are nano-sized (30–150 nm) extracellular vesicles released virtually by all types of cells and their content robustly mirrors that of the parental cells.**

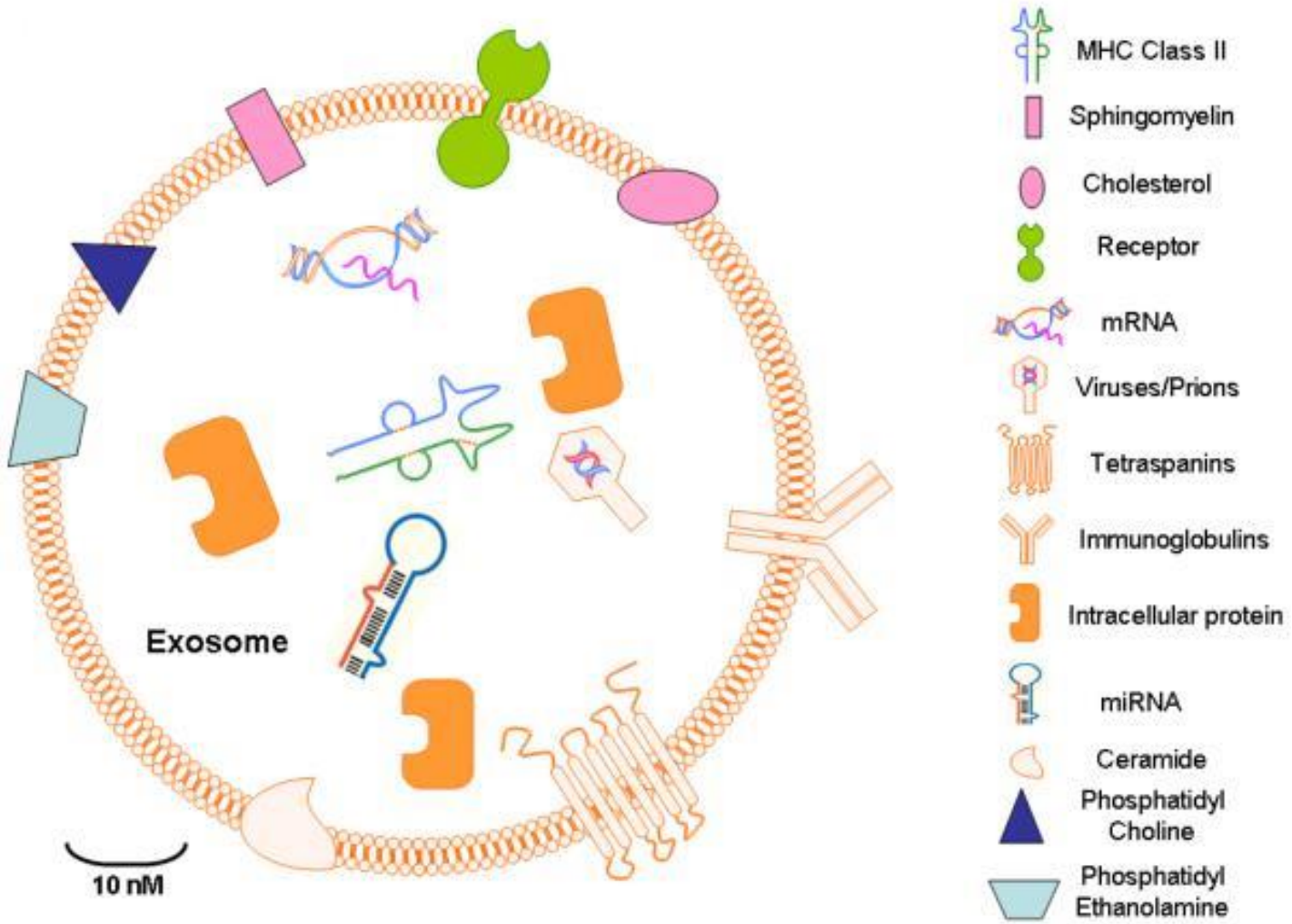
- **Body fluid exosome:**
- **Urine**
- **Breast milk**
- **CSF**
- **Bile**
- **Blood**

Exosomes

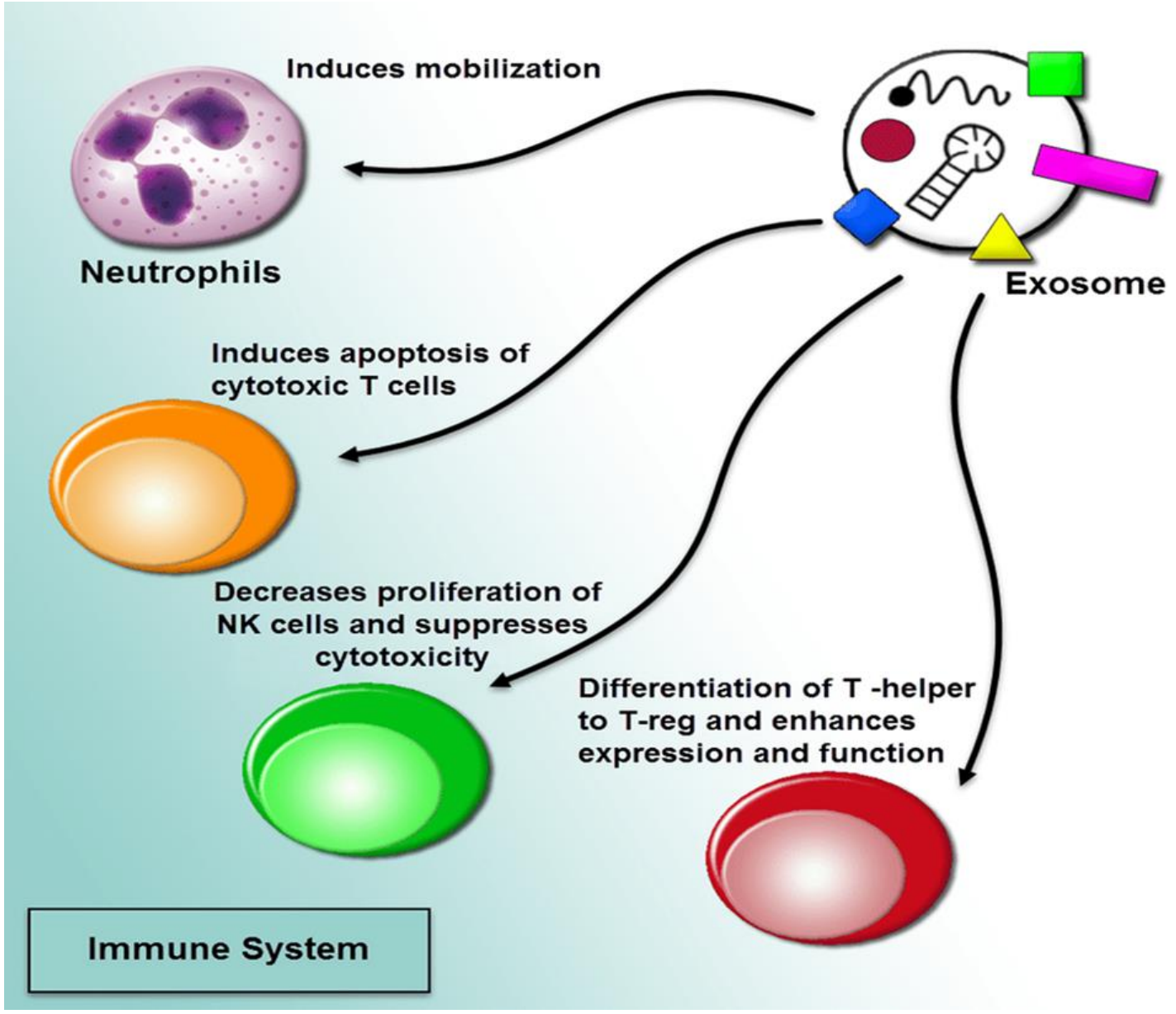

Extracellular space
Exosomes
Cell Membrane
Endosome
Cytosol
Lysosome
Nucleus

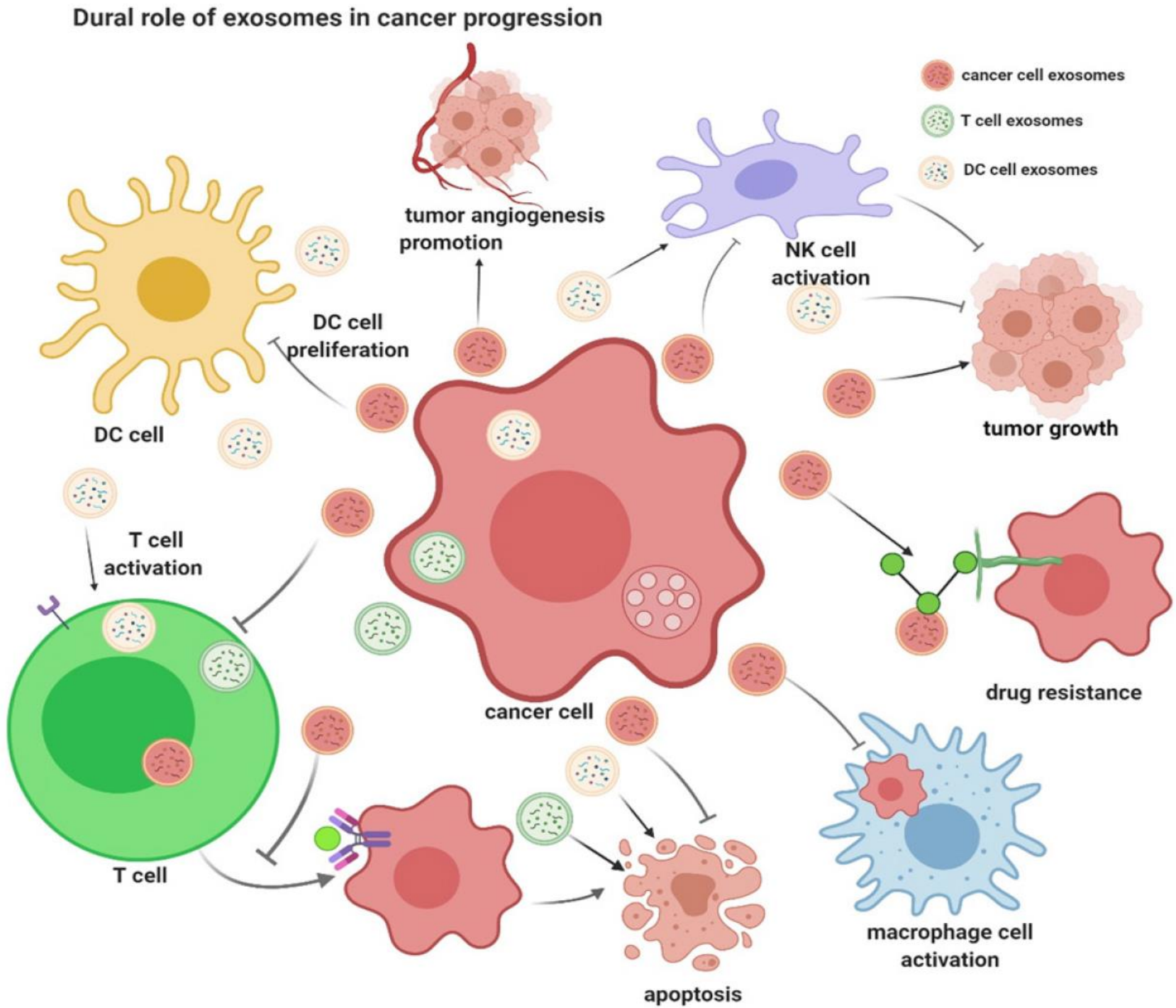

CD42
Integrins
Protein
miRNA
mRNA
Selectin
Receptor
Microvesicle (100-1000nm)
Degradation
Release
Lysosome
Late MVB
Nucleus
Early endosome
Large exosome (90-120nm)
Small exosome (60-80nm)
Exosome (50-150nm)
CD63
Receptor
ALIX
TSG101
HSC10
miRNA
mRNA
Apoptosis
Apoptotic vesicle
(1000-5000nm)
Receptor
Protein
Histone
DNA
mRNA
miRNA

Exosome Structure

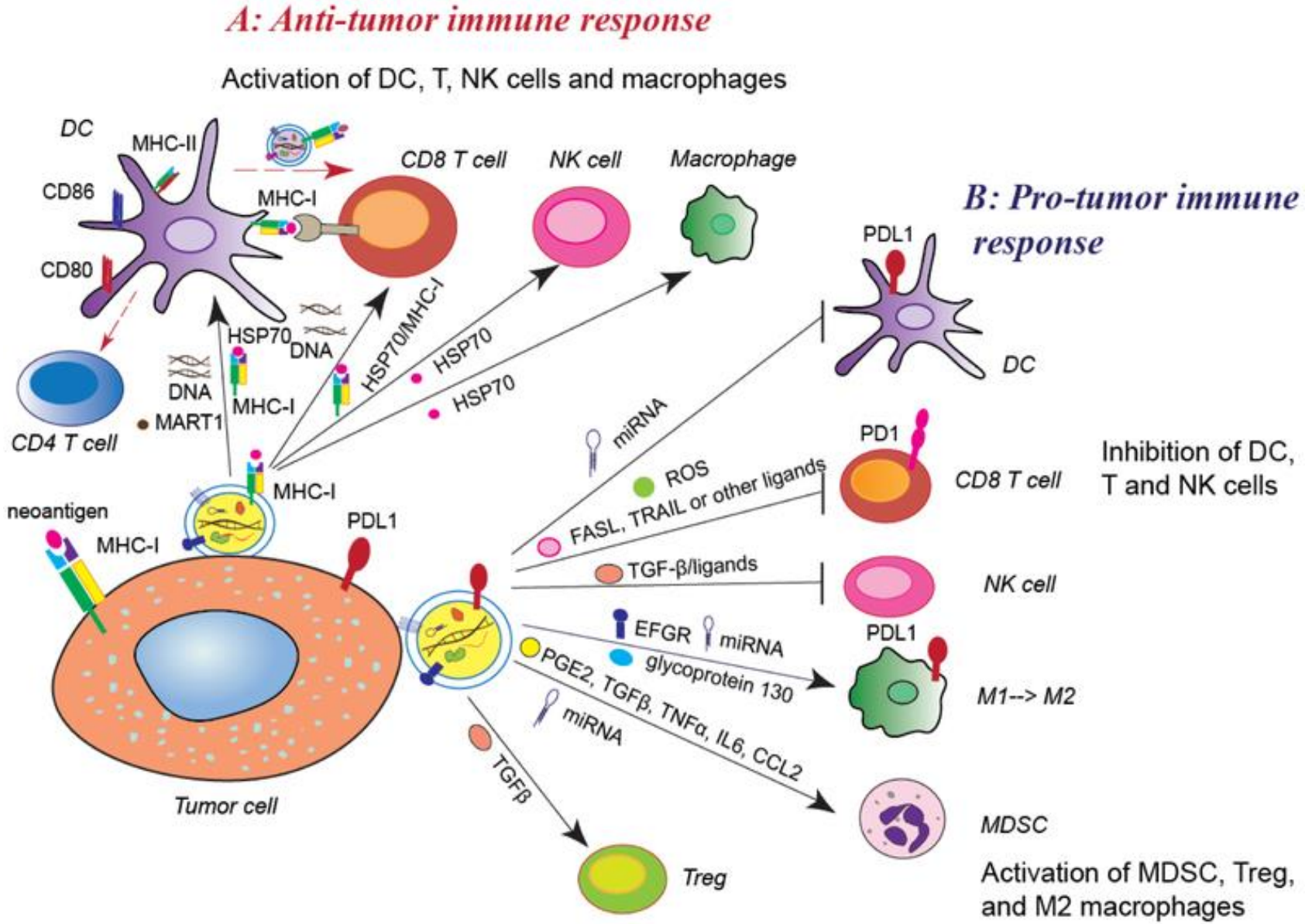


exosome-immune suppression" concept




Dural role of exosomes in cancer progression
cancer cell exosomes
T cell exosomes
DC cell exosomes
tumor angiogenesis promotion
NK cell activation
DC cell preliferation
DC cell
tumor growth
T cell activation
cancer cell
drug resistance
T cell
macrophage cell activation
apoptosis

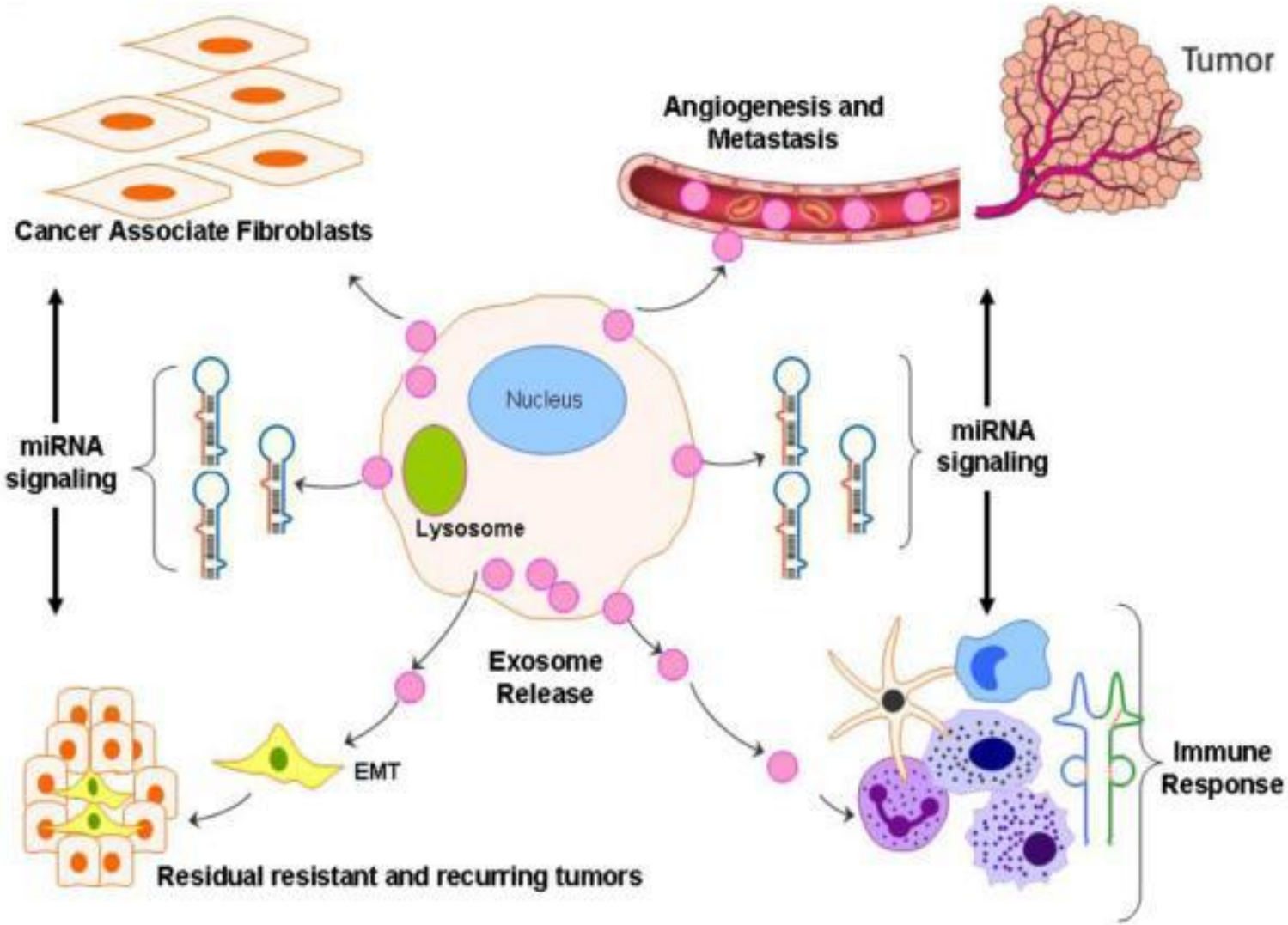
Exosomes functions in tumor immunity



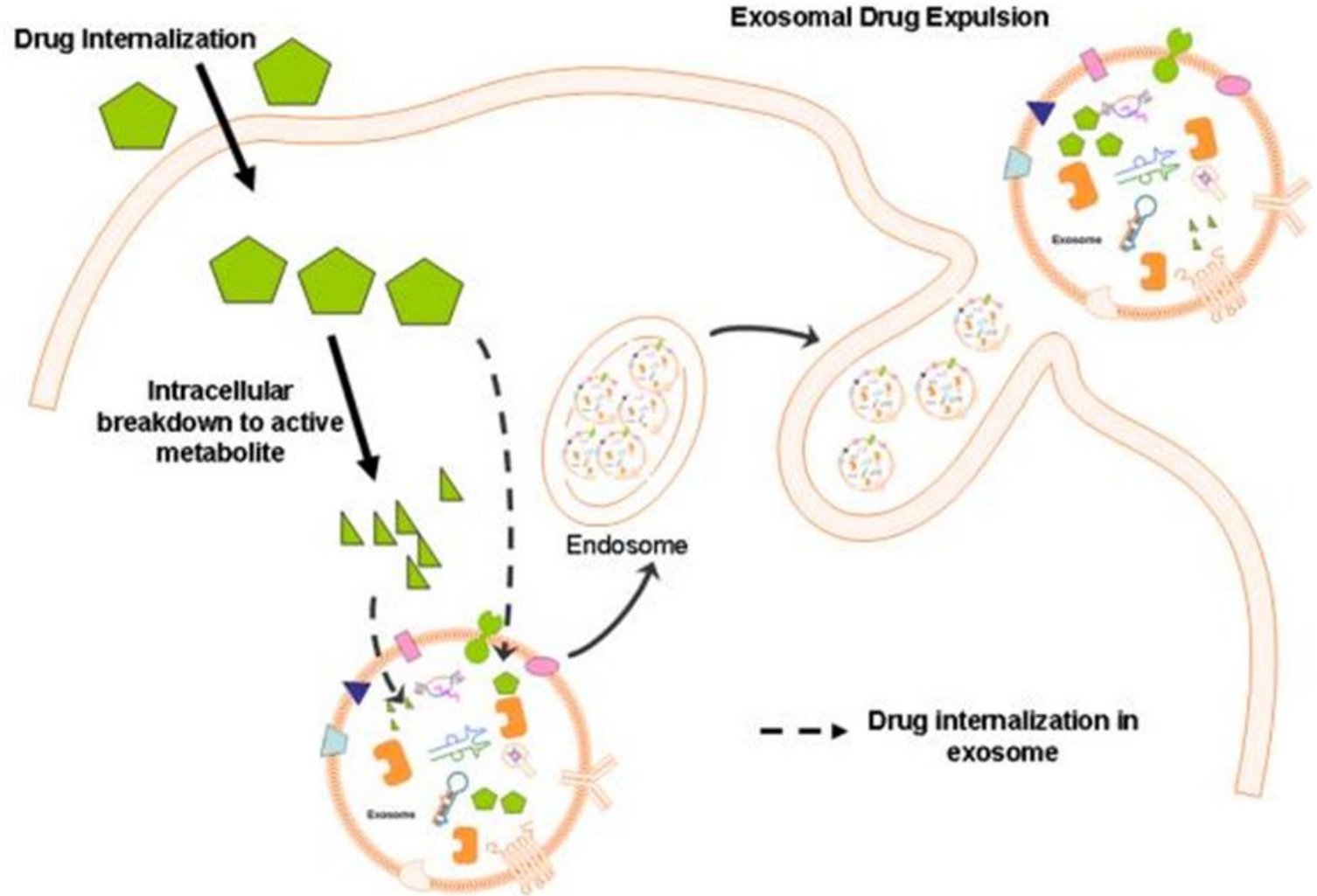
Desmoplastic reaction?

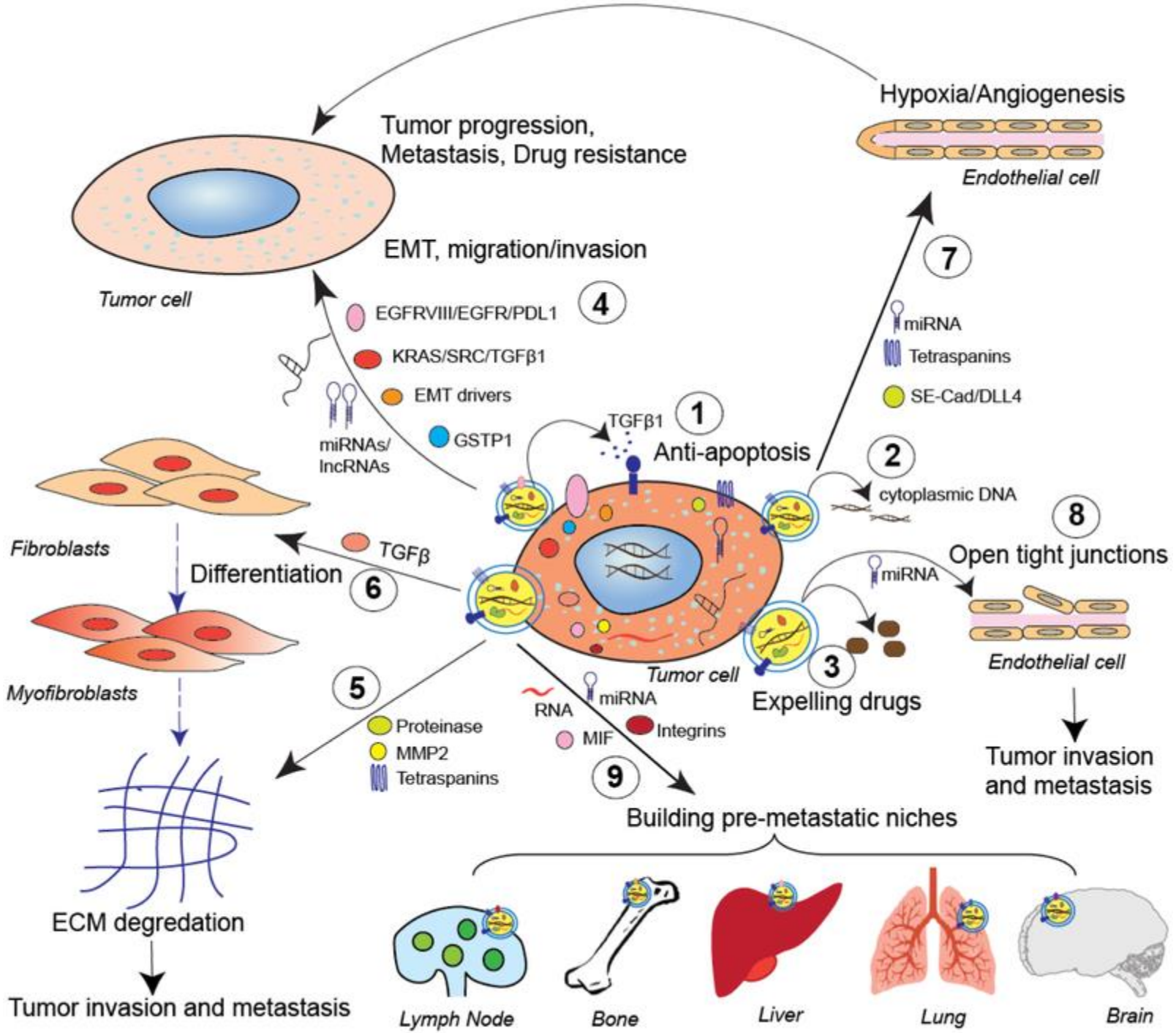
- Over the last decade, a number of studies have revealed that exosomes cross-talk and/or influence major tumor related pathways such as hypoxia driven EMT, cancer stemness, angiogenesis and metastasis involving many cell types within the tumor microenvironment. Emerging evidence suggest that exosome secreted proteins can also propel fibroblast growth, resulting in Desmoplastic reaction (DR); a major barrier in effective cancer drug delivery.

Exosomes in Cancer Resistance



Drug exclusion mechanism of Exosome



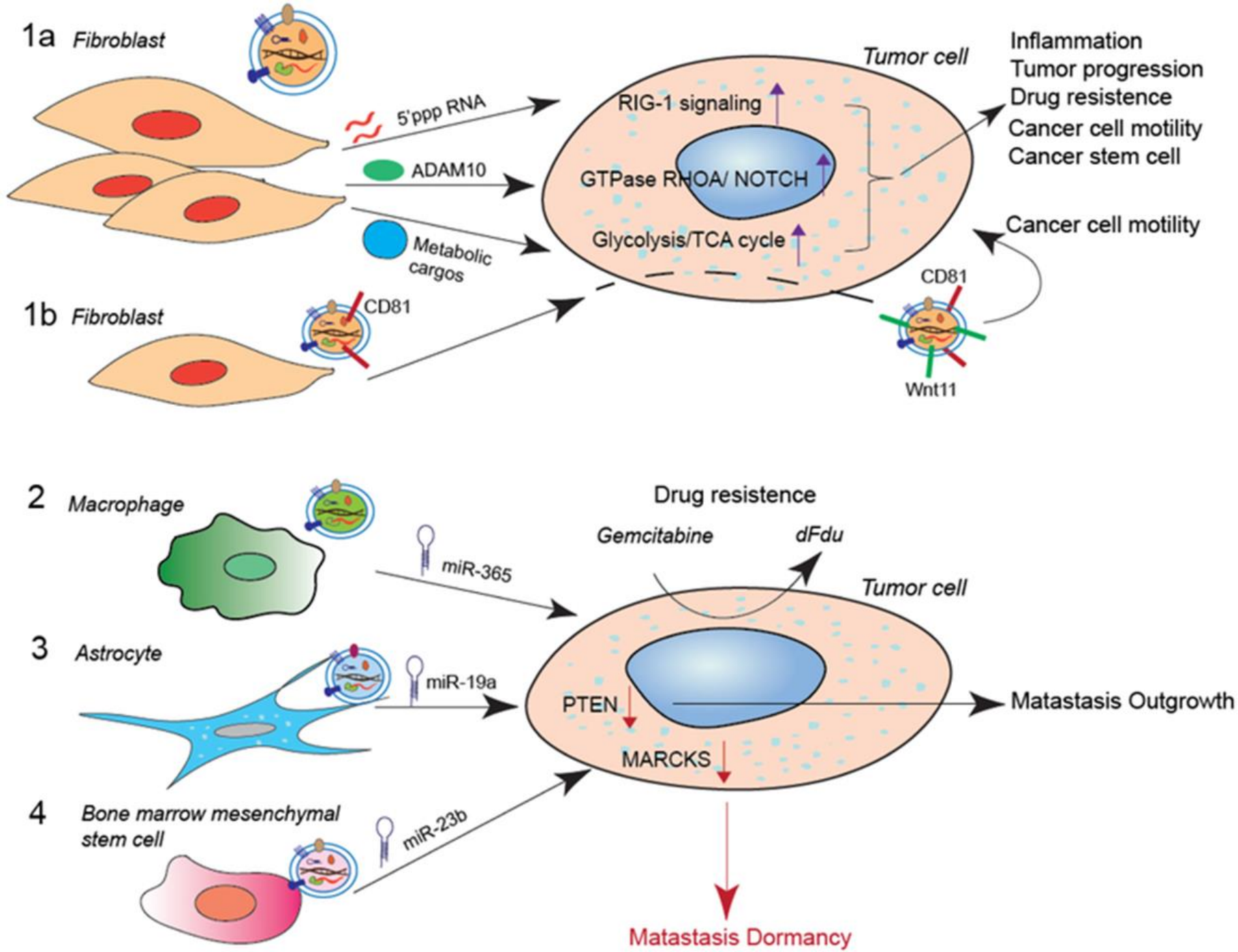

Hypoxia/Angiogenesis
Endothelial cell
Tumor progression,
Metastasis, Drug resistance
EMT, migration/invasion
Tumor cell
EGFRVIII/EGFR/PDL1
KRAS/SRC/TGFβ1
EMT drivers
GSTP1
miRNAs/
lncRNAs
4
7
miRNA
Tetraspanins
SE-Cad/DLL4
TGFβ1
1
Anti-apoptosis
2
cytoplasmic DNA
8
Open tight junctions
Fibroblasts
TGFβ
Differentiation
6
miRNA
Myofibroblasts
Tumor cell
3
Expelling drugs
Endothelial cell
5
RNA
miRNA
Integrins
MIF
Proteinase
MMP2
Tetraspanins
9
Tumor invasion
and metastasis
Building pre-metastatic niches
ECM degredation
Tumor invasion and metastasis
Lymph Node
Bone
Liver
Lung
Brain

- presence of a sub-population of highly resistant cancer stem like cells with enhanced plasticity such as epithelial-to-mesenchymal transition (EMT) phenotype, low drug penetrance (due to Desmoplastic reaction or DR in the tumor microenvironment)

- **Most cancer deaths are the result of metastasis which in is generally refractory to any form of available therapies.**

messages from dying cells

- apoptosis is not just a ‘silent’ type of cell death but an active form of communication from dying cells to live cells through exosomes.


1a Fibroblast
5'ppp RNA
ADAM10
Metabolic cargos
Tumor cell
RIG-1 signaling
GTPase RHOA/ NOTCH
Glycolysis/TCA cycle
Inflammation
Tumor progression
Drug resistence
Cancer cell motility
Cancer stem cell
Cancer cell motility
1b Fibroblast
CD81
CD81
Wnt11
2 Macrophage
miR-365
Drug resistence
Gemcitabine
dFdu
Tumor cell
3 Astrocyte
miR-19a
PTEN
MARCKS
Matastasis Outgrowth
4 Bone marrow mesenchymal stem cell
miR-23b
Matastasis Dormancy

- **Researchers are still grappling to understand the underlying drivers of migratory cells and their ability to escape the site of origin in primary tumors. Exosomes are known mobile elements that function as escape routes for proteins and miRNAs (some of which can be promoters of metastatic pathways) from one cell (site of origin) to distant locations.**

- **Hypoxia is an emerging area that is a critical component promoting the sustenance and spread of epithelial tumors. The seeding of tumor stroma [Desmoplastic reaction (DR)], a barrier to efficient drug delivery, has been clearly linked to be supported by hypoxia and related pathways. The hypoxic environment (a niche within tumor) is recognized to harbor cells that are drug resistant (compared to the bulk of the tissue) carrying markers that are reminiscent of epithelial-to-mesenchymal transition (a hall mark of cancer stem like cells) . It was recently documented that hypoxia promotes the secretion of various tumor promoting factors that influence adjacent tissues in the tumor microenvironment.**