

During this module, discuss Optimal Tumor Cancer Treatment. What is the muddiest point? What surprises you the most? What else can you add to what we've learned on this topic in this module (provide references to resources)?

What is the muddiest point?

The challenge in optimal tumor cancer is that this treatment needs to inhibit proliferation and induce differentiation.

- If you decrease proliferation, you get fewer cycling CSCs, which also means there are fewer CSCs available for differentiation. Slowing down CSC proliferation also leads to a larger pool of non-cycling CSCs, which remain resistant.
- If you only promote differentiation, you increase the number of DCs that eventually die, but you will also reduce proliferation; and with not enough cycling CSCs, you will also end up slowing down differentiation: with fewer cycling CSCs, differentiation slows, as cycling CSCs ultimately divide into two non-cycling CSCs.

What surprises you the most?

I was surprised to learn how quorum sensing acts as a regulatory feedback mechanism on both differentiation and proliferation, particularly that the differentiation probability increases as CSC density increases. This makes sense, as a high-density CSC environment may trigger differentiation to free up space for proliferating CSCs, since differentiated cells (DCs) have a limited lifespan. What also is counter-intuitive is the fact that reducing the proliferation rate does not affect non-cycling CSCs.

What else can you add to what we've learned on this topic in this module (provide references to resources)?

I was curious to know more about CSC due to their critical role in metastasis, drug resistance, and the development of CSC-targeted therapeutics.

CSCs are difficult to identify and isolate due to their low prevalence, only 0.01-2% of the tumor population, and the fact that they share similar pathways and transcription factors with normal stem cells.

Although various biomarkers, including CD133, CD44, CD34, EpCAM, and CD38, have been linked to CSCs, none are entirely specific. Magnetic-activated cell sorting (MACS), the most widely used technique to separate CSCs is cumbersome and requires a high CSC count, making it less effective for rare CSC populations.

CSC can originate from normal stem cells, progenitor cells, or mutated and epigenetically altered stem-cell fusions. Major transcription factors include Oct4, Sox2, Nanog, KLF4, and MYC:

- High levels of Oct4 have been associated with glioma tumors, chemoresistance, and poor clinical outcomes.
- Sox2 is found in squamous carcinoma cancers and drives metastasis of the cells.
- Abnormal expression of Nanog4 has been reported in breast, cervical, brain, colon, head and neck, lung, and gastric cancers.

- Downregulation of KLF4 is found in colorectal and gastric cancers and other diseases.
 - Deregulated MYC plays an important role in maintaining CSC population. Wnt/ β pathway regulates the pluripotency of CSCs and determines their differentiation; other important pathways for CSCs include Notch, Hedgehog, JAK-STAT, PI3K/AKT/mTOR, TGF/Smad and PPAR pathways.
- Some extracellular factors that influence CSC formation and maintenance include TAM, CAF and hypoxia.
- Several clinical trials are investigating therapies targeting CSC surface markers, signaling pathways, and microenvironmental interactions. However, fundamental questions remain, particularly regarding whether CSCs should be activated (to force differentiation) or arrested (to inhibit proliferation) for optimal therapeutic outcomes ¹⁻³.

References

1. Yang, L. *et al.* Targeting cancer stem cell pathways for cancer therapy. *Signal Transduct. Target. Ther.* **5**, 8 (2020).
2. Chu, X. *et al.* Cancer stem cells: advances in knowledge and implications for cancer therapy. *Signal Transduct. Target. Ther.* **9**, 170 (2024).
3. Masciale, V. *et al.* The molecular features of lung cancer stem cells in dedifferentiation process-driven epigenetic alterations. *J. Biol. Chem.* **300**, 107994 (2024).