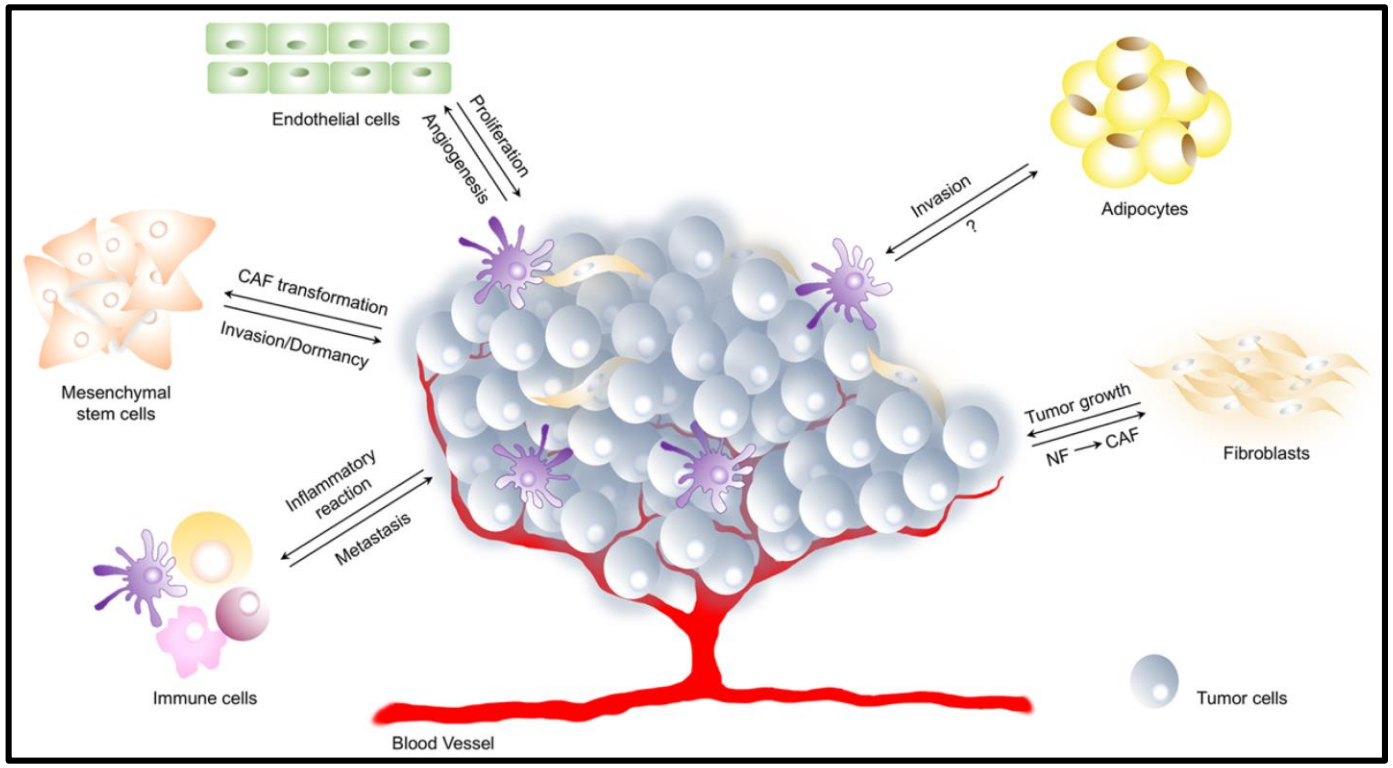
CELL DORMANCY and SENESCENCE

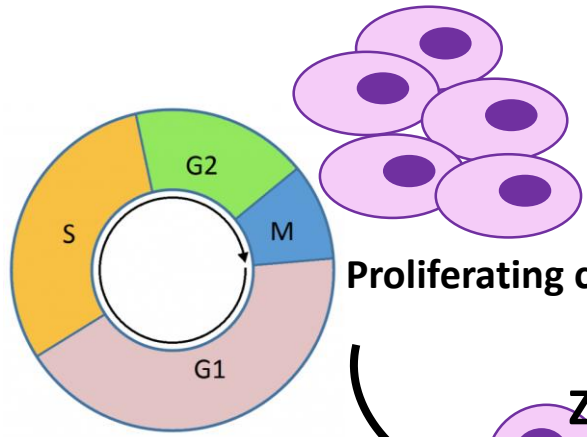
TUMOR HETEROGENEITY → Tumors are composed by various cell populations with distinct properties. Tumor cells show different morphological and phenotipic features.

Intense crosstalk between stromal and cancer cells

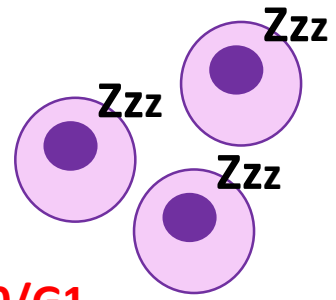


Butturini *et al.*, 2019

Stressful conditions
Hypoxia
Nutrient deprivation
Cytokines
ECM remodeling
Chemotherapeutic drugs



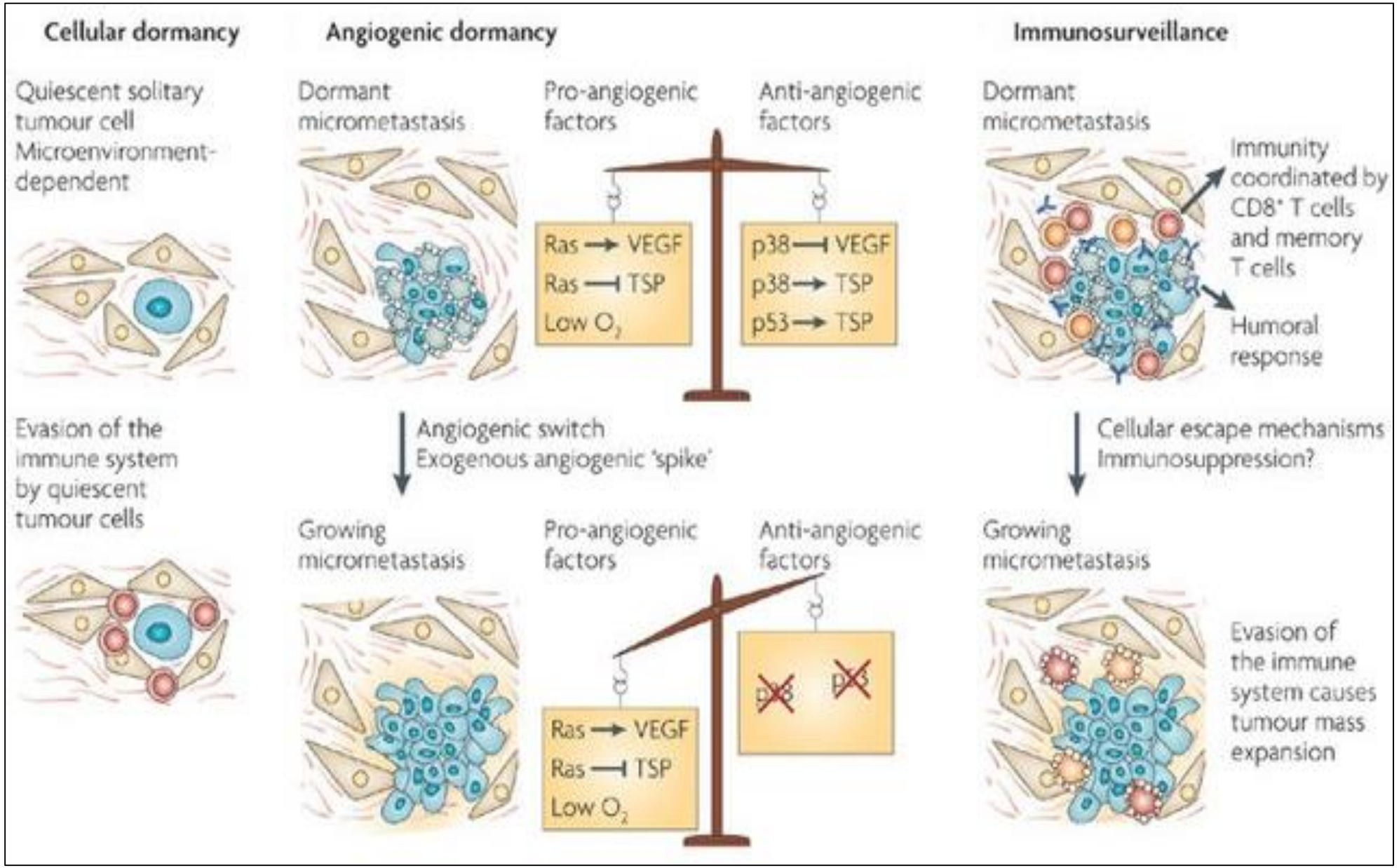
Proliferating cells



Cell cycle arrest in G0/G1

Dormant cells

The tumor microenvironment influences the behavior of cancer cells



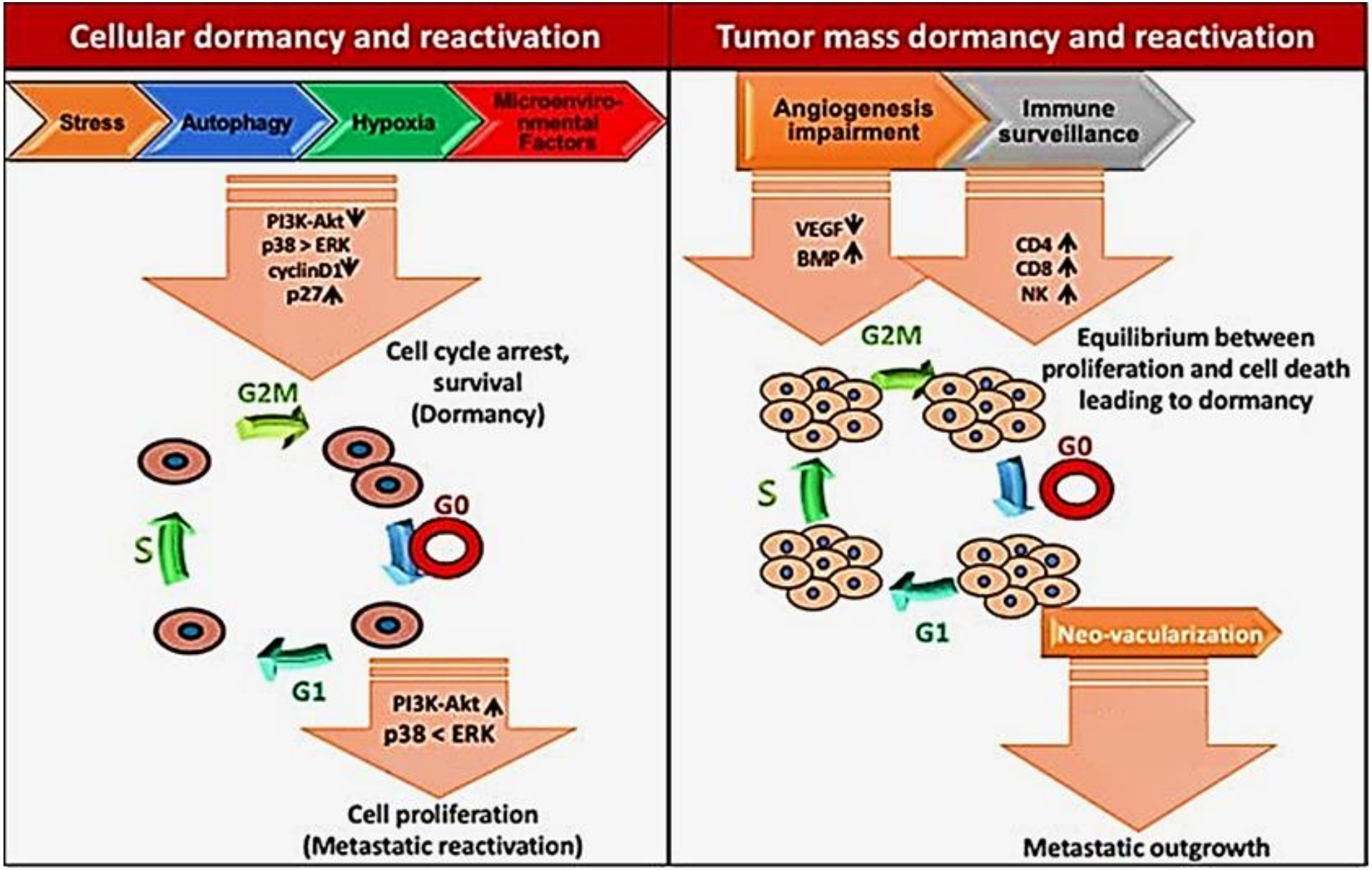
Different mechanisms of cancer dormancy (Aguirre-Ghiso, 2007)

- Cell dormancy: a mitotic arrest in G0-G1 phase along with a downregulation of Ki-67, a marker associated with elevated cell proliferation (Yeh and Ramaswamy, 2015; Yadav *et al.*, 2018).

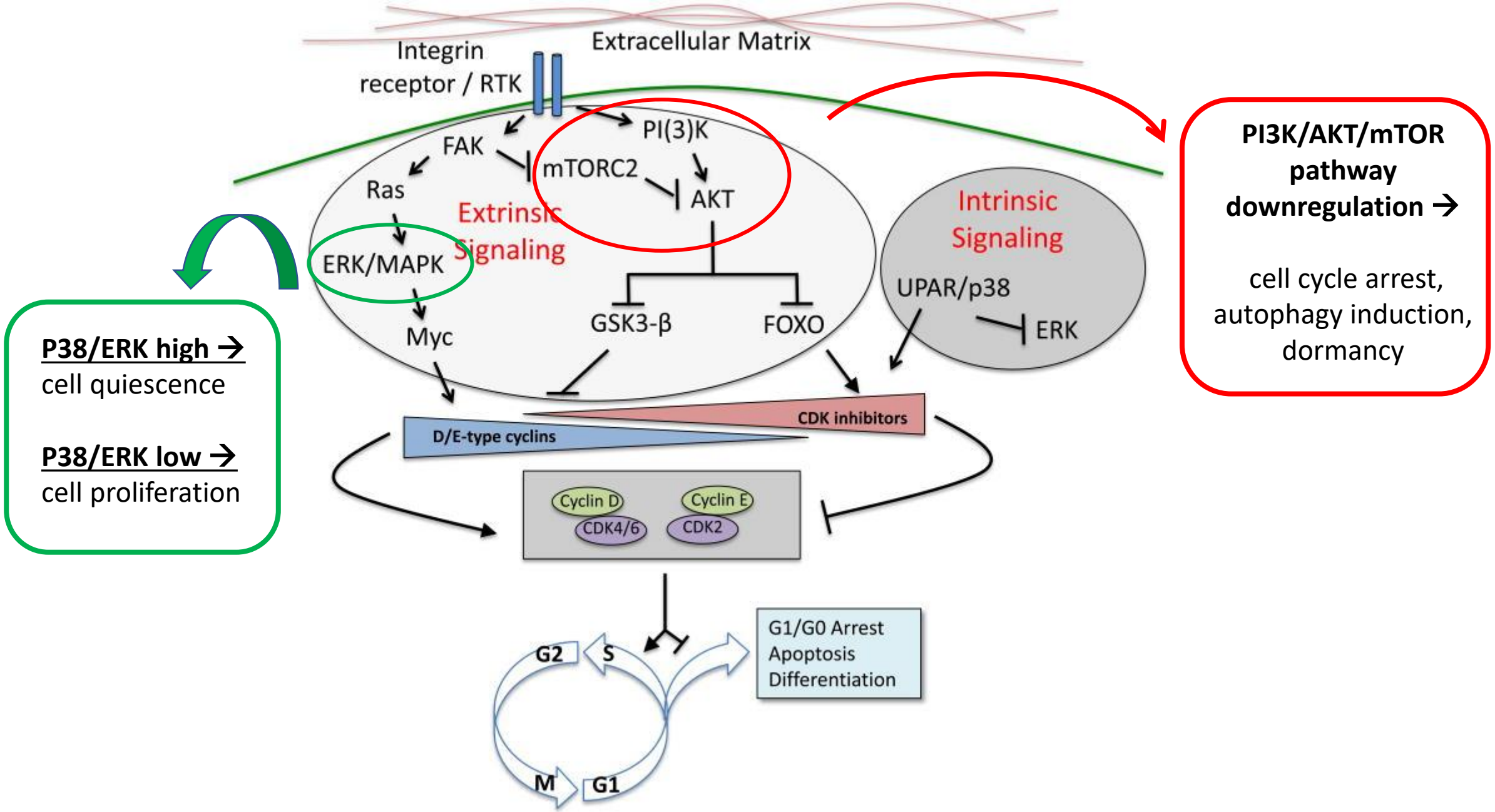
- Tumor mass dormancy: the dormant cancer mass has a defined size, that it is kept constant by the fine-tuned balance between cell division and apoptosis (Aguirre-Ghiso, 2007).

- Immunologic dormancy: cancer growth arrest that occur because of immunosurveillance mechanisms, mostly mediated by cytotoxic CD8+ T lymphocytes, which induce cytolysis of tumor cells, thus preventing residual cancer cell expansion (Müller *et al.*, 1998).

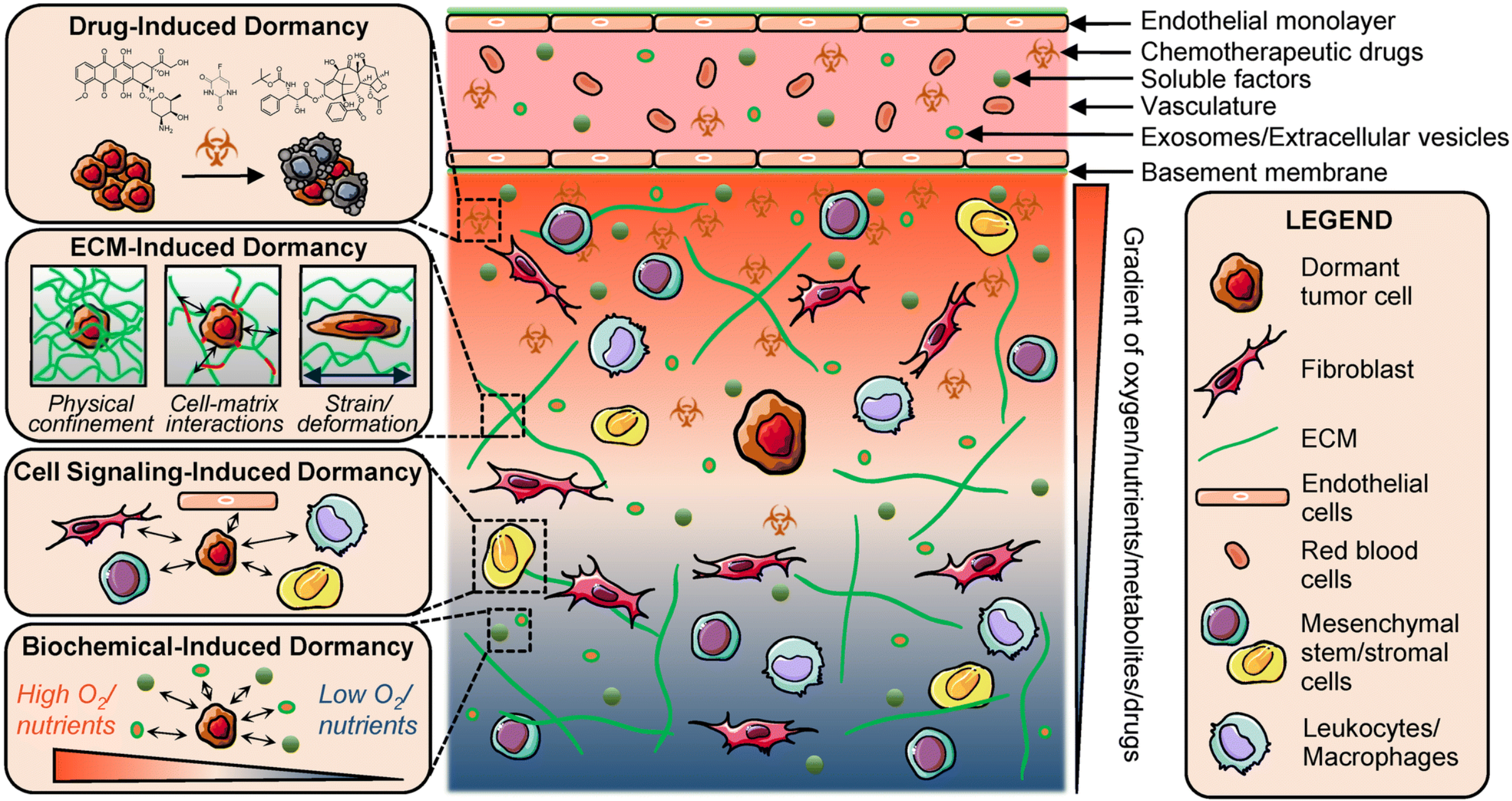
- Angiogenic dormancy: cancer cells are unable to recruit new blood vessels or remodel the pre-existing vasculature; once the tumor reaches a certain size, cancer cells arrest their proliferation because of impaired vascularization (Naumov *et al*., 2006).



Molecular mechanisms of tumor dormancy (Yadav et al., 2018).



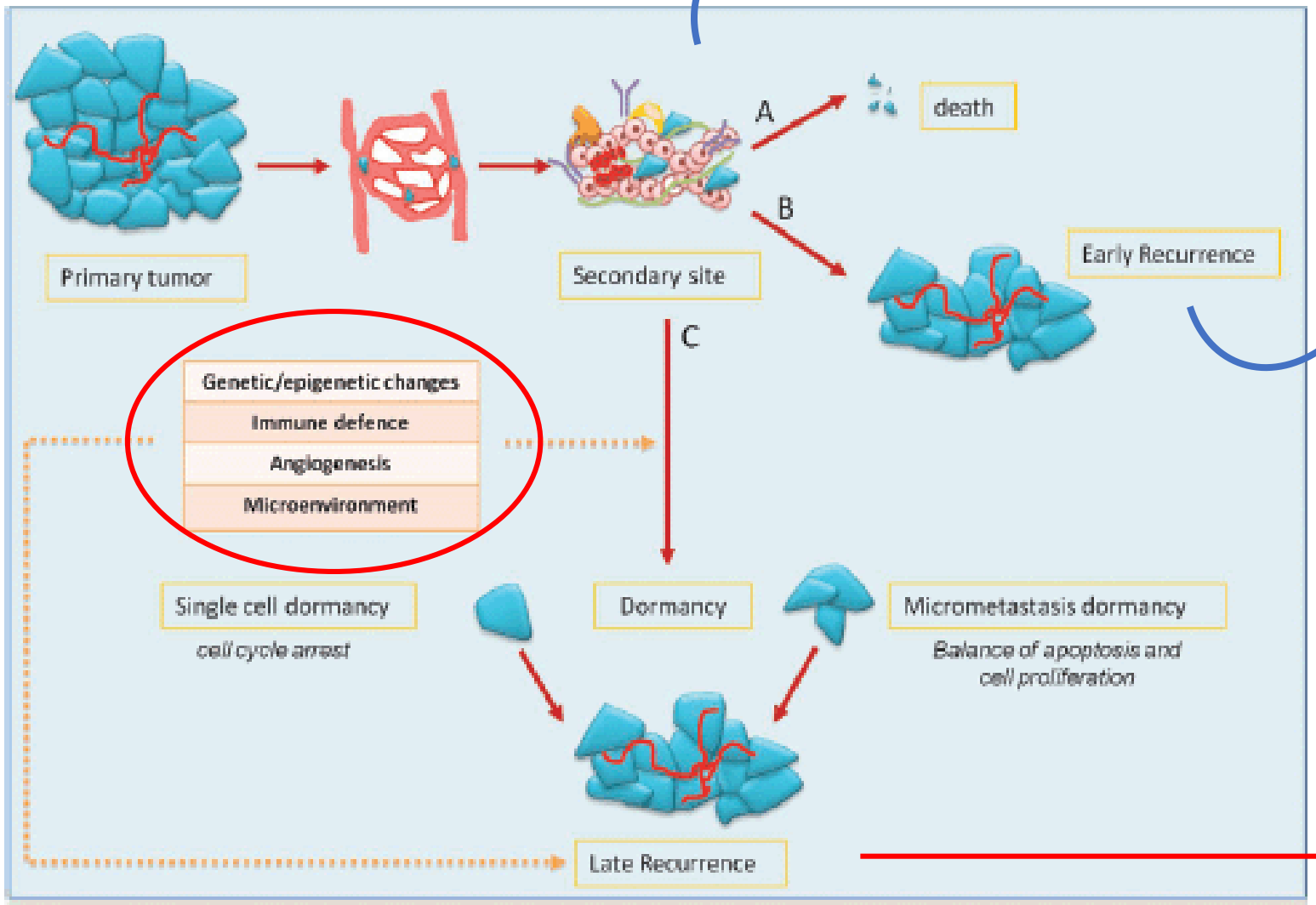
Hallmarks of cancer dormancy (Yeh and Ramaswamy, 2015).



Stimuli impinging on dormancy induction (Pradhan et al., 2018).

Dormant cells responsible for tumor relapse

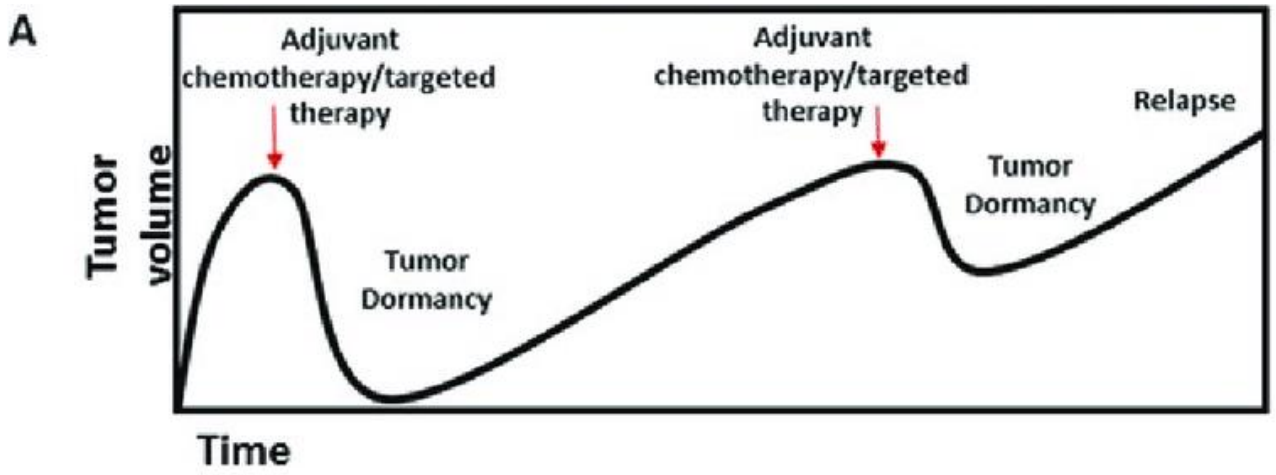
Metastasis are one of the major cause of death among cancer patients

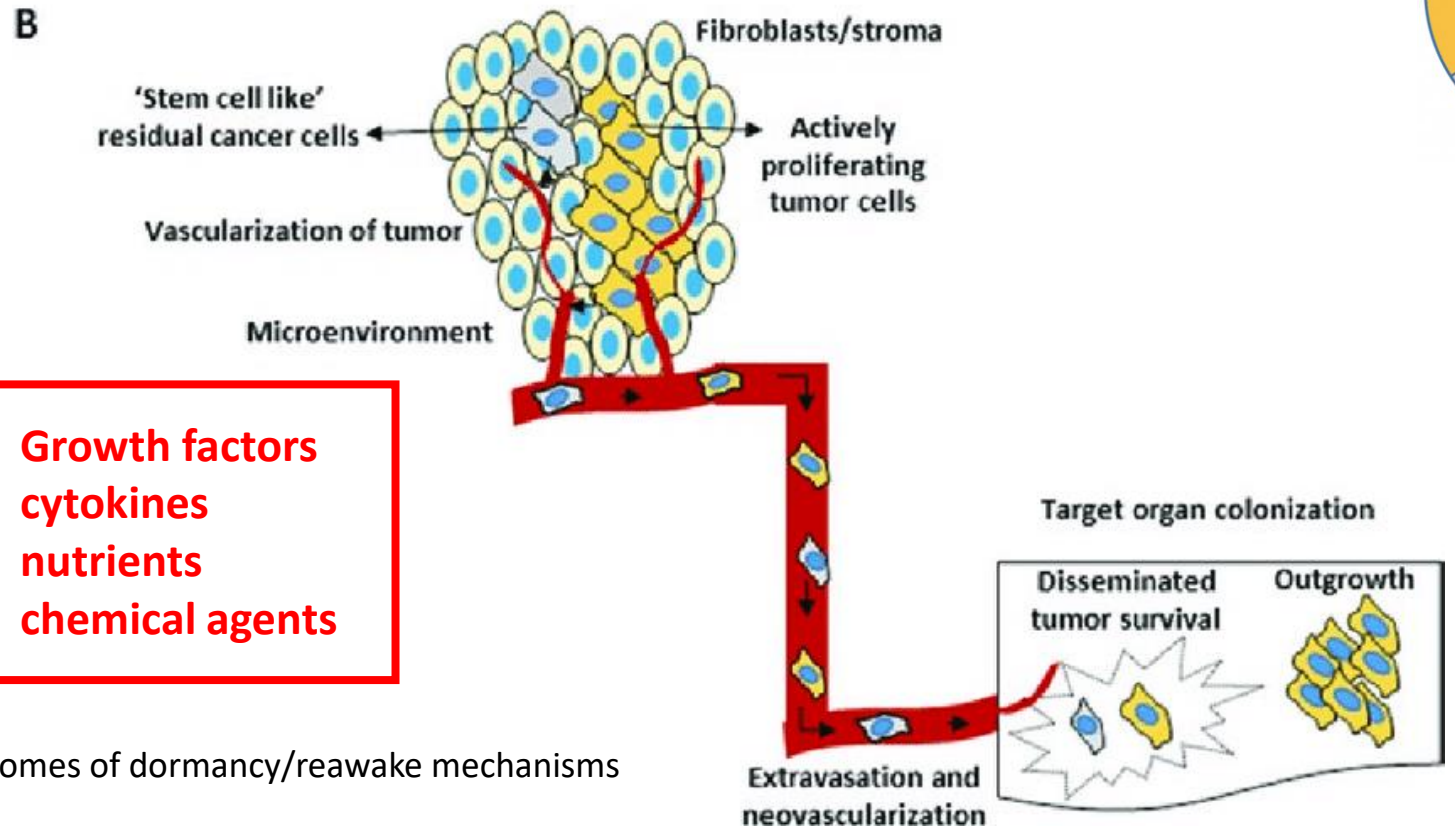


Tumor cells are already expanding at time of diagnosis and have colonized distant organs

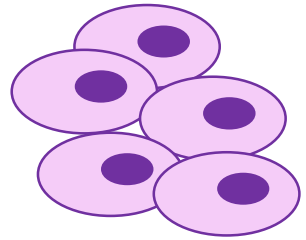
Tumor relapse after a prolonged time is due to the presence of disseminated tumor cells (DTCs) in a dormant state

Cell fate of cancer cells in metastatic process and dormancy/relapse balance (Gelao et al., 2013).

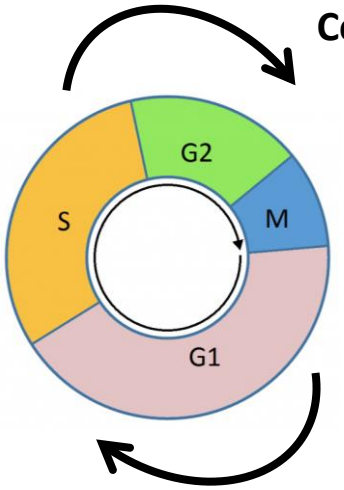


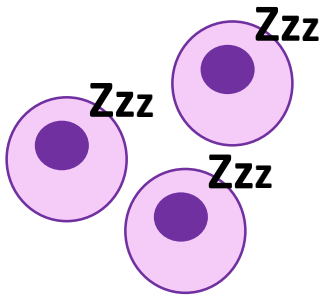


Growth factors
cytokines
nutrients
chemical agents



Cell proliferation→ tumor relapse





Dormant cells

Cell cycle arrest in G0/G1

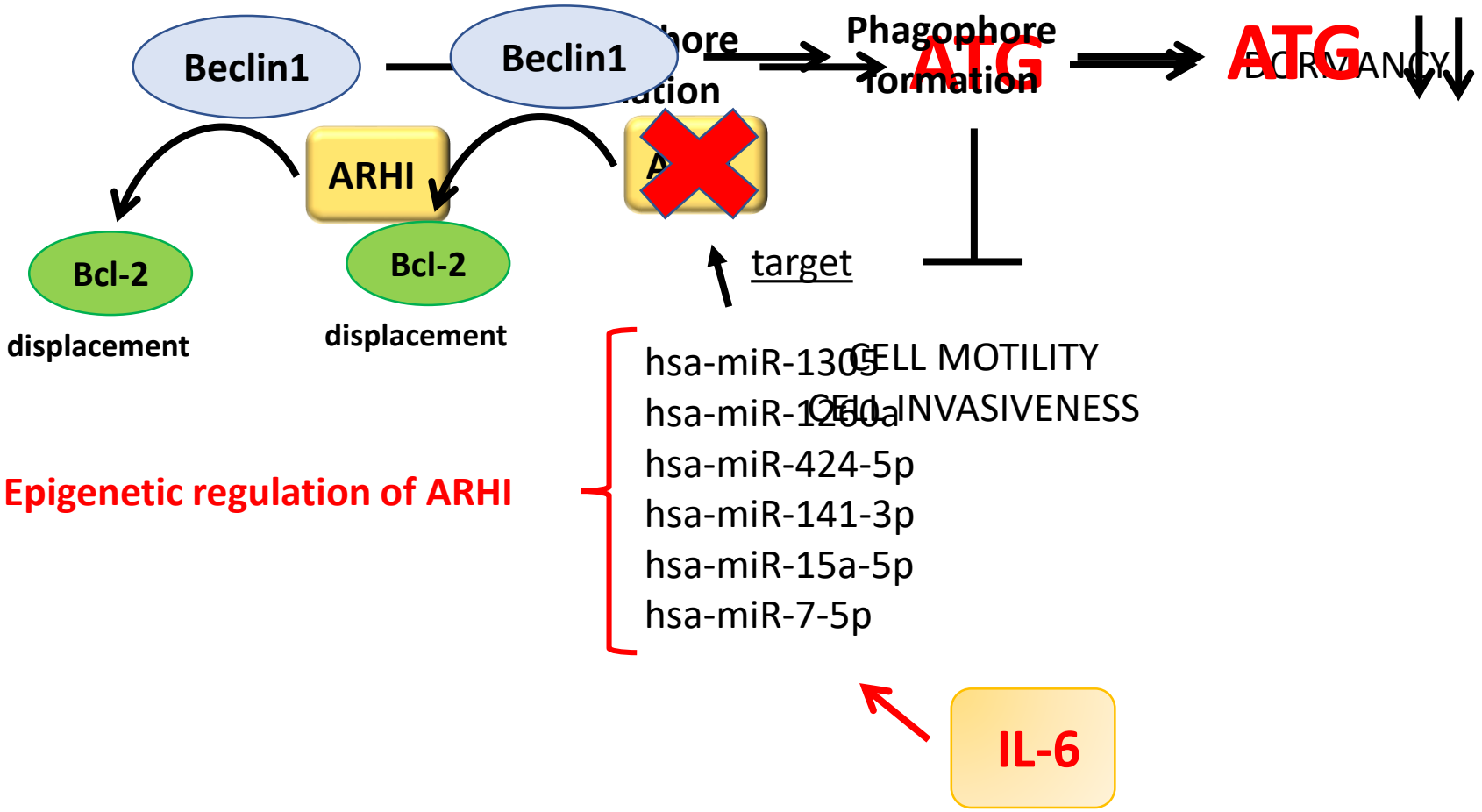
Clinical outcomes of dormancy/reawake mechanisms

(Nabavi et al., 2017).

Tumor suppressor gene ARHI (DIRAS3): a molecular marker of cancer dormancy

ARHI (DIRAS3)

- Imprinted tumor suppressor gene, genetically silenced in the majority of breast and ovarian cancers
- Positive autophagy regulator
- Induces dormancy
- ARHI overexpression correlates with p21 increase, Cyclin D1 downregulation and cell cycle arrest
- Inhibition of cell motility by sequestering STAT3 in the cytoplasm



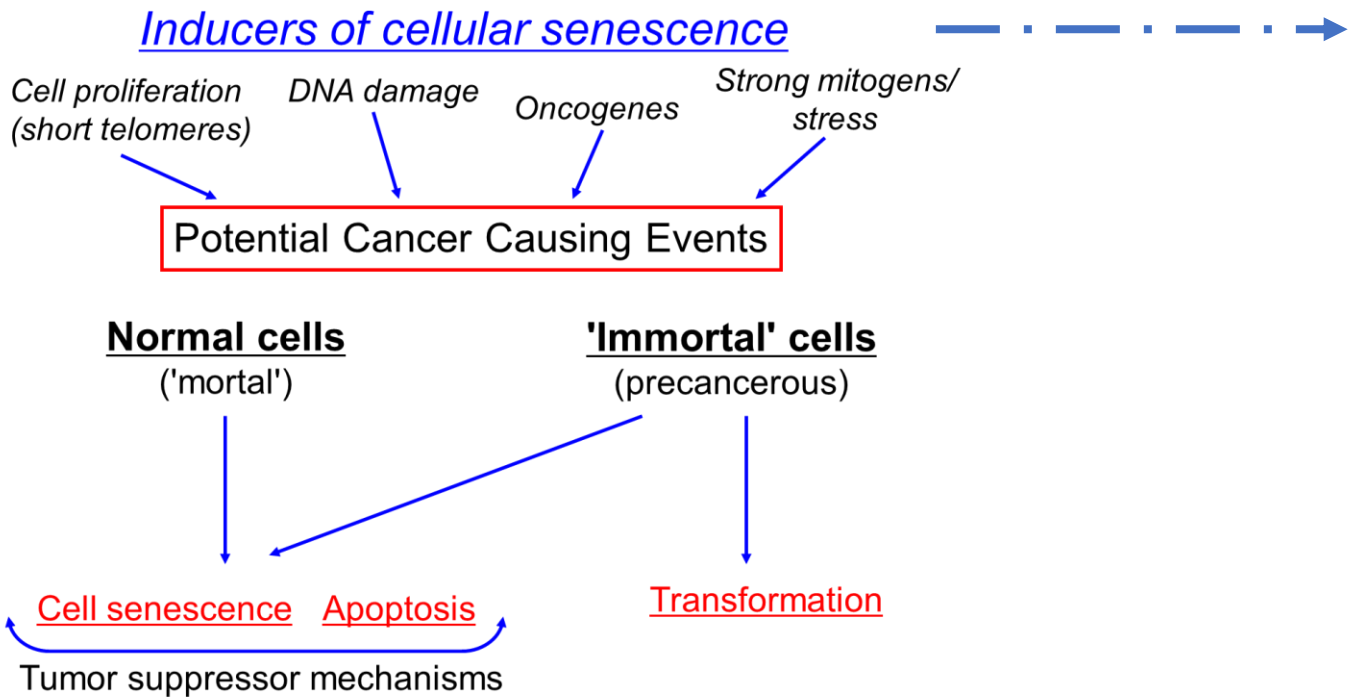
Epigenetic regulation of ARHI

Ferraresi *et al.,* 2017. Molecular Carcinogenesis

CELLULAR SENESCENCE

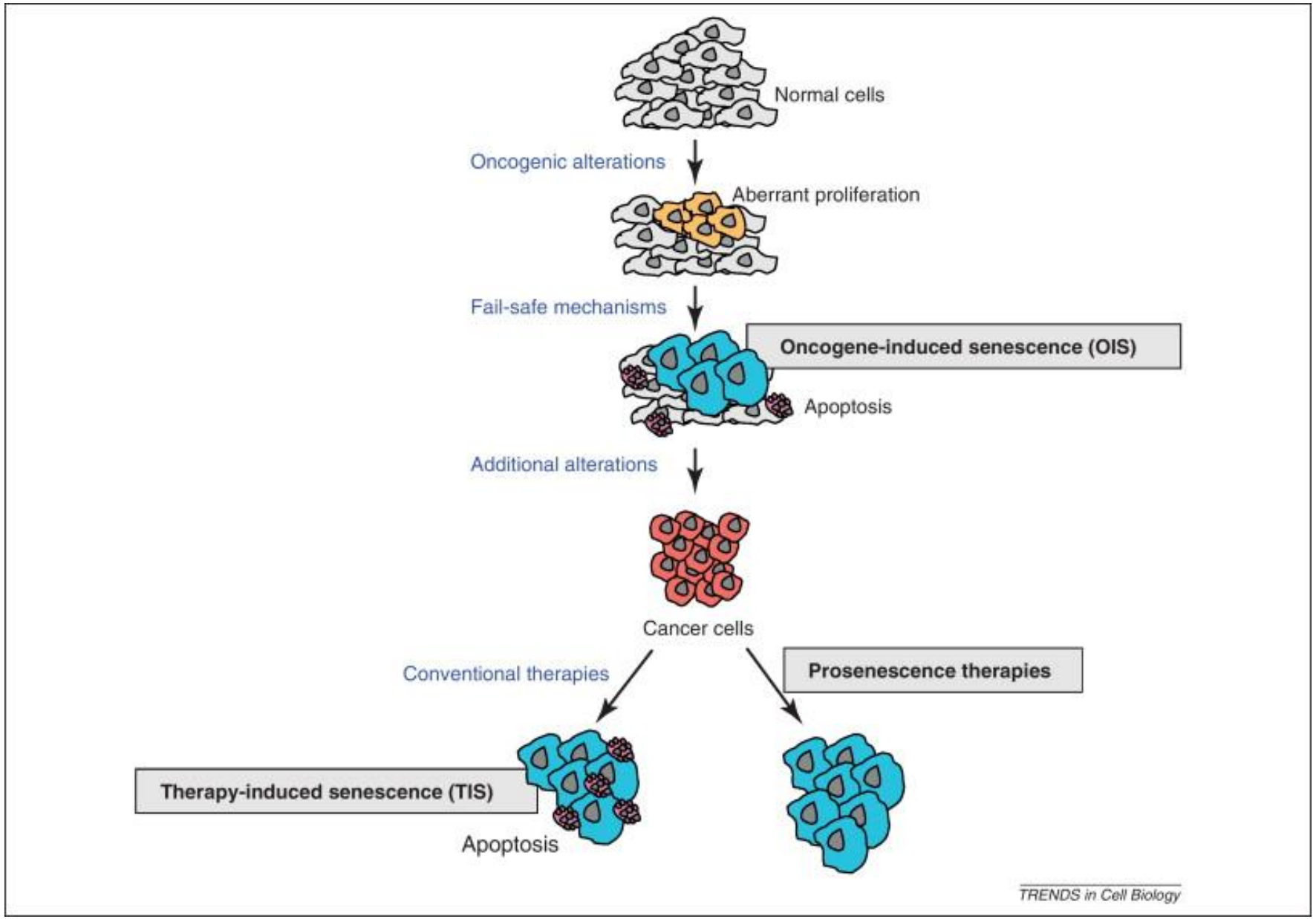
- Senescence is a stable cell cycle arrest that can be activated by oncogenic signaling and manifests with changes in cellular organization and gene expression thus limiting tumor progression

- Cell senescence is an anti-cancer mechanism that prevents the proliferation of damaged or dysfunctional cells (potential cancer cells)

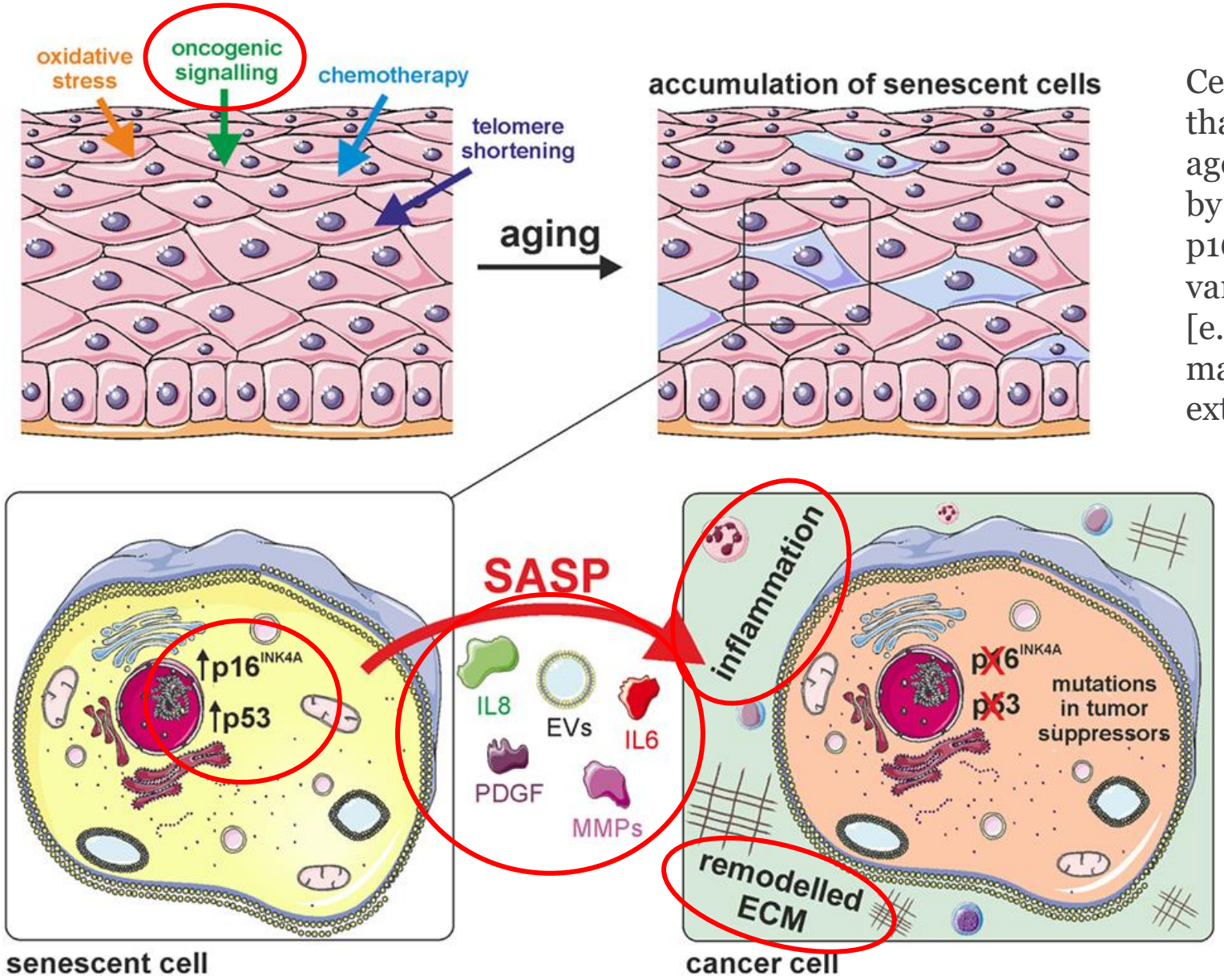


P53 and **RB** are the most important tumor suppressor genes that control cell senescence

The activity of both proteins allows normal cells to sense and respond to senescent signals



Role of senescence in cancer progression and therapy (Acosta and Gil, 2012).

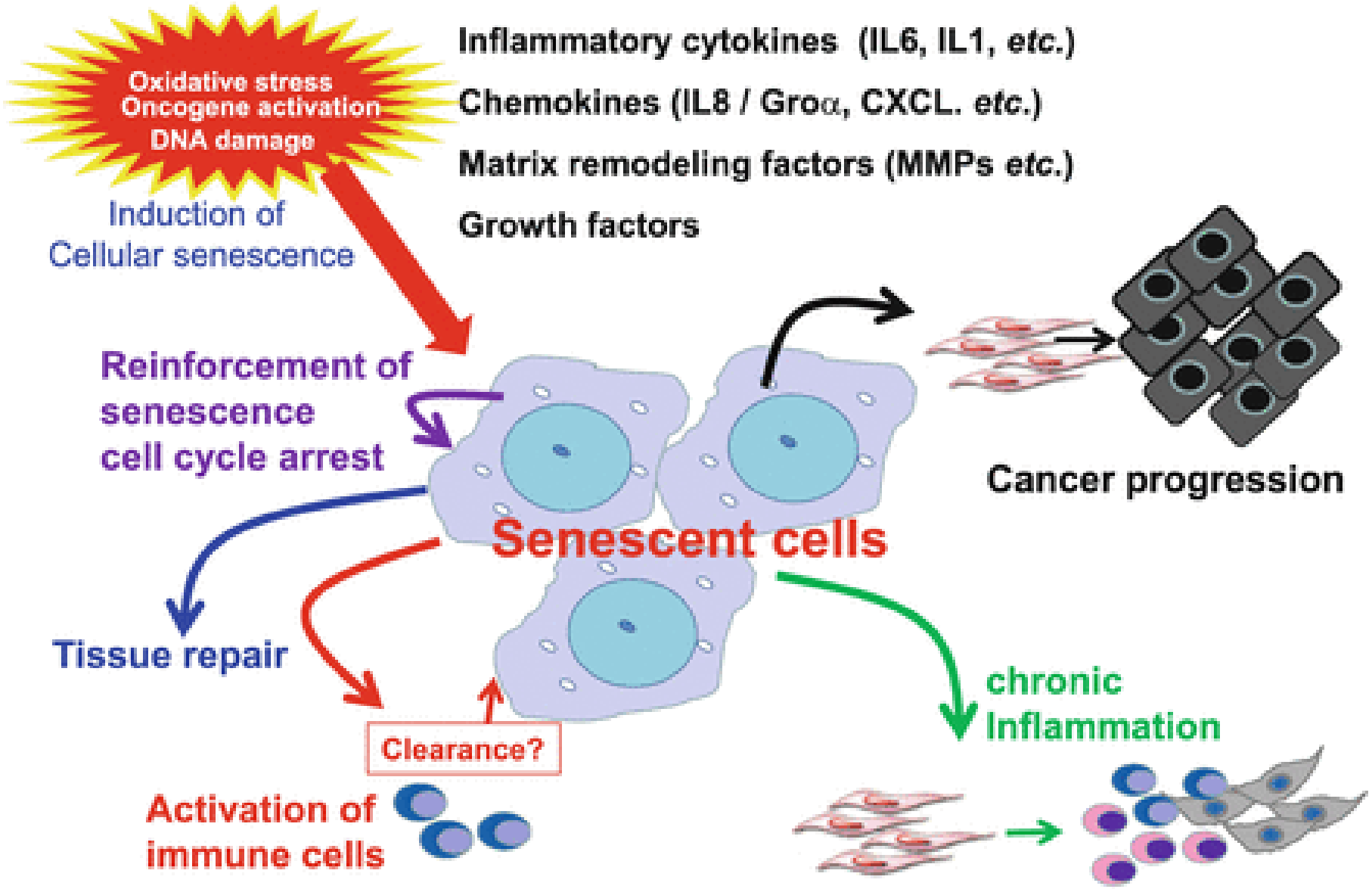


Cellular senescence is induced by various stimuli that lead to the accumulation of senescent cells in aged tissues. The senescent state is characterized by activation of the potent tumor suppressors $p16^{INK4A}$ and/or p53, as well as by secretion of various cytokines (e.g., IL-6, IL-8), growth factors [e.g., platelet-derived growth factor (PDGF)], matrix-metalloproteinases (MMPs), and extracellular vesicles (EVs).

Senescence-associated secretory phenotype (SASP) generates a pro-tumorigenic microenvironment by inducing extracellular matrix remodeling and inflammation.

Cellular senescence generates a pro-tumorigenic microenvironment (Schosserer et al., 2017).

Senescence-associated secretome



(Ohtani, 2016).