

Ο Κομβικός Ρόλος του Αρχέγονου Μεσεγχυματικού Κυττάρου στην Παθογένεια και Θεραπεία των Σαρκωμάτων

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● **Fact: Sarcomas Display Tremendous variability!**

1. Bone/Osteoid
2. Cartilage/Chondroid
3. Fibrous matrix
4. Muscle
5. Fat
6. Myxoid matrix
7. Any possible combination
8. Minimal/No ECM



The tremendous STS heterogeneity implies

**Distinct cells of origin
for each subtype**

**Multipotent cell of origin
for all subtypes**

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**Distinct cells of origin
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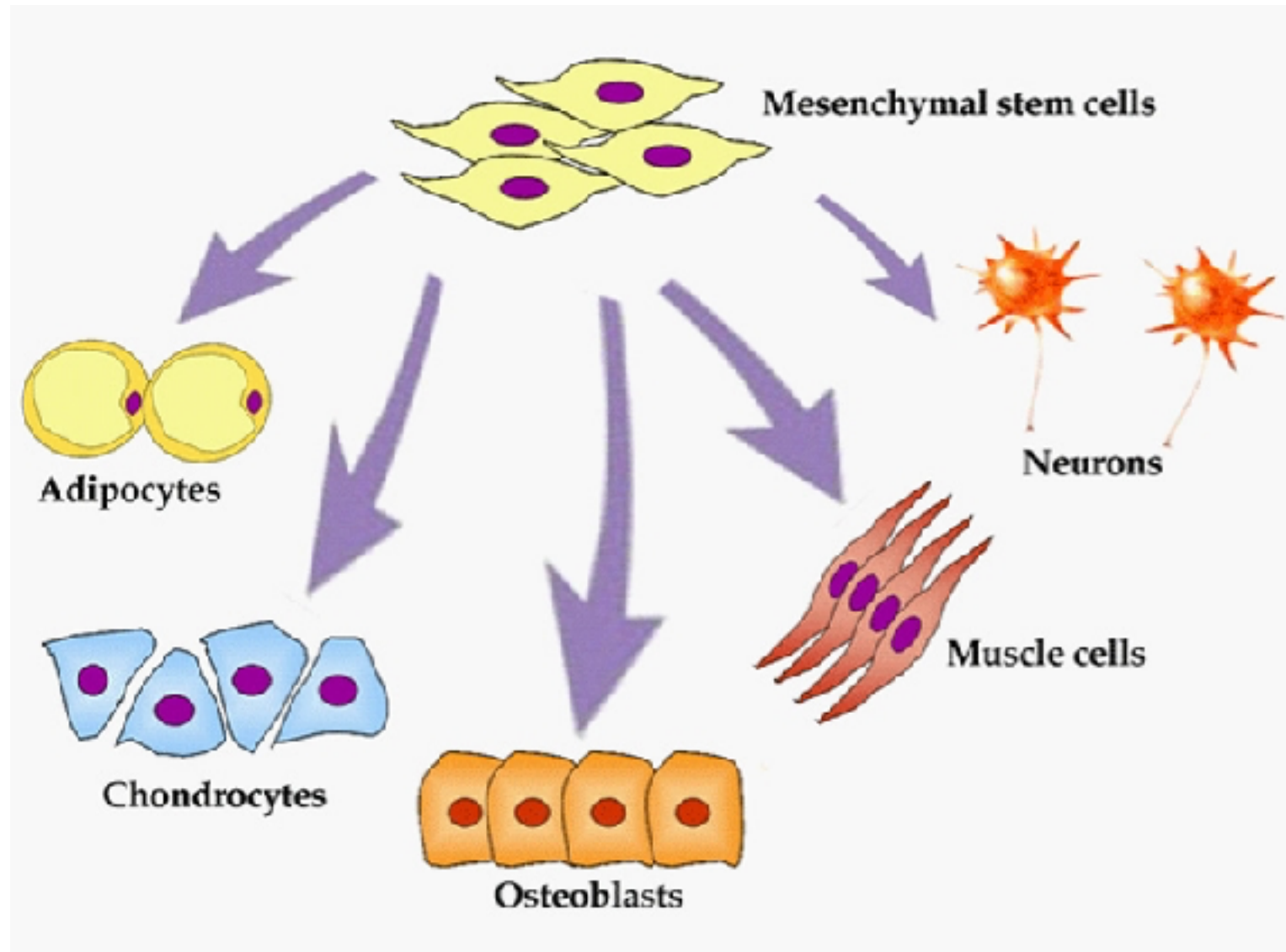
**Multipotent cell of origin
for all subtypes**

Infantile fibrosarcoma	ST	int	<i>ETV6-NTRK3 fusion</i>
Mesoblastic nephroma	kidney	ben	>>
Secretory Ca	SG	maligna	>>
Clear cell sarcoma	Extr	malign	<i>EWSR1-CREB1, -ATF1</i>
Angiomatoid FH	Ext/Tr	ben	>>
EWS	bones	mal	<i>FUS-ERG fusion</i>
AML	blood	mal	>>
different OS subtypes			

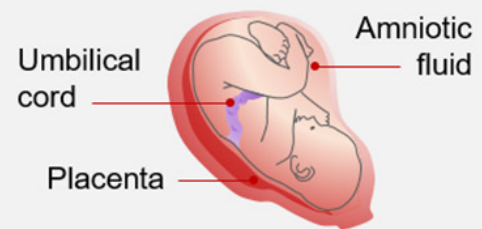
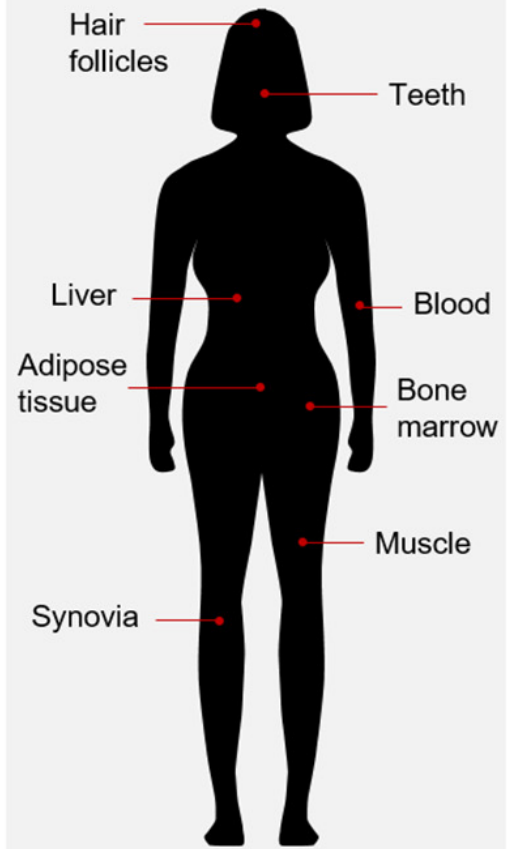


...but which cell could serve as the stem of sarcomatogenesis?

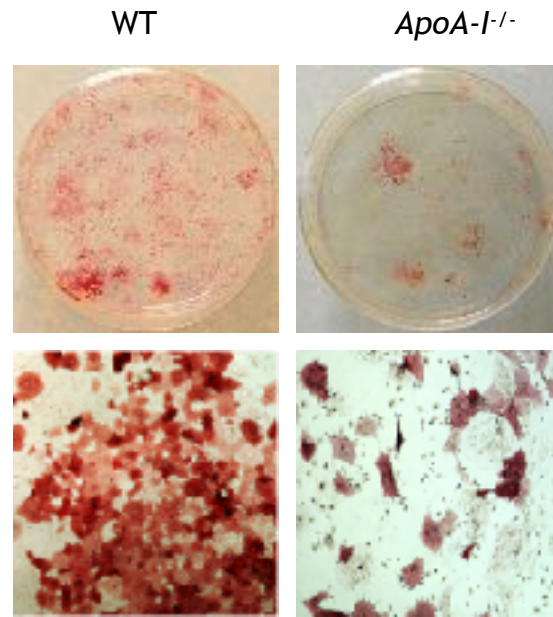
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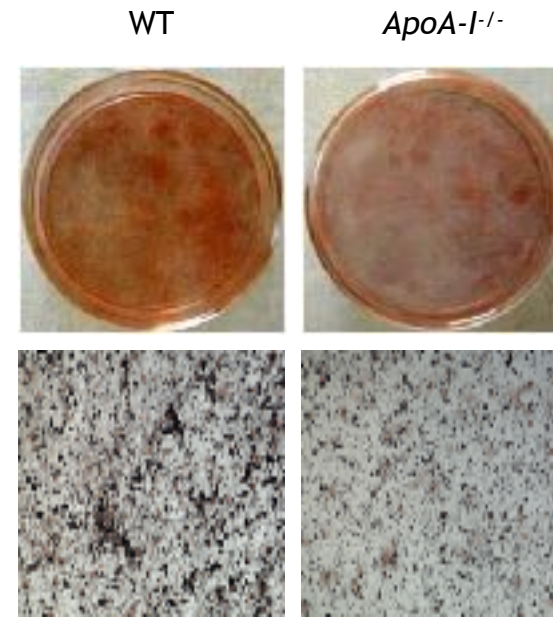
Multiple sources



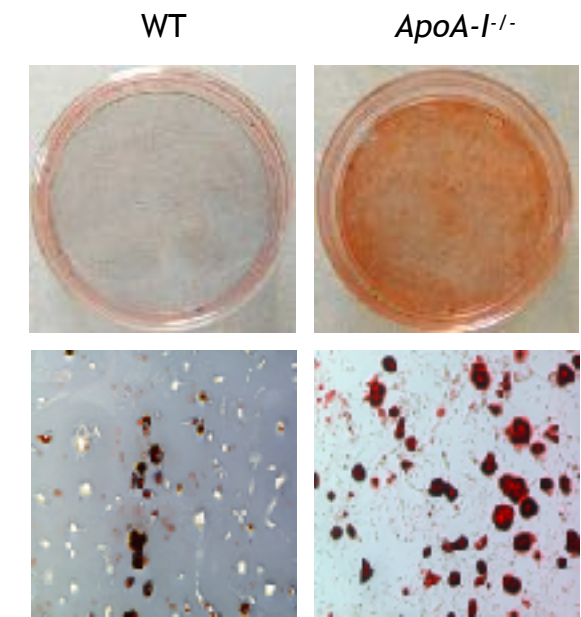
Osteoblasts (Alkaline Phosphatase/ALP)



Mineral Deposition (Von Kossa)

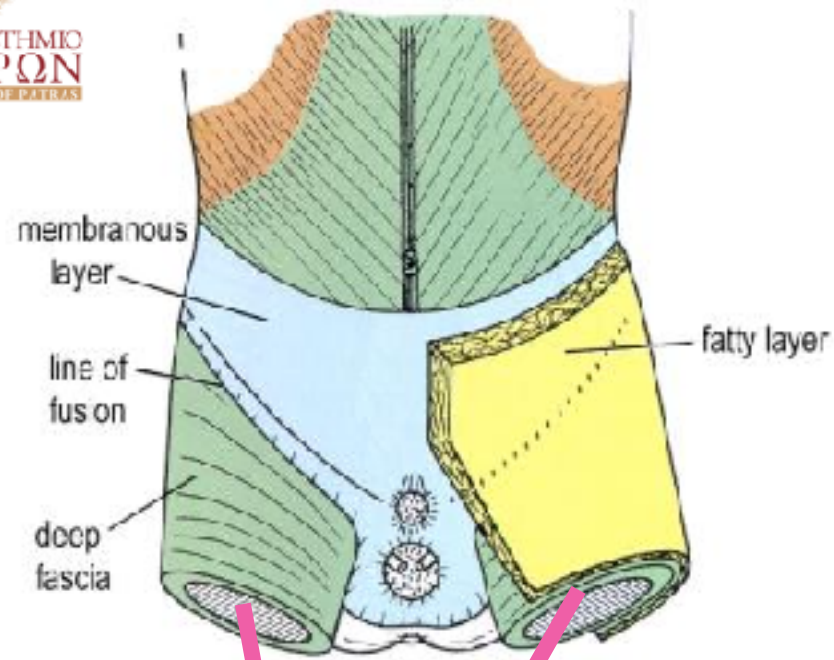


Adipocytes (Oil Red O)

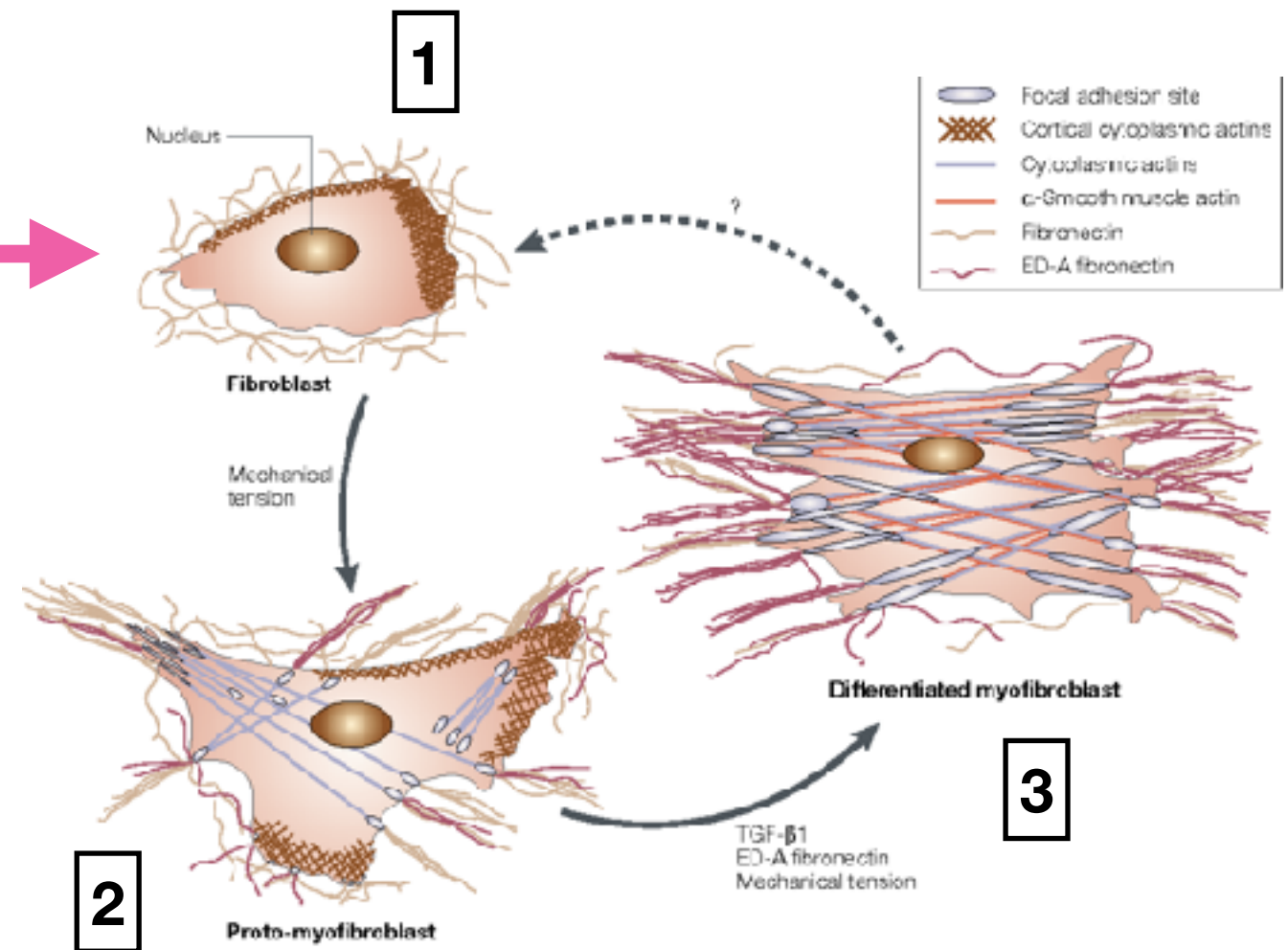
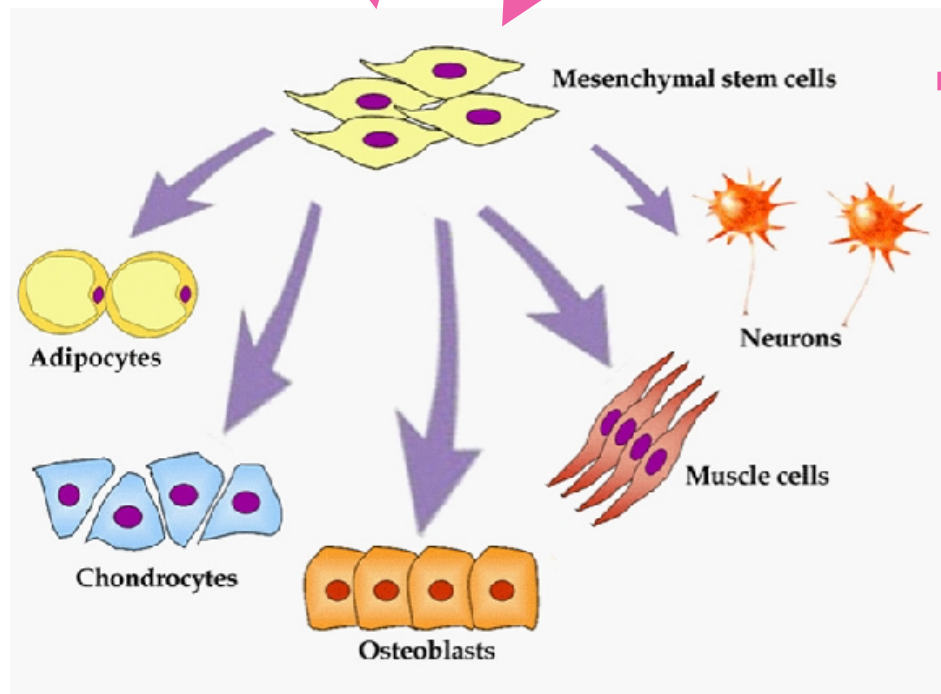


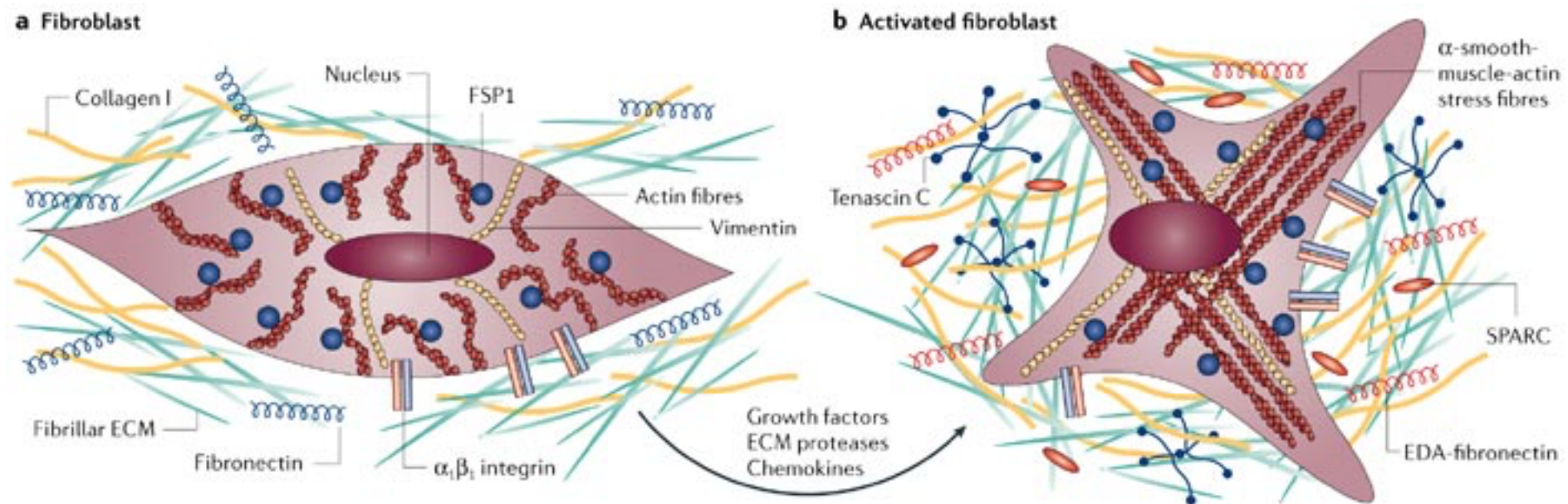
10x

Kalyvioti et al, Lab Invest 2017
Papachristou et al, 2018

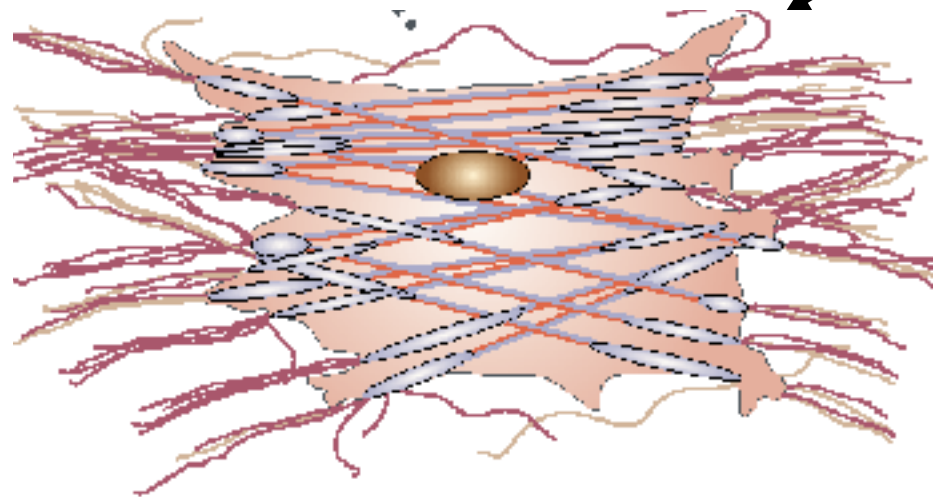


The Amazing Fascia

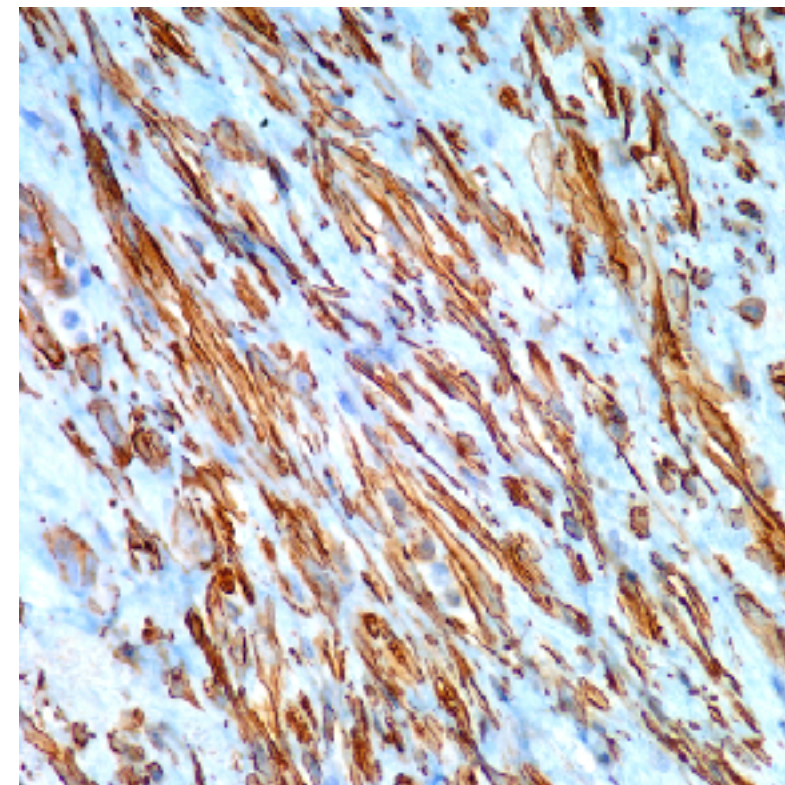




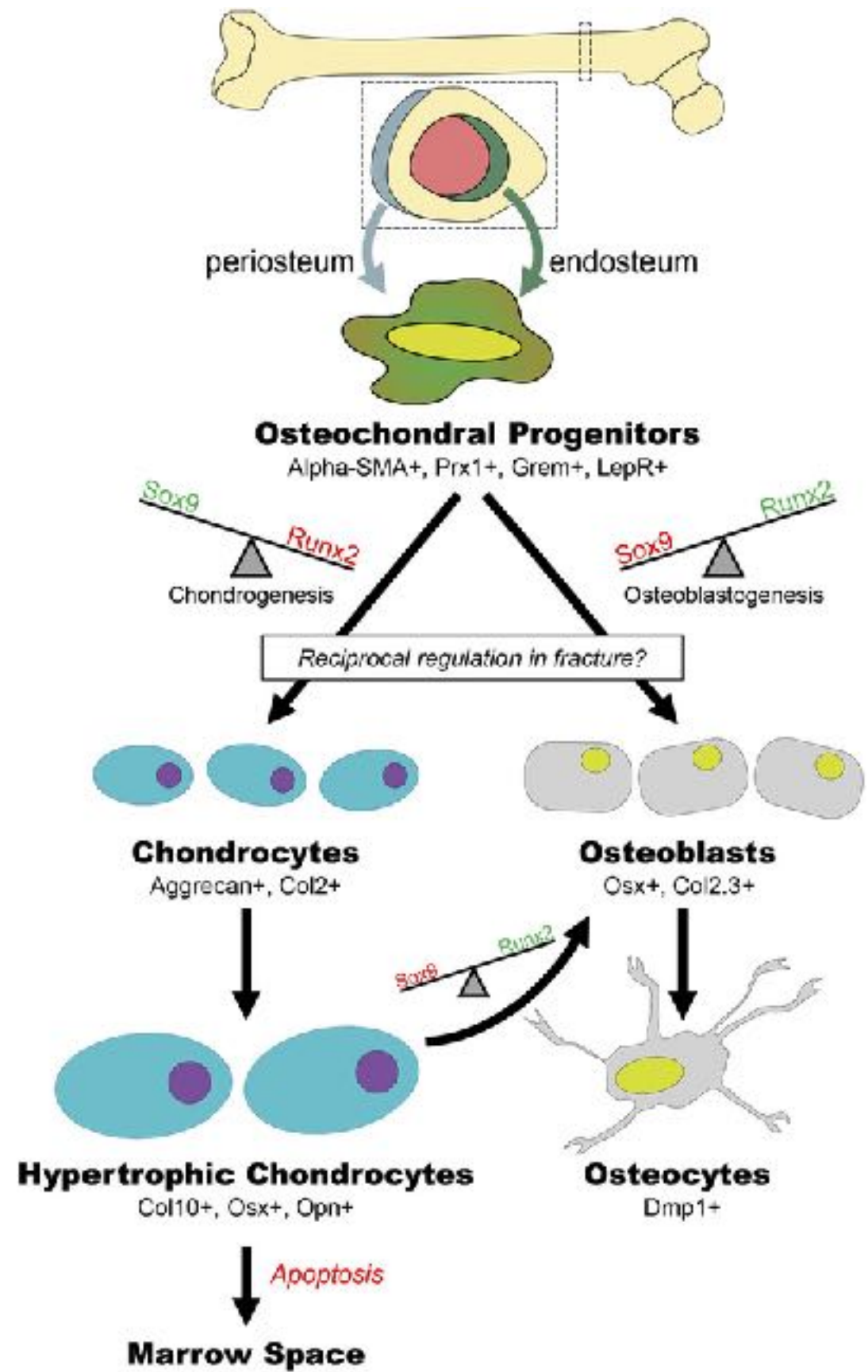
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Nature Reviews | Cancer



The Myofibroblast



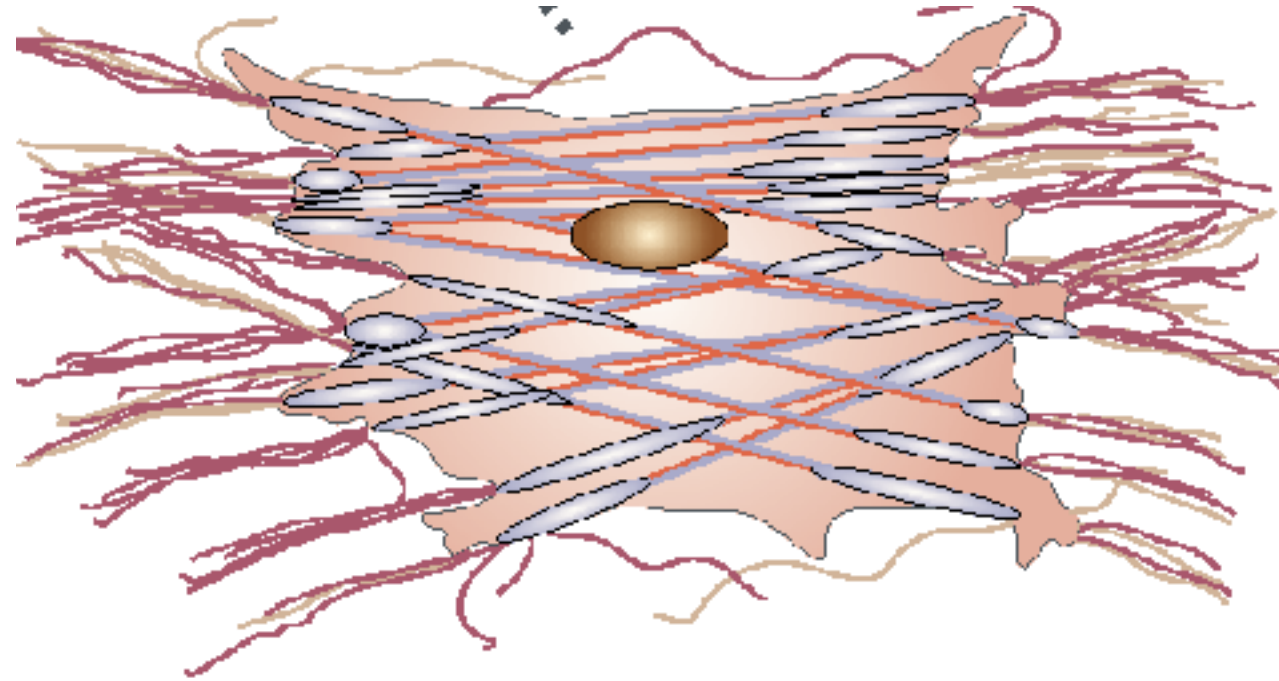
α -SMA.tram track.400X



Proliferative Fasciitis

Nodular Fasciitis

Proliferative Myositis

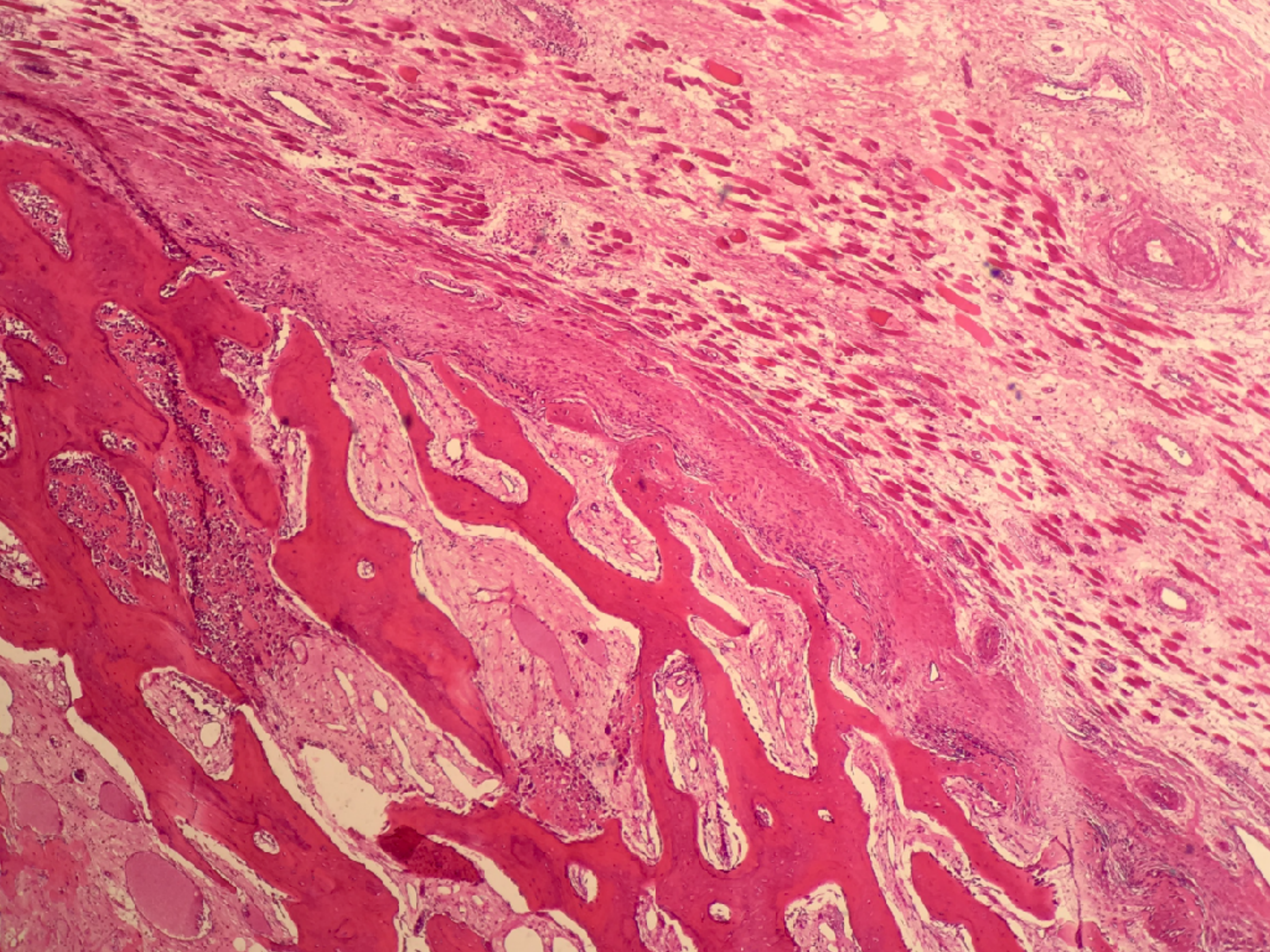


Myositis Ossificans

Florid Reactive Periostitis

BPOPs

Subungual Exostosis





...but are MSC the CSC of sarcomatogenesis?



The 3 minimal criteria for MSC characterization (ISCT)

- Plastic-adherent properties in standard culture medium
- CD105+, CD73+, CD90+,
CD45-, CD34-, CD14- or CD11b-, CD19- or CD79a-, HLH-
DR markers-
- The ability to differentiate into OBL, CHBL, LBL, MyoBL

- **Bone Marrow Stromal cells**

- **Skeletal stem cells** (CD146/MCAM+, and PDGFA+,
CD45-, CD31-)



CSC are characterised by:

- asymmetric division
- high migratory ability
- resistance to systemic Tx
- sarcomatogenesis at high turnover locations (growth plate, fascia)
- immunomodulation
- **these characteristics fit the “MSC=CSC” model**



Hallmarks of cancer

- invasion
- migration
- angiogenesis
- immunosuppression
- homing
- metastasis
- drug resistance

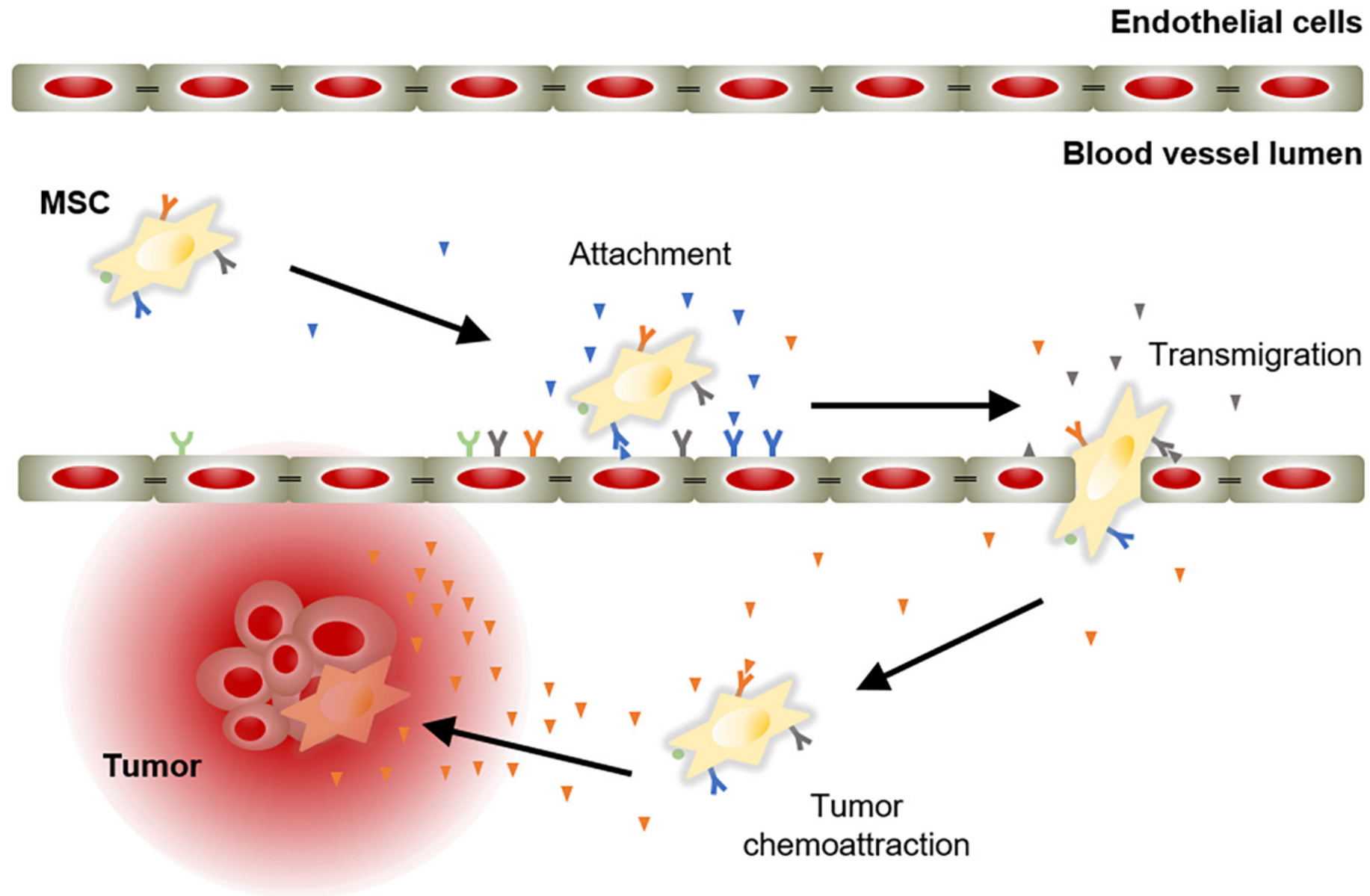
Hallmarks of cancer

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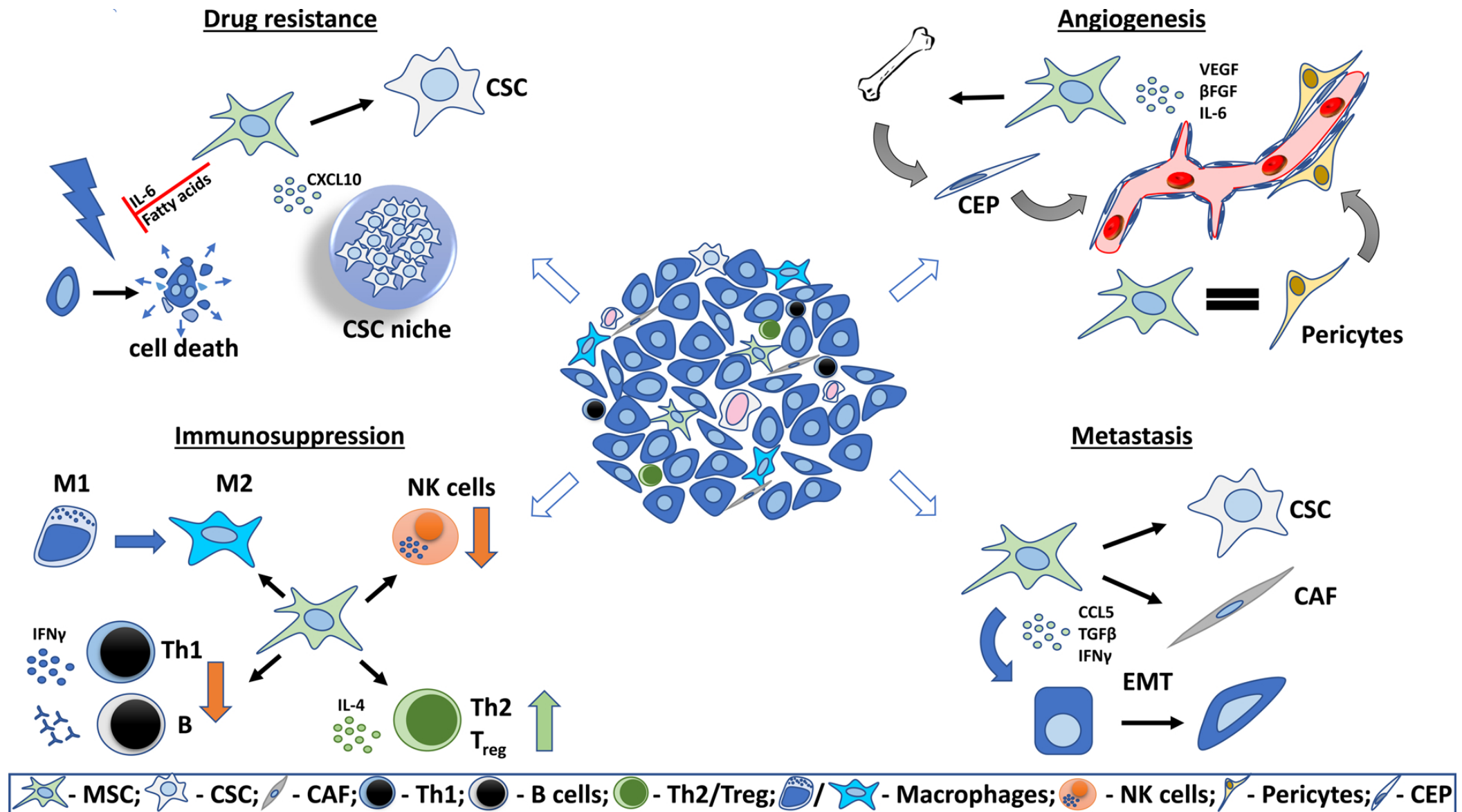


MSC?

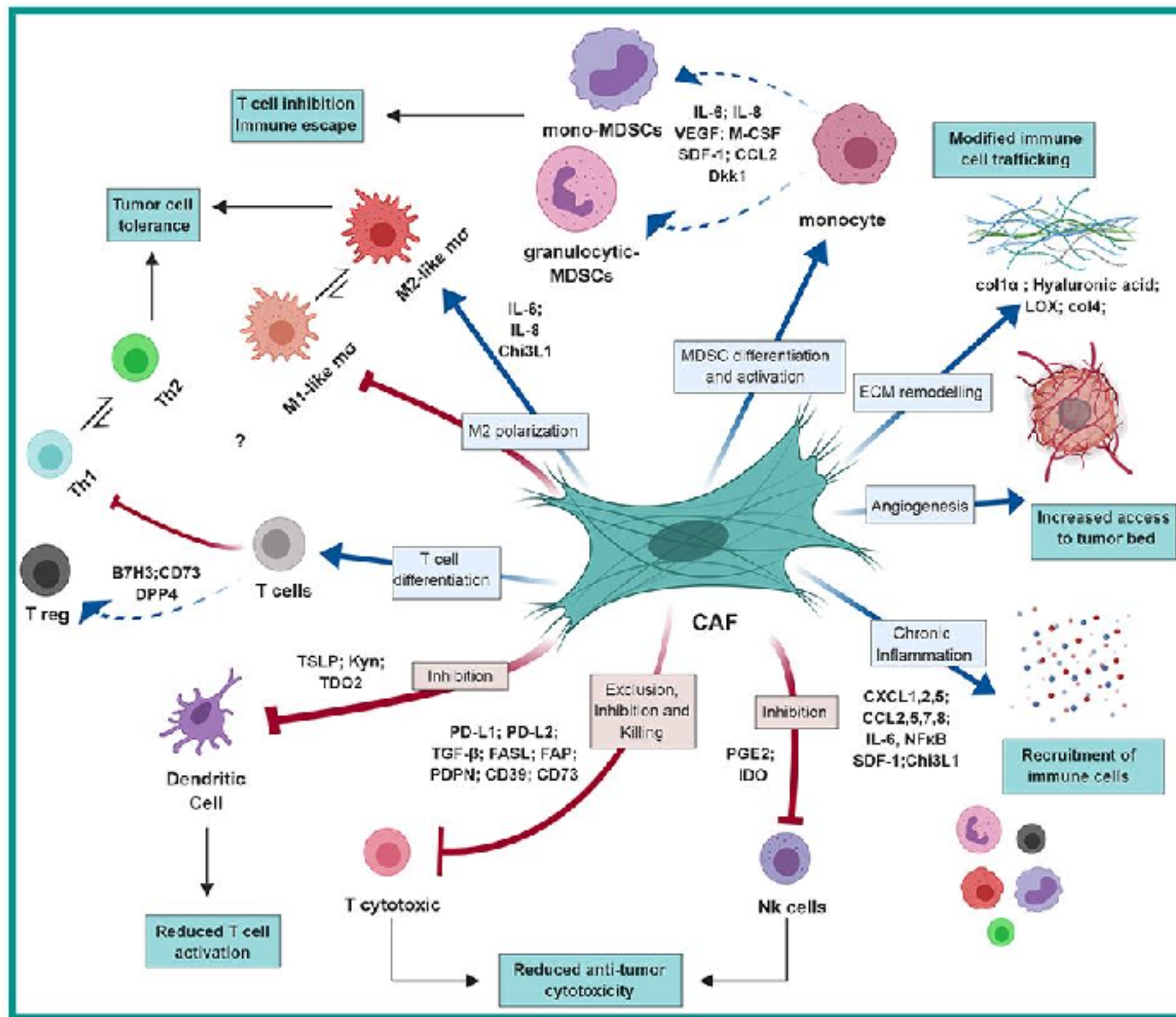
MSC and tumor invasion, transmigration and chemoattraction



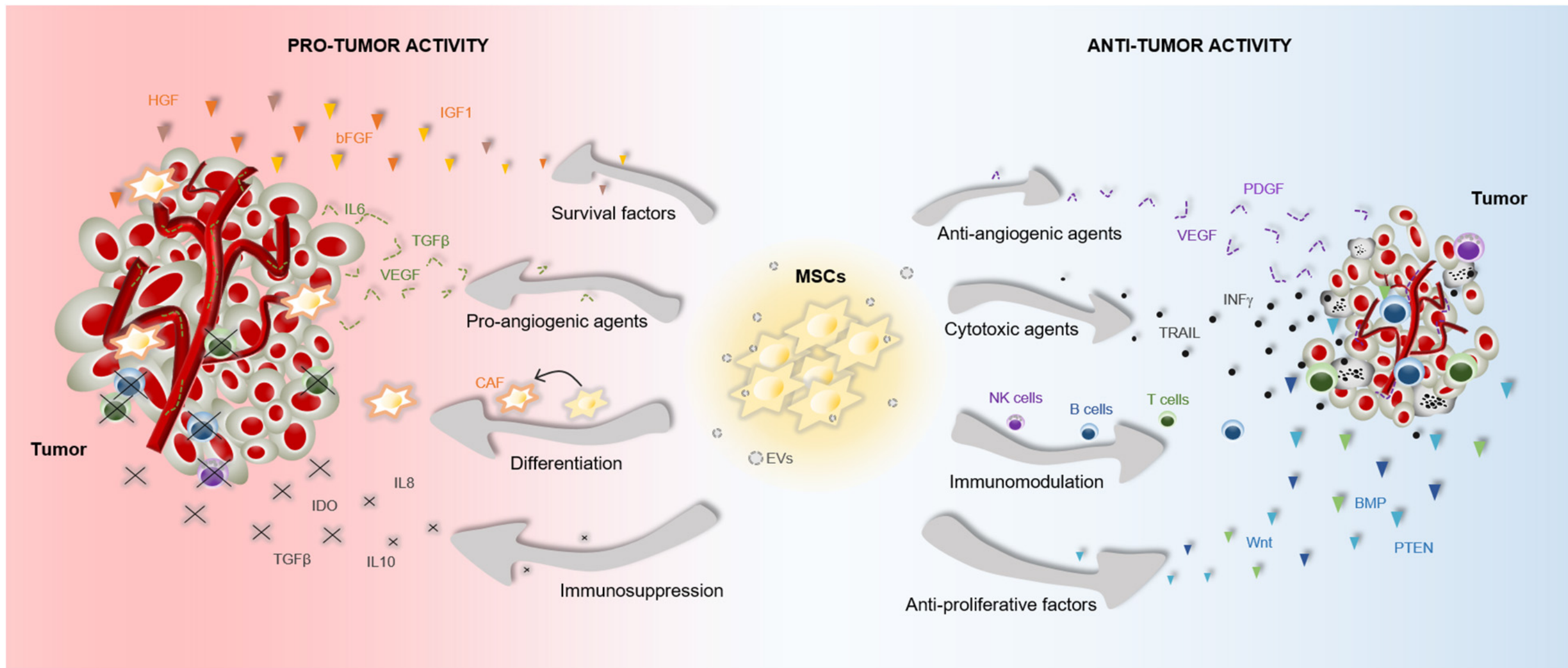
The tumor supportive function of MSC



CAFs and Tumor Progression



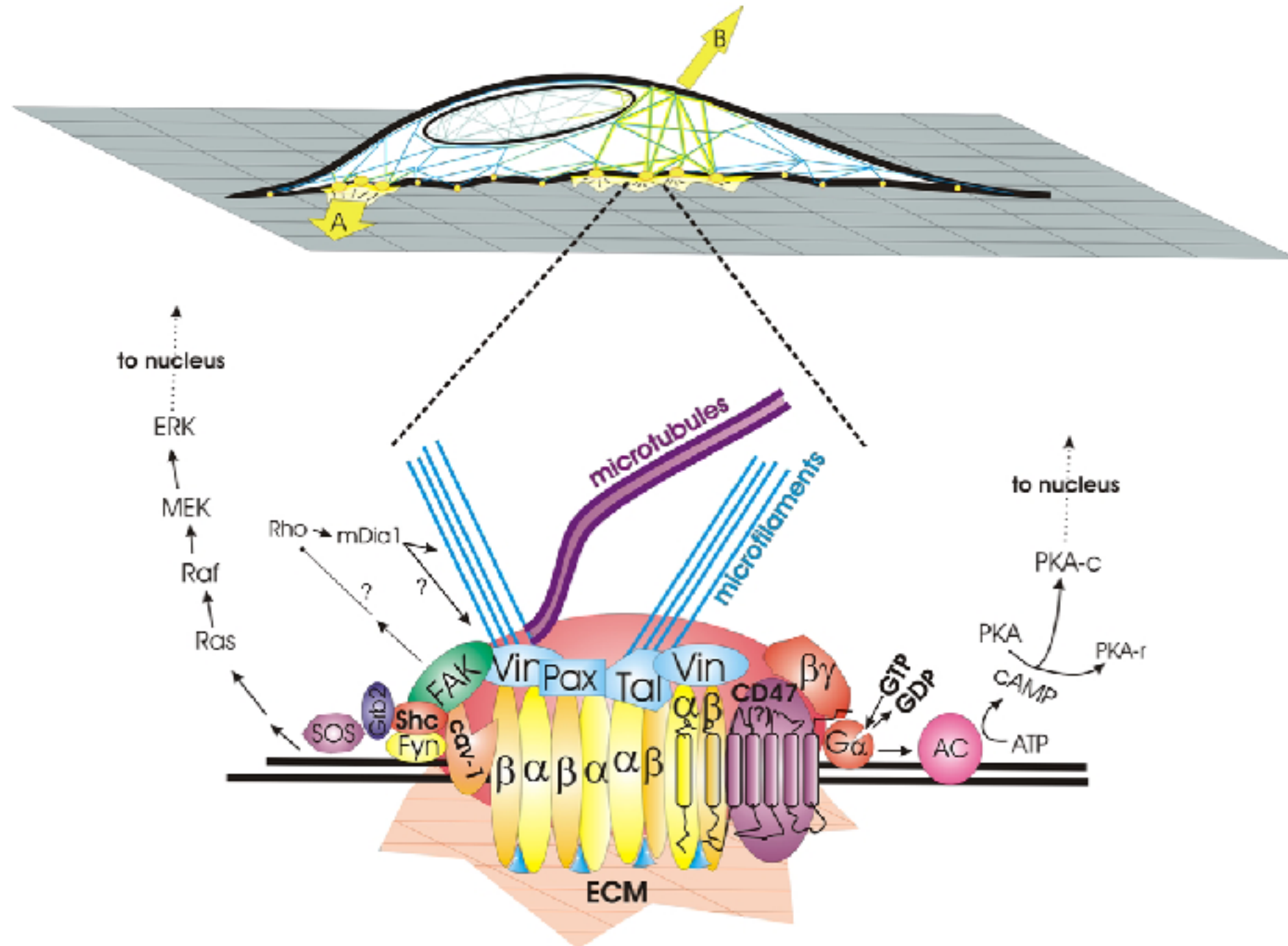
...there is also anti-tumoral role of MSC in cancer

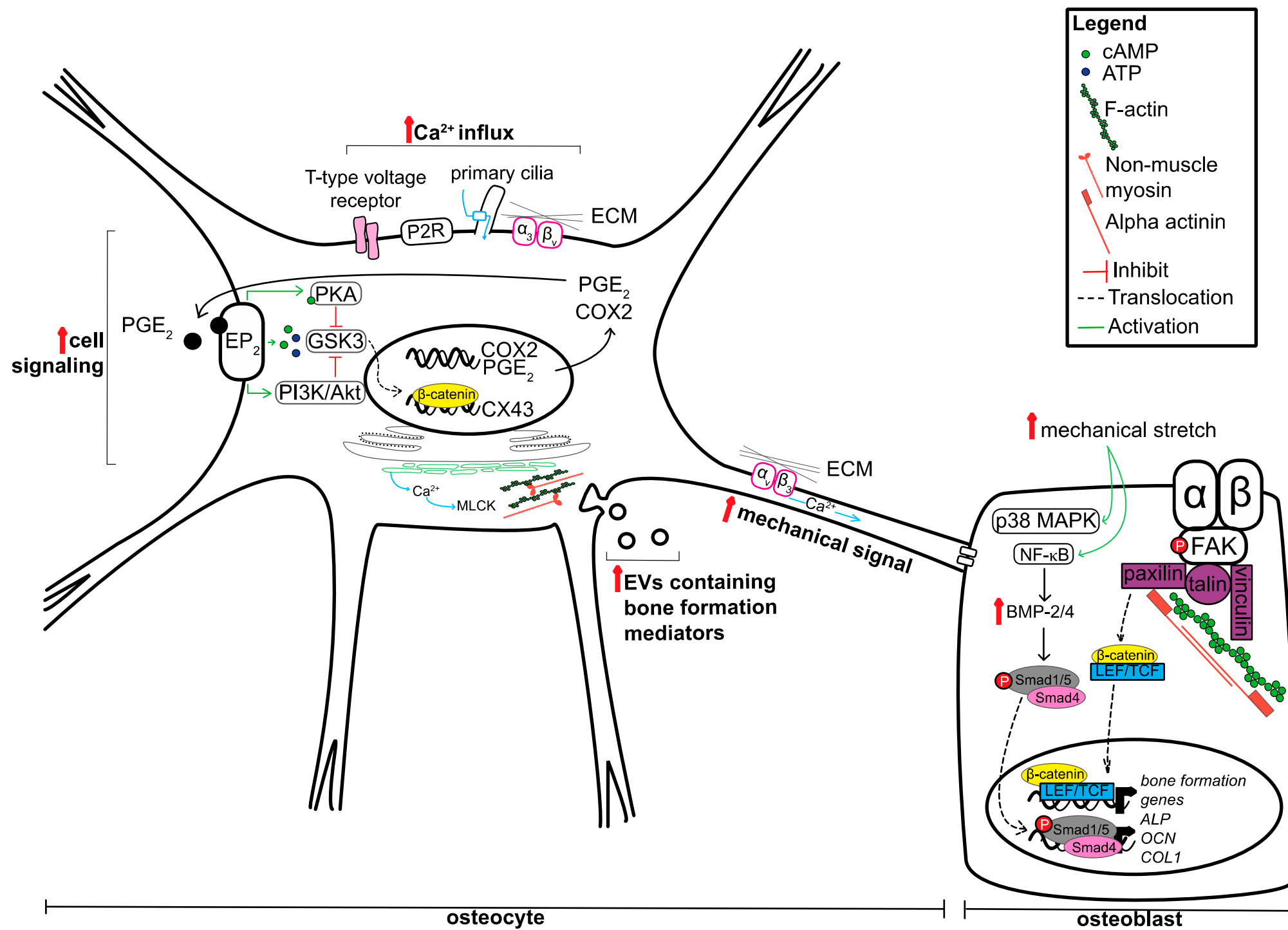




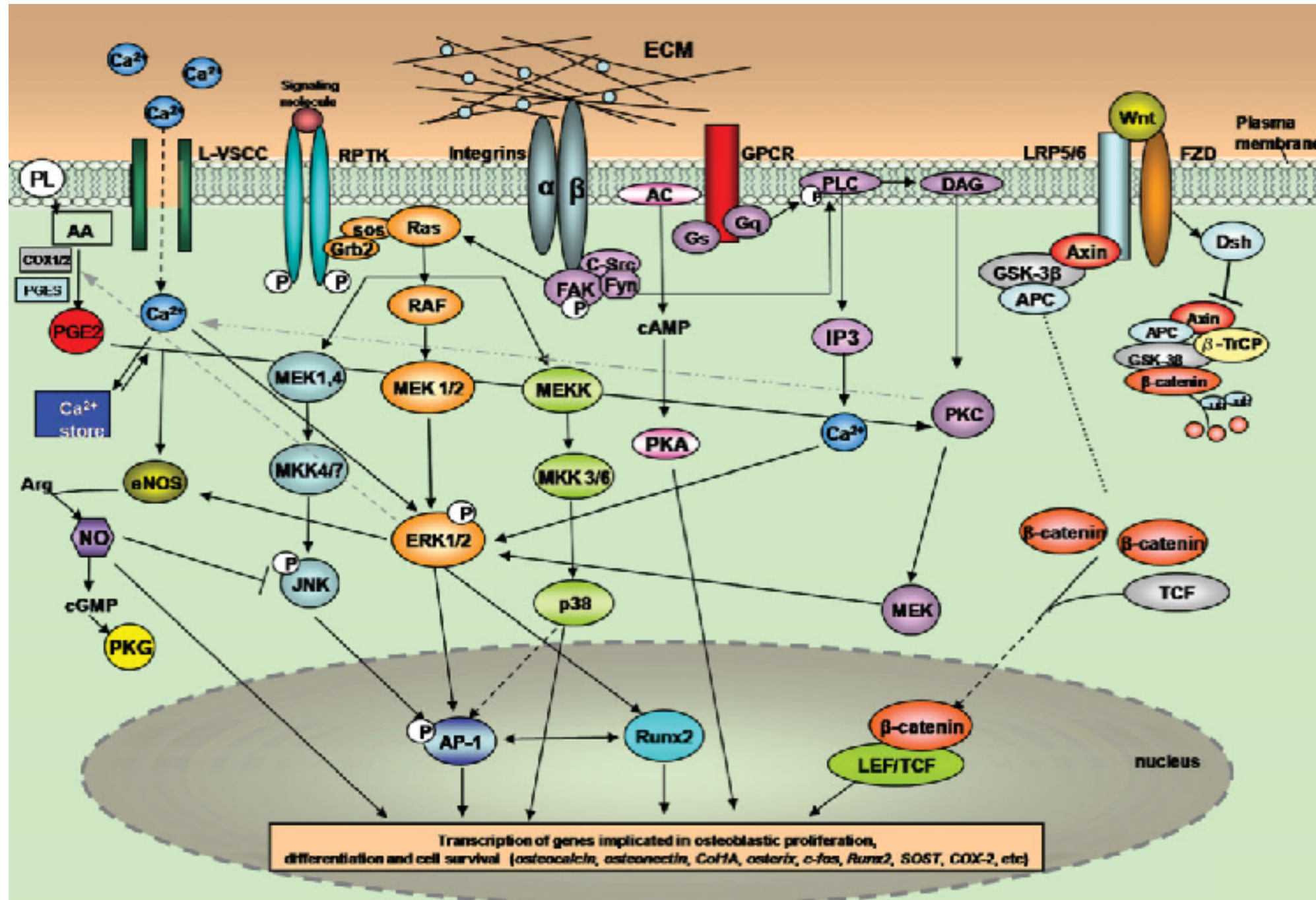
Mechanical Stimulation, MSCS and Sacromatogenesis

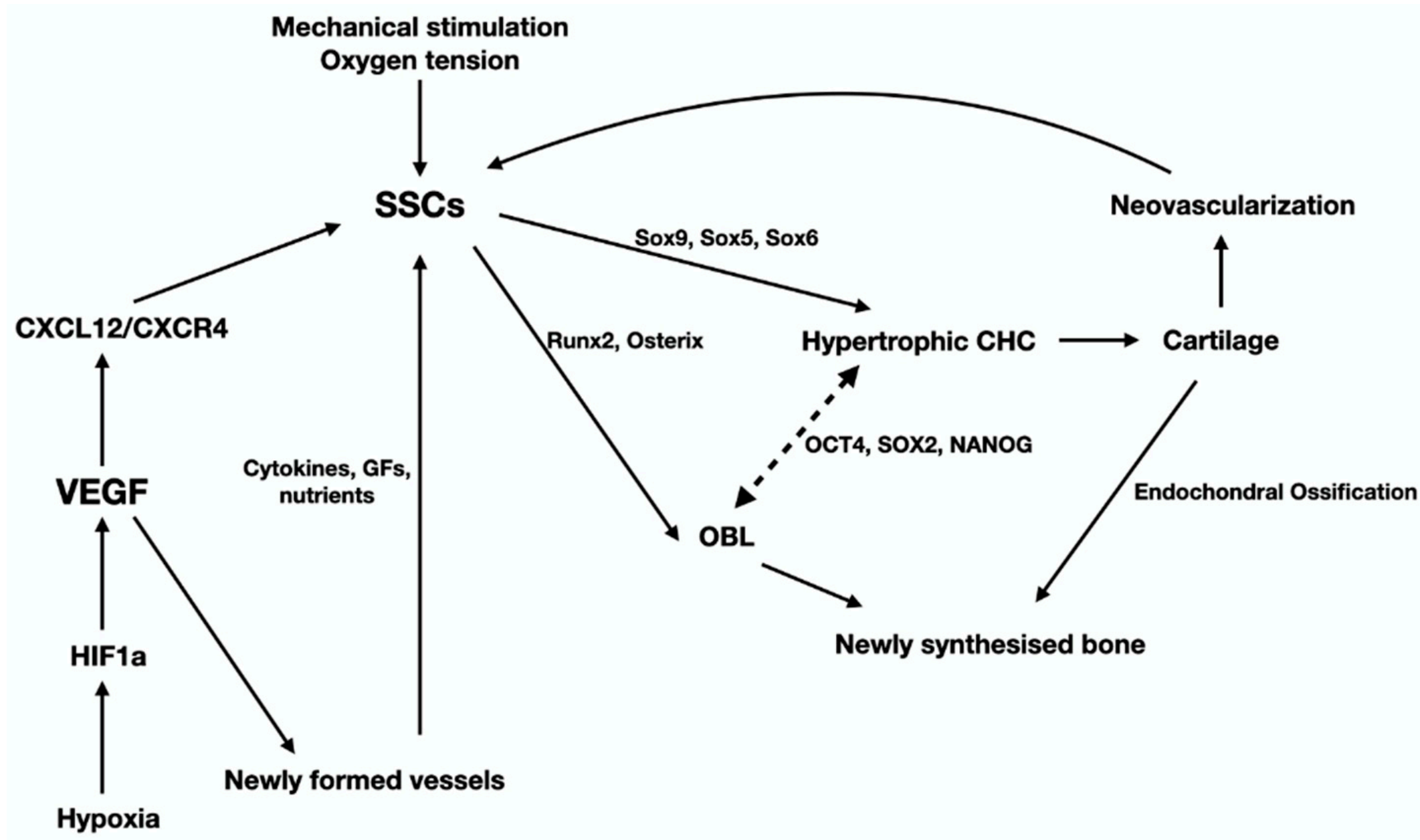
MSCs and Mechanotransduction

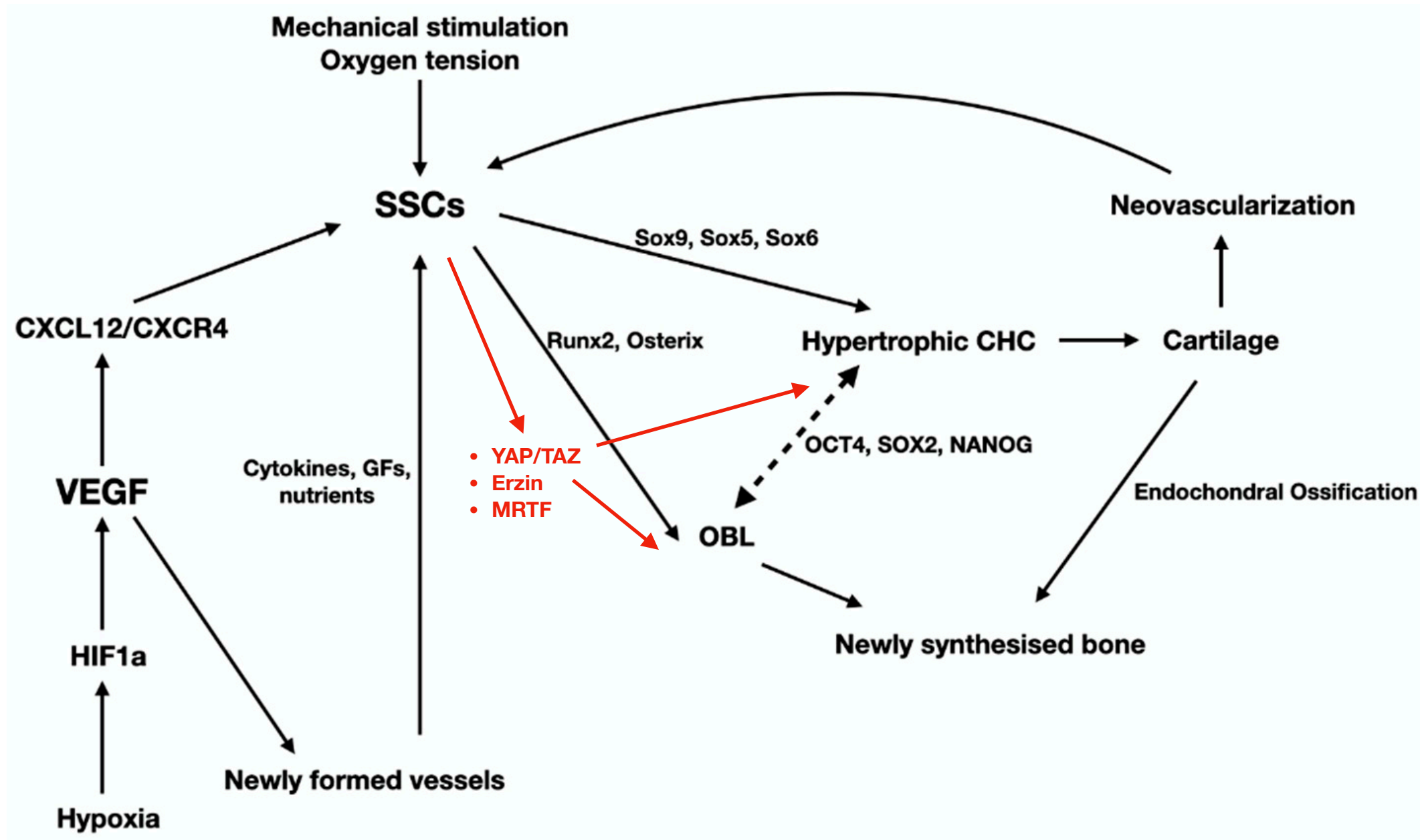


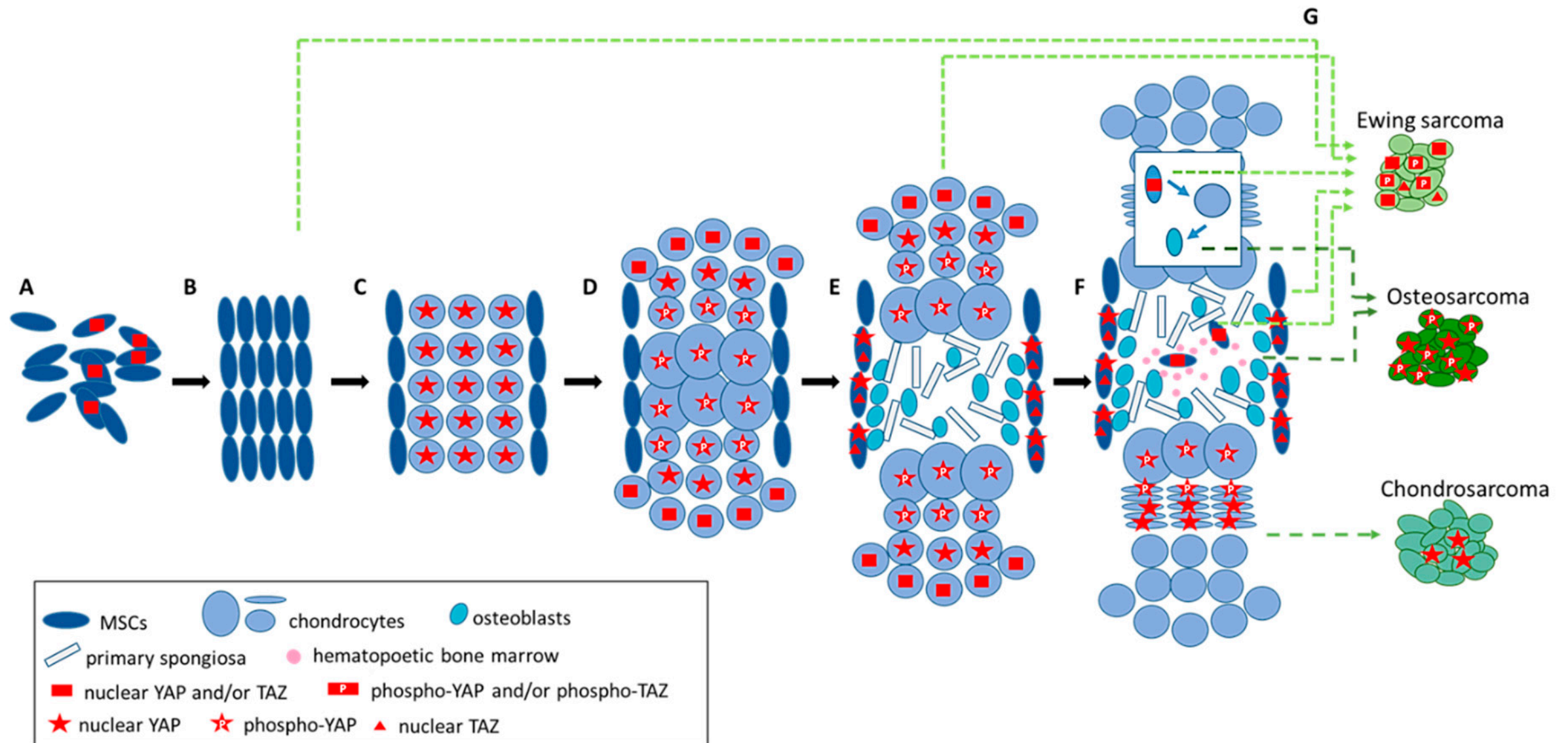


Mechanotransduction Signaling and MSCs

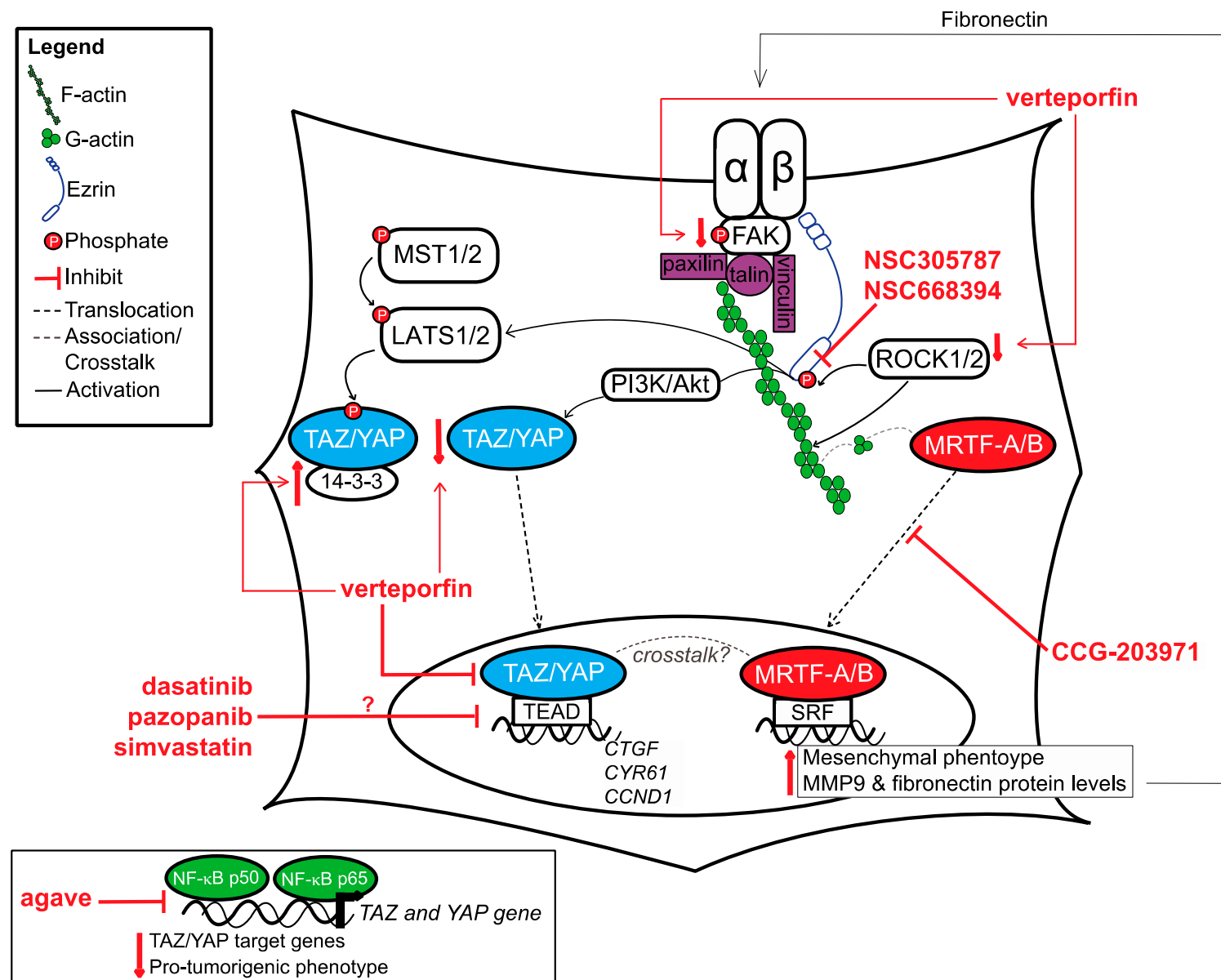








New Targets for OS Tx?





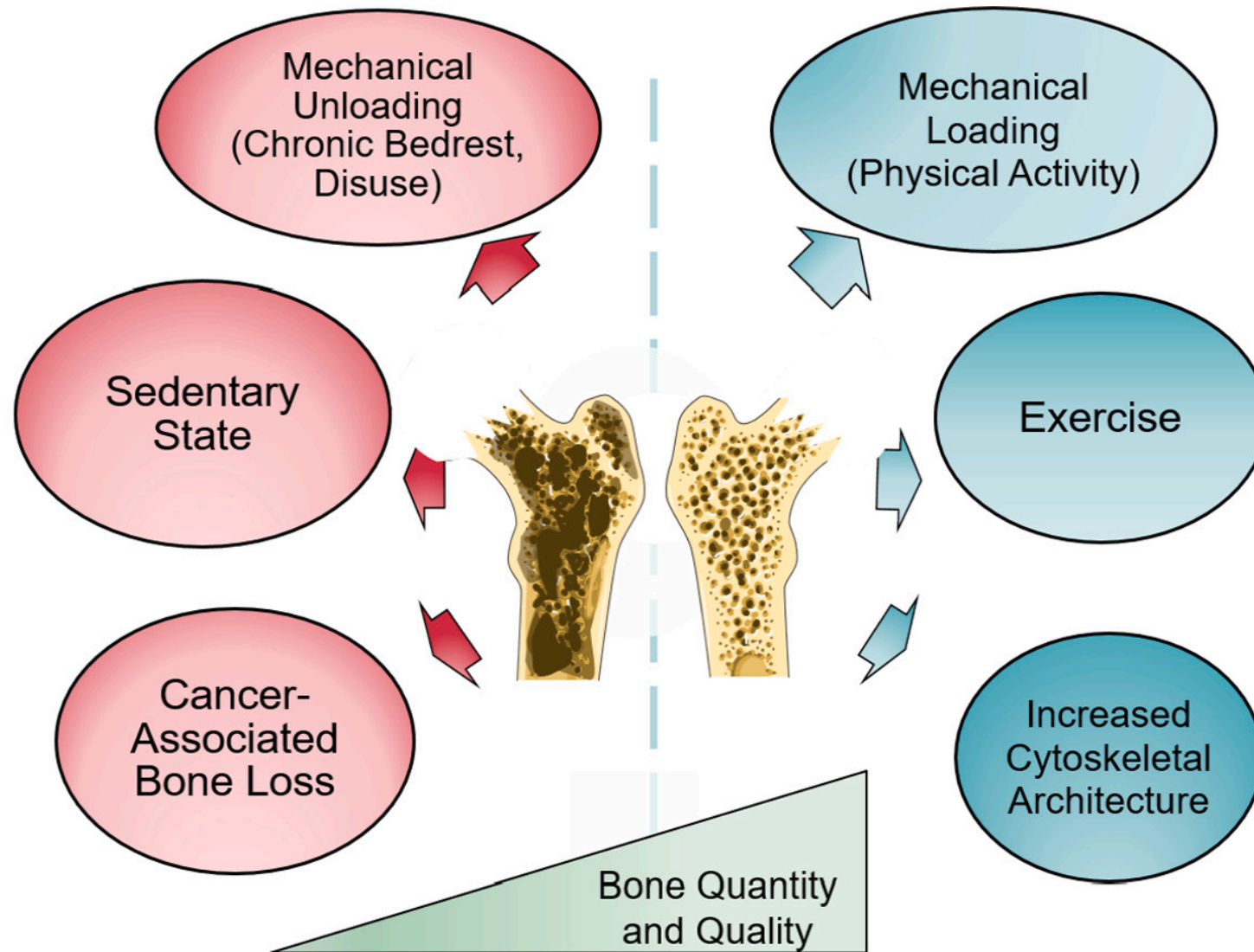
Mechanical Stimulation, MSCS and Bone Mets

Bone Loss

Bone Gain

Negative Effects

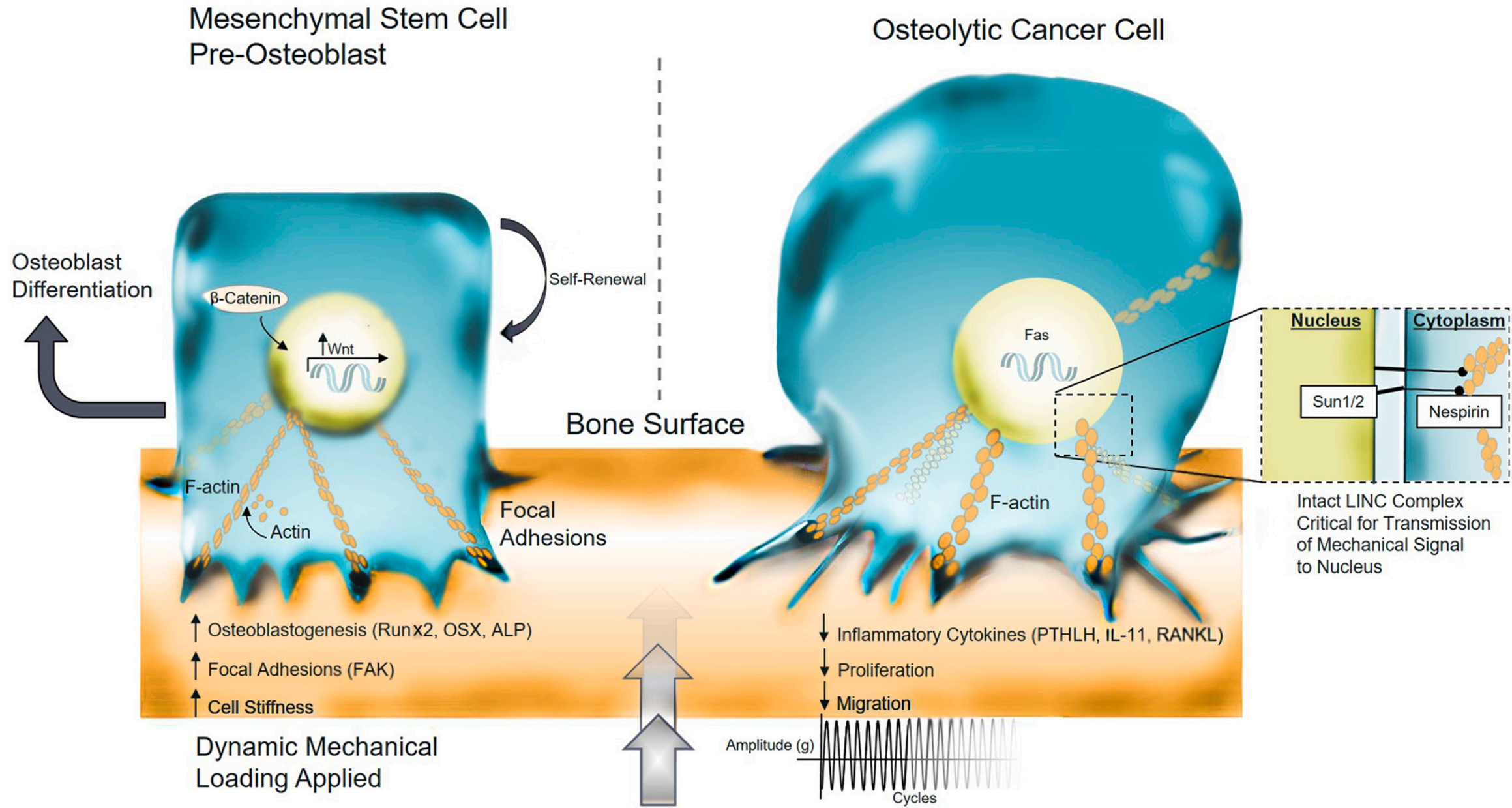
- Increases mortality and risk of secondary complications
- Degrades skeletal microarchitecture
- Bone remodeling favors bone resorption
- Elevated tumor burden
- Decreases actin assembly
- Increases tumor invasiveness
- Increases adiposity



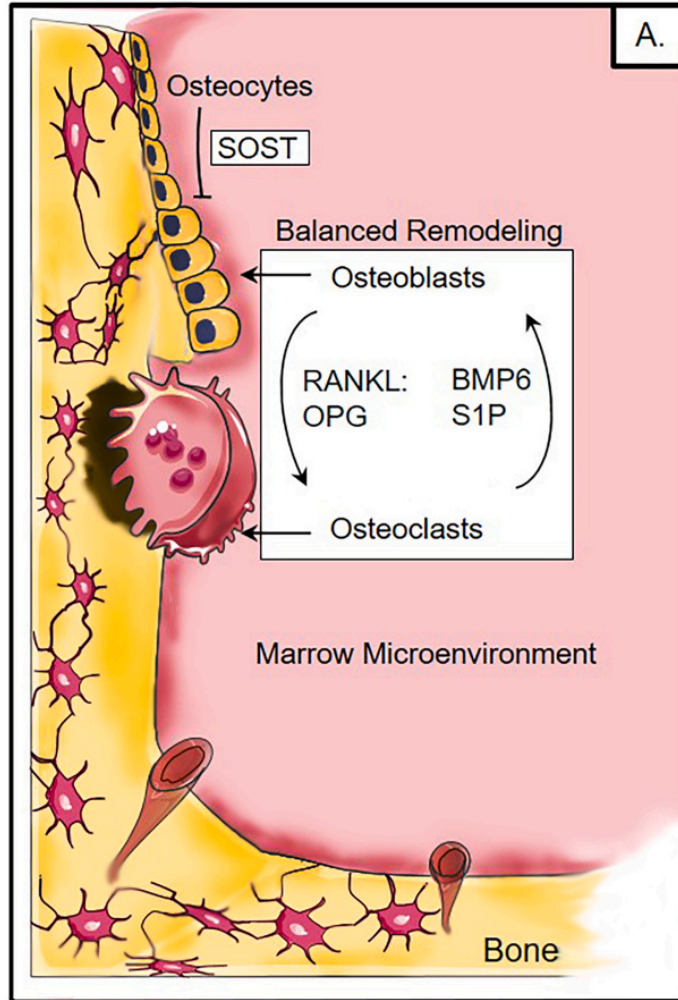
Positive Effects

- Decreases mortality
- Administration is safe without negatively impacting survival
- Preserves skeletal microarchitecture
- Balances bone remodeling: increase formation decrease resorption
- Indications of reduced tumor burden
- Increases F-actin density
- Reduces migratory capacity of tumor cells *in vitro*

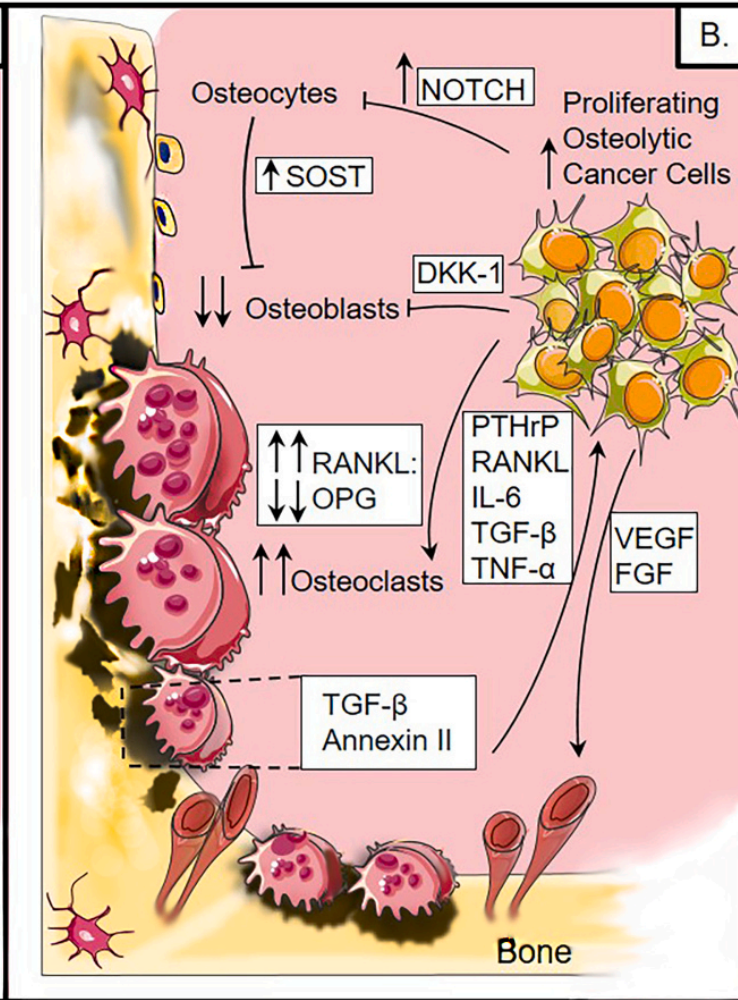
Diverging Effects on Osteoblastic Versus Tumorigenic Cells



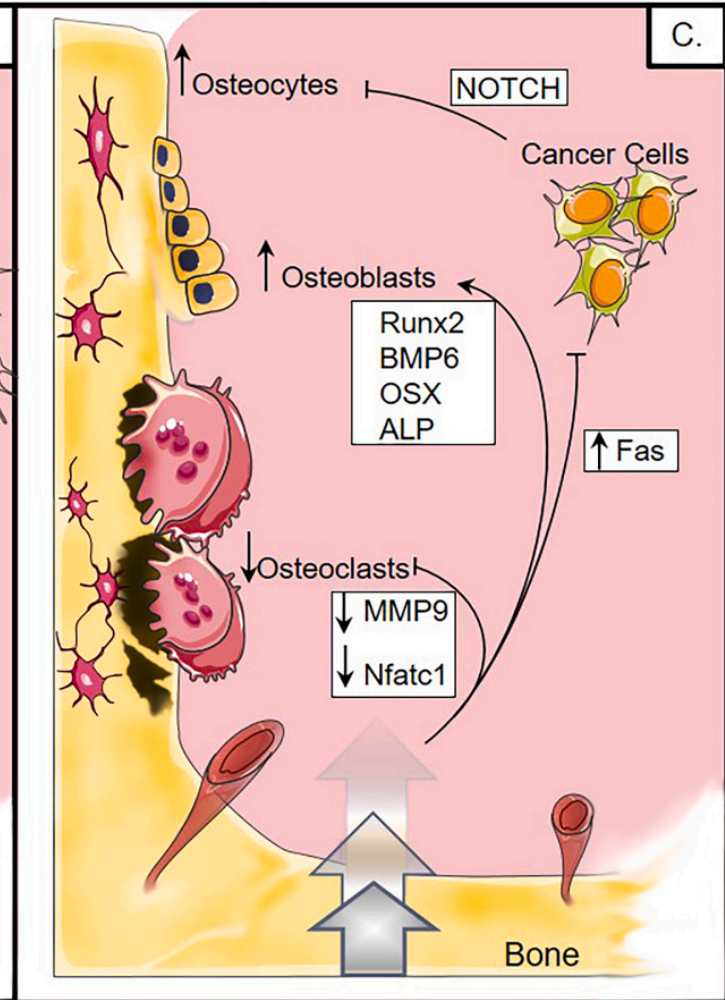
Normal Bone Remodeling



Cancer-Containing Bone



Mechanically-Loaded Bone Harboring Cancer Cells





**Is there a role of
MSC in sarcoma Tx?**

MSCs: the “Trojan Horse” for the battle against Cancer

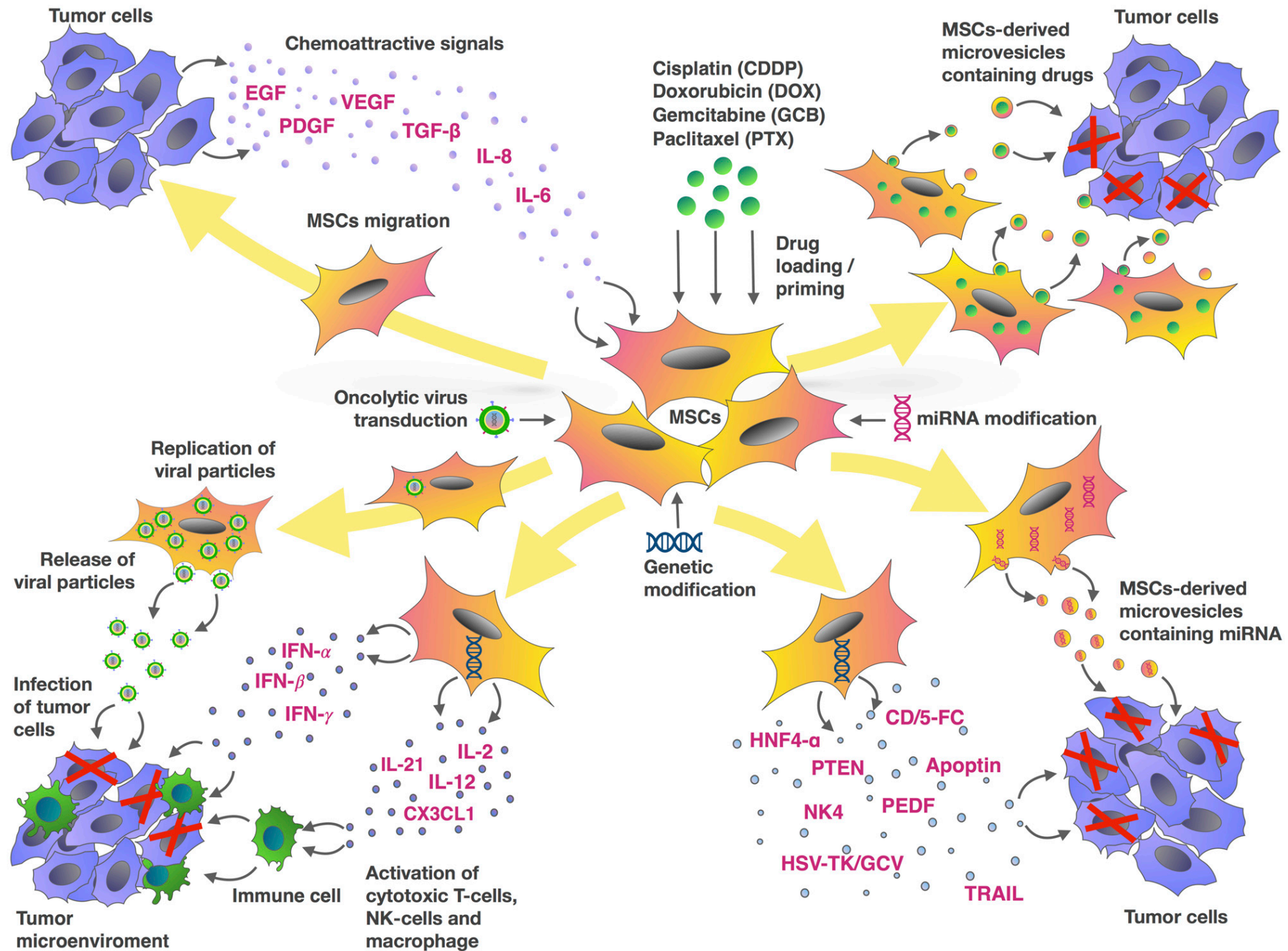




TABLE 1 | Clinical studies using MSC-based therapies for cancer treatment.

NCT Number	Purpose	Condition	Therapeutic agent	Phase	Start date	Status	Locations
NCT03896568	To determine the maximal tolerated and toxicity of allogeneic bone marrow-derived MSCs loaded with the oncolytic adenovirus DNX-2401 (BM-MSCs-DNX2401)	Glioma	BM-MSCs-DNX2401	I	2019	Recruiting	United States
NCT03608631	To determine the maximal tolerated and toxicity of MSC-derived exosomes loaded with KrasG12D siRNA (iExosomes)	Pancreatic cancer	iExosomes	I	2019	Not yet recruiting	United States
NCT03298763	To evaluate the safety and anti-tumor activity of MSCs genetically modified to express TRAIL (MSC-TRAIL)	Adenocarcinoma of lung	MSC-TRAIL	I, II	2019	Recruiting	United Kingdom
NCT03184935	To determine the safety and efficacy of human umbilical cord-derived MSCs (UC-MSC)	Myelodysplastic syndromes	UC-MSC	I, II	2017	Unknown	China
NCT02530047	To find the highest tolerable dose of bone marrow-derived MSCs expressing INF β (BM-MSC-INF β) that can be given To patients with ovarian cancer and to test their safety	Ovarian cancer	BM-MSC-INF β	I	2016	Active, not recruiting	United States
NCT02181478	To evaluate feasibility and safety of combining intra-osseous umbilical cord blood hematopoietic stem cells (UC-HSC) and MSC	Hematologic malignancies	MSCs UC-HSC	I	2015	Recruiting	United States
NCT02068794	To study the side effects and best dose of adipose tissue-derived MSCs infected with oncolytic measles virus encoding thyroidal sodium iodide symporter (AdMSC-MV-NIS)	Ovarian cancer	AdMSC-MV-NIS	I, II	2014	Recruiting	United States
NCT02079324	To determine maximum tolerable dose, safety and efficacy of intratumoral injected GX-051	Head and neck cancer	GX-051	I	2014	Unknown	Korea
NCT02270307	To evaluate the effectiveness of the use of MSCs and cyclophosphamide	Hematological malignancies	MSCs and cyclophosphamide	II, III	2014	Unknown	Russian Federation
NCT01983709	To evaluate home of bone marrow-derived MSCs (BM-MSCs) to sites of prostate cancer after systemic administration	Prostate cancer	BM-MSCs	I	2013	Terminated	United States
NCT01844661	To evaluate the safety of bone marrow-derived autologous MSCs infected with ICOVIR5 (CELYVIR) in children and adults with metastatic and refractory solid tumors	Solid tumors metastases	CELYVIR	I, II	2013	Completed	Spain
NCT01129739	To evaluate the safety and efficacy of MSCs derived from human umbilical cord/placenta (UC/PL-MSC) at a dose of 1.0E + 6 MSC/kg	Myelodysplastic syndromes	UC/PL-MSC	II	2010	Unknown	China
NCT01092026	To determine the feasibility of umbilical cord blood hematopoietic stem cell (UCB-HSC) transplantation with co-infusion of third party MSCs	Hematological malignancies	UCB-HSC with MSCs	I, II	2010	Unknown	Belgium
NCT01045382	To evaluate the capacity of MSCs to improve 1-year overall survival of patients transplanted with HLA-mismatched allogeneic hematopoietic cells	Hematological malignancies	MSCs	II	2010	Recruiting	Belgium



...conclusions and perspective

- MSC are a **heterogenous mix** of distinct cell subtypes with different morphology, function and immunoregulatory properties !
- Have we identified the true MSC? **NO!!!**
- Beware of the extraordinary pleomorphism of sarcoma esp. in small Bx (...**sampling error**)
- The significant heterogeneity of these cells strongly **affects sarcoma Tx** strategies and their **response to Tx**
- **wide surgical/oncologic excision** is needed!
- Promising role in sarcoma Tx (**Trojan horses**)
- Full **characterisation of MSC** is vital! —> another **reclassification of sarcomas?**

Thank you!

