CANCER STEM CELL BIOLOGY and CANCER VACCINES
(13)

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Fall-2021

Therapy Resistence of Cancer Stem Cells

Problems in CSC Therapies

- However, there are also multiple hurdles that need to be solved to effectively eliminate CSCs.

1. The characteristics of many CSCs in specific types of tumors are not well identified.
2. Since most studies on CSCs are performed in immune-deficient mice in the absence of an adaptive immune system, these models do not reflect the biological complexity of tumors in the clinic.
3. CSCs exist in a specific niche that sustains their survival. However, isolated CSCs are used in most current studies that lacks a microenvironment.
4. The environmental factors in CSC niches are not well understood, and the relationship between TAMs/CAFs and CSCs has not been well studied.
5. Since CSCs also share some signaling pathways with normal stem cells, not all the regulatory factors that contribute to CSCs are appropriate for use as therapeutic targets in cancer treatment.

Problems in CSC Therapies

6. Whether CSCs should be activated or arrested is an open question in cancer therapy.

7. Novel signaling and more regulatory levels, such as RNA editing, epigenetics, and cellular metabolism, should be considered in cancer therapy because they also contribute to the stemness of CSCs.

8. Some inhibitors that target CSC signaling are not very specific, and so new inhibitors need to be designed.

9. Natural products that target CSCs should also be studied in the future.

10. Novel ways of targeting the microenvironment of CSCs are also promising and need to be explored.

Therapy Resistance

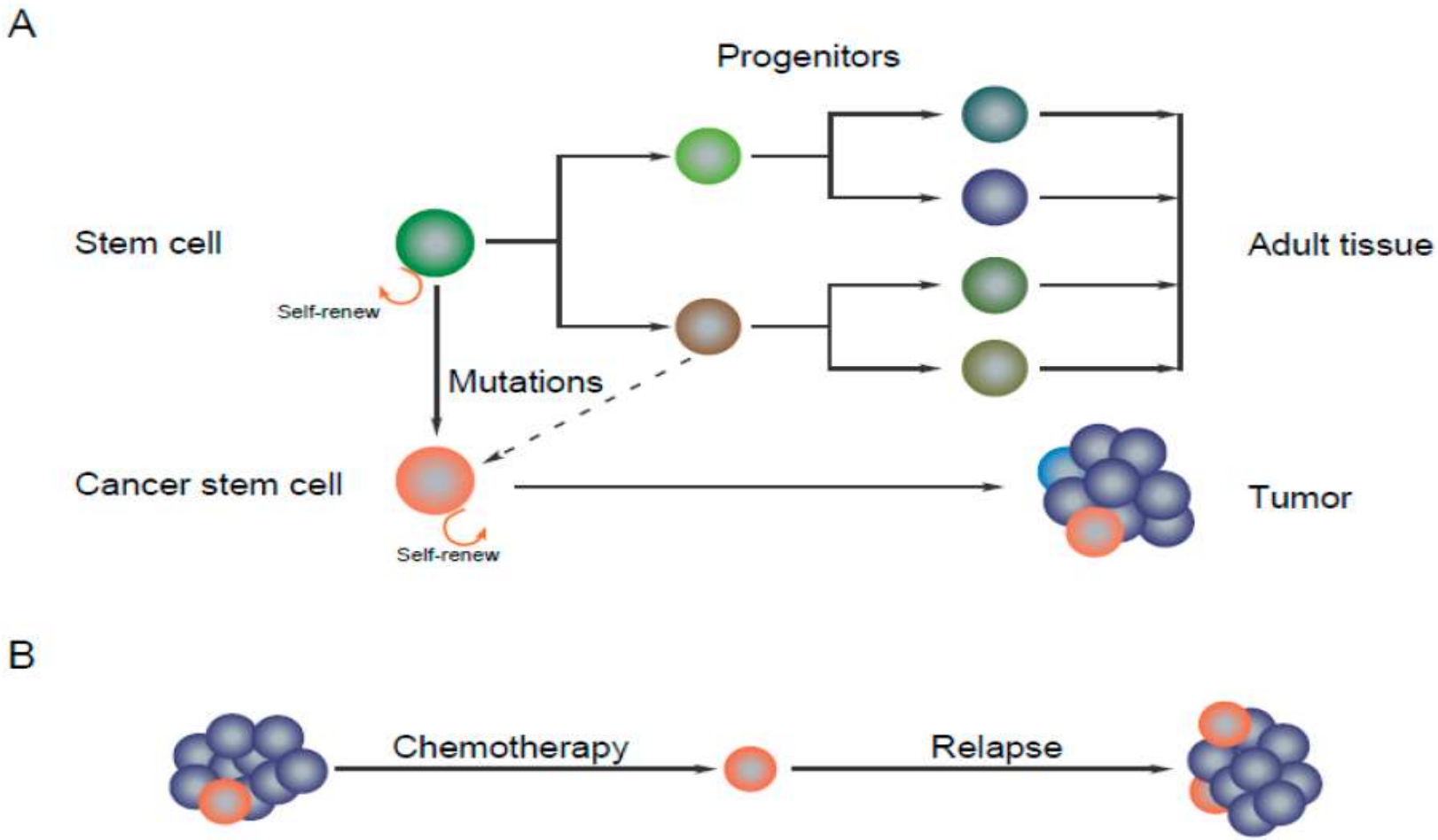
- Cancer stem cells display resistance to chemotherapy or radiotherapy-induced cell death and, thus, can form new tumors.

- Almost all chemotherapies target rapidly proliferating cell by inducing DNA damage or by inhibiting mitotic division.

- Cells exhibiting CSC or mesenchymal-like phenotype show enhanced resistance to conventional chemotherapeutic agents when compared with more differentiated or epithelial-like cancer cells.

- These therapy-resistant mesenchymal-like cells populations are responsible for cancer relapse after treatments.

- In addition, the augmentation of CSCs phenotype after therapy could be due to the increased symmetric division of these cells, and due to the shift of non-CSCs to the CSC state.


A
Progenitors
Stem cell
Self-renew
Mutations
Adult tissue
Cancer stem cell
Self-renew
Tumor
B
Chemotherapy
Relapse

Kazi, 2020

Therapy Resistance

- The gaining of therapeutic resistance may be a dynamic and reversible process, and under therapeutic pressure, cells can switch between the drug-resistant and drug sensitive states.

- Also, resistance against therapies is gained through promoting of a de-differentiated state by increasing the expression of stemness-related genes.

Therapy Resistance

- During drug treatment, cancer stem cells can enter into a dormant state and thereby avoid chemotherapy-induced apoptosis. Several factors including cell cycle regulatory genes, angiogenesis, hypoxia and tumor microenvironment play important roles in keeping the cells in this state.

- Furthermore, cancer stem cells show deregulation of several cellular signaling pathways. Activation of anti-apoptotic pathways such as PI3K, Wnt/-catenin and Notch signaling can provide survival benefit. Increased expression of ATP-binding cassette (ABC) transporters (ABCB1, ABCC1 and ABCG2) helps cancer stem cells to pump out drugs.

CSC Plasticity and Therapy Resistance

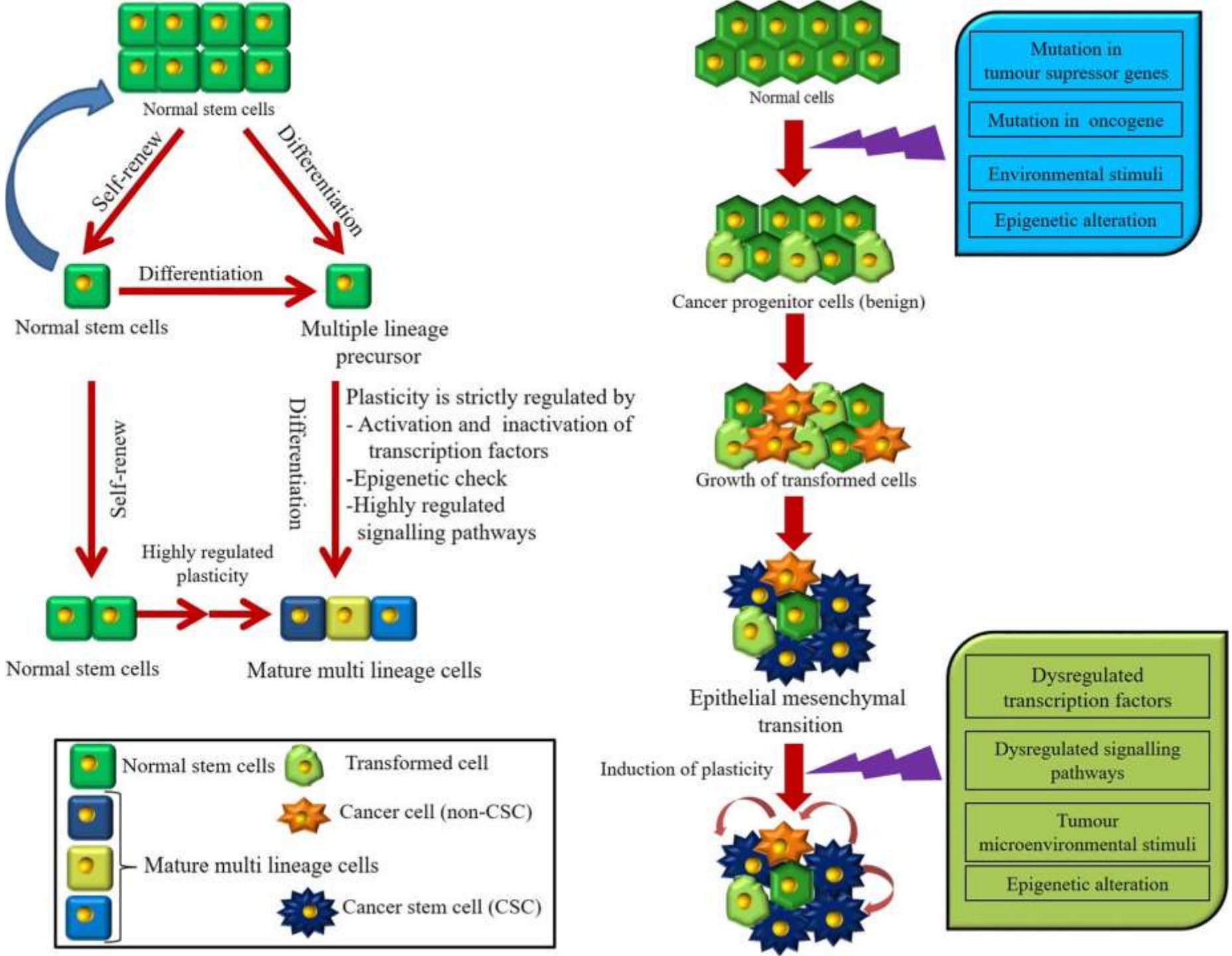
- Therapy resistance property of CSCs depends on the interplay between microenvironmental signals, metabolic adaptation, expression of transcription factors and epigenetic alterations etc., which in turn contribute to the plasticity of CSCs.

- Sustained hypoxic microenvironment might promote therapy resistance by activation of hypoxia-inducible factor (HIF). HIF pathway confers chemo- and radioresistance of certain tumors.

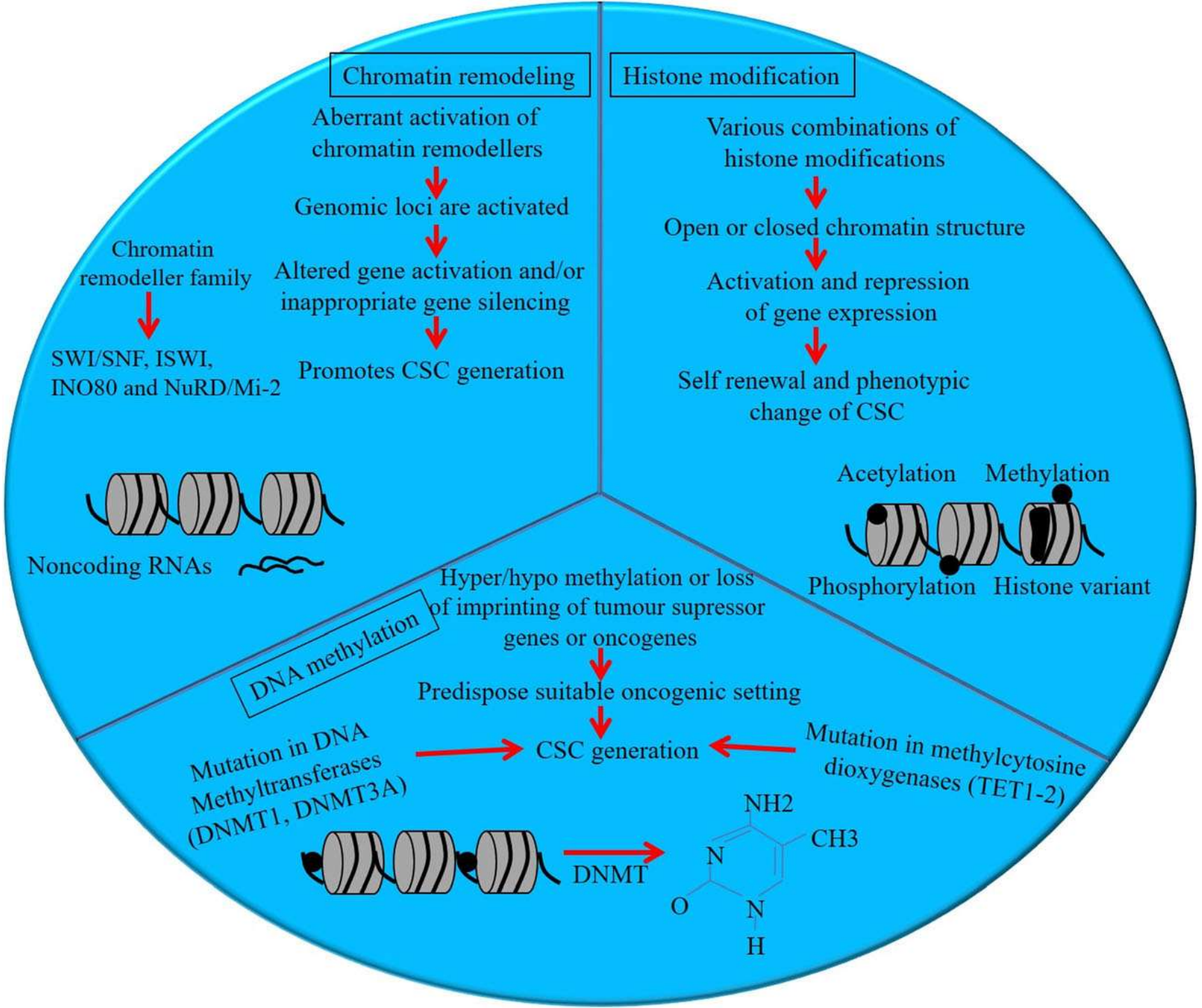
- Mitochondria represent another defense line against DNA insults caused by reactive oxygen species (ROS) during radio- or chemotherapy.

- The RedOx system of these organelles provides a universal protection against ROS excess and helps eliminating oxidative damage without activation of DDR pathways.

- High activity of aldehyde dehydrogenases (ALDHs), the enzymes responsible for the scavenging of radiation-induced free radicals and the production of the antioxidant NAD(P)H, is also characteristic of chemoresistant cancer cells and CSC but not the regular cancer cells.



Das et al., 2020



Das et al., 2020

-CSC Microenvironment and Therapy Resistance

- Cancer stem cells actively interact with the microenvironment through paracrine factors, cell surface receptors and adhesion molecules.

- The cancer stem cell microenvironment plays an important role in maintaining its self-renewal capability and differentiation potential. The microenvironment protects cancer stem cells from chemotherapy-induced apoptosis and increases radiological tolerance.

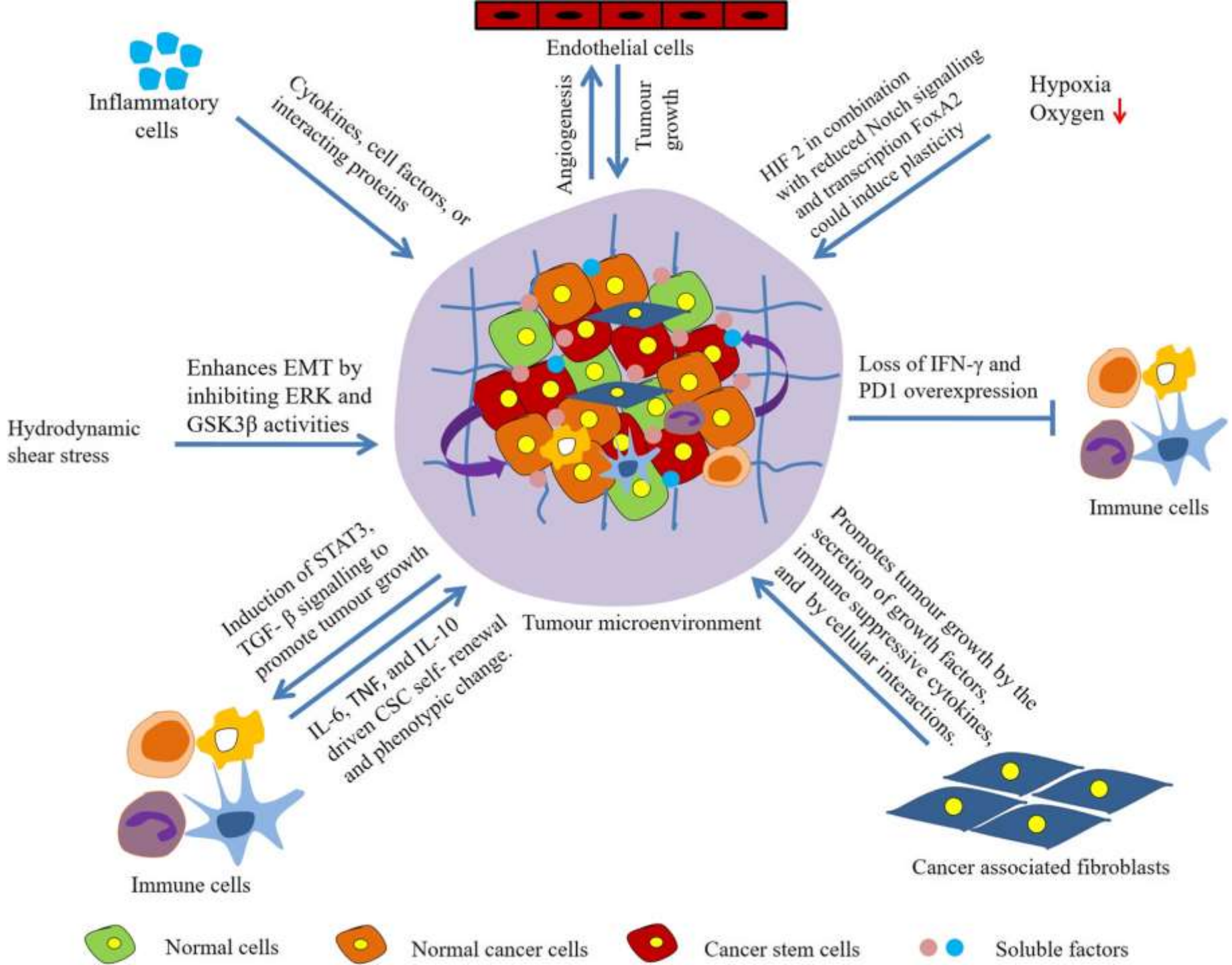
-CSC Microenvironment and Therapy Resistance

- Tumour microenvironment is very important in the therapy resistance property of CSCs. Local signals from tumour microenvironment influence the generation of several drug-tolerant phenotypes such as EMT and CSC-like states in region-specific manner in the tumour.

- TGFβ, IL-6, exosomes, and many other cancer associated fibroblasts(CAF)-secreted cytokines as well as growth factors have been identified to push the formation of drug-resistant EMT phenotypes in the heavily localized CAFs invasive tumour front.

- Hypoxia can induce therapeutic resistance by creating a signalling network suitable for drug-tolerant EMT states.

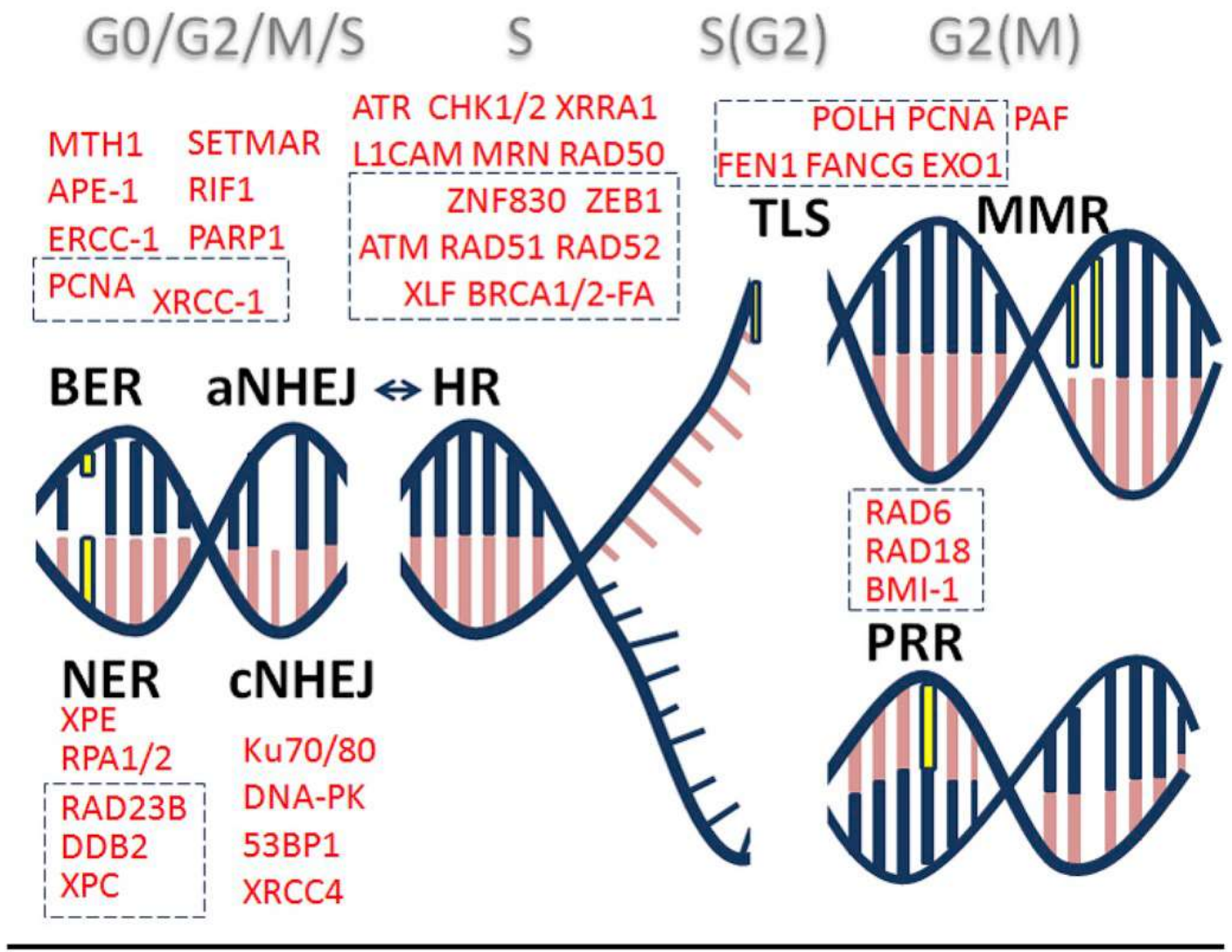
- Cancer stem cells can undergo epithelial-to-mesenchymal transition (EMT) and EMT is associated with drug resistance.



Das et al., 2020

DNA Damage Response and CSCs

- Recent findings suggest that activation of DDR pathways can be responsible for the resistance of CSC and radio-/chemo-resistant cancer cells.
- The DDR is a very complex network that is comprised of several pathways, each of which is involved in much cross-talk both within the network and with other signalling systems.
- Several recent studies linked stemness of cancer cells with the activation of DDR pathways and chemoresistance.
- Population of lung cancer cells expressing stemness marker CD133 contained altered expression of DNA repair genes that are inducible upon exposure to chemotherapy.
- DDR and the expression of various repair proteins are also found to be highly upregulated in Lin−CD29HCD24H tumor-initiating cells isolated from mammary gland tumors, indicating an elevated DDR in these CSC.



Abad et al.,2020

Conclusion

- Several mechanisms might decrease efficiency of radio- and chemotherapy in CSC comparatively to non-CSC.

- Among those like autophagy, microRNAs and exosome-containing microRNAs, EMT-related pathways, signalling pathways, tumor microenvironment, DNA damage responses and CSC plasticity which promotes tumor cell reprogramming into CSC are the main ways of resistance of CSCs to therapy.

References

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