Tumor immune stemness at the interface of cancer plasticity and immune evasion

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The idea of cancer stem cells no longer sits comfortably within a strict hierarchical model, and over time it has drifted toward a more flexible, state-based view, especially once immune regulation enters the picture. A growing body of evidence points to the notion that what we loosely call "tumor immune stem cells" does not correspond to a clearly bounded lineage. Instead, it seems to reflect a functional condition in which stemness-related programs and immune-evasive properties come together. This overlap shows up across different tumor types, experimental systems, and treatment settings, which gently suggests that immune privilege is not simply an added feature layered onto cancer stem cells, but may be woven into the stemness program itself.[1] To conceptualize this emerging view, tumor immune stemness can be considered as a dynamic functional state arising at the interface of cancer plasticity and immune evasion (Figure. 1).

At the cellular level, cancer stem-like populations tend to exhibit a consistently low level of immunogenicity. Components of the antigen presentation machinery are often suppressed, MHC class I expression is reduced, and tumor-associated antigens can be selectively silenced, a combination that quietly undermines effective T cell recognition. What becomes more apparent over time is that these traits do not remain fixed. Under immune surveillance or therapeutic stress, cancer cells that are not initially stem-like can slip back into a stem-like state while simultaneously acquiring immune evasive features, suggesting that immune stemness is a condition that can be induced and reversed, rather than something permanently hard-wired into a specific cell population.[2]

Therapeutic pressure acts as a key driver of this transition by selectively eliminating highly immunogenic and differentiated tumor cells, while favoring cells capable of adaptive reprogramming. Immune checkpoint blockade, cytotoxic chemotherapy, and targeted therapies can all impose strong selective stress that activates stress-response pathways, epigenetic remodeling, and inflammatory signaling, including interferon, TGF-β, and hypoxia-associated programs. These signals lower the threshold for non-stem tumor cells to re-enter stem-like transcriptional states, often in parallel with the induction of immune-evasive features such as reduced antigen presentation and enhanced checkpoint expression. Rather than inducing stemness *de novo*, therapeutic pressure reshapes the fitness landscape of the tumor, making stem-like, immune-resistant states more evolutionarily advantageous under sustained treatment.

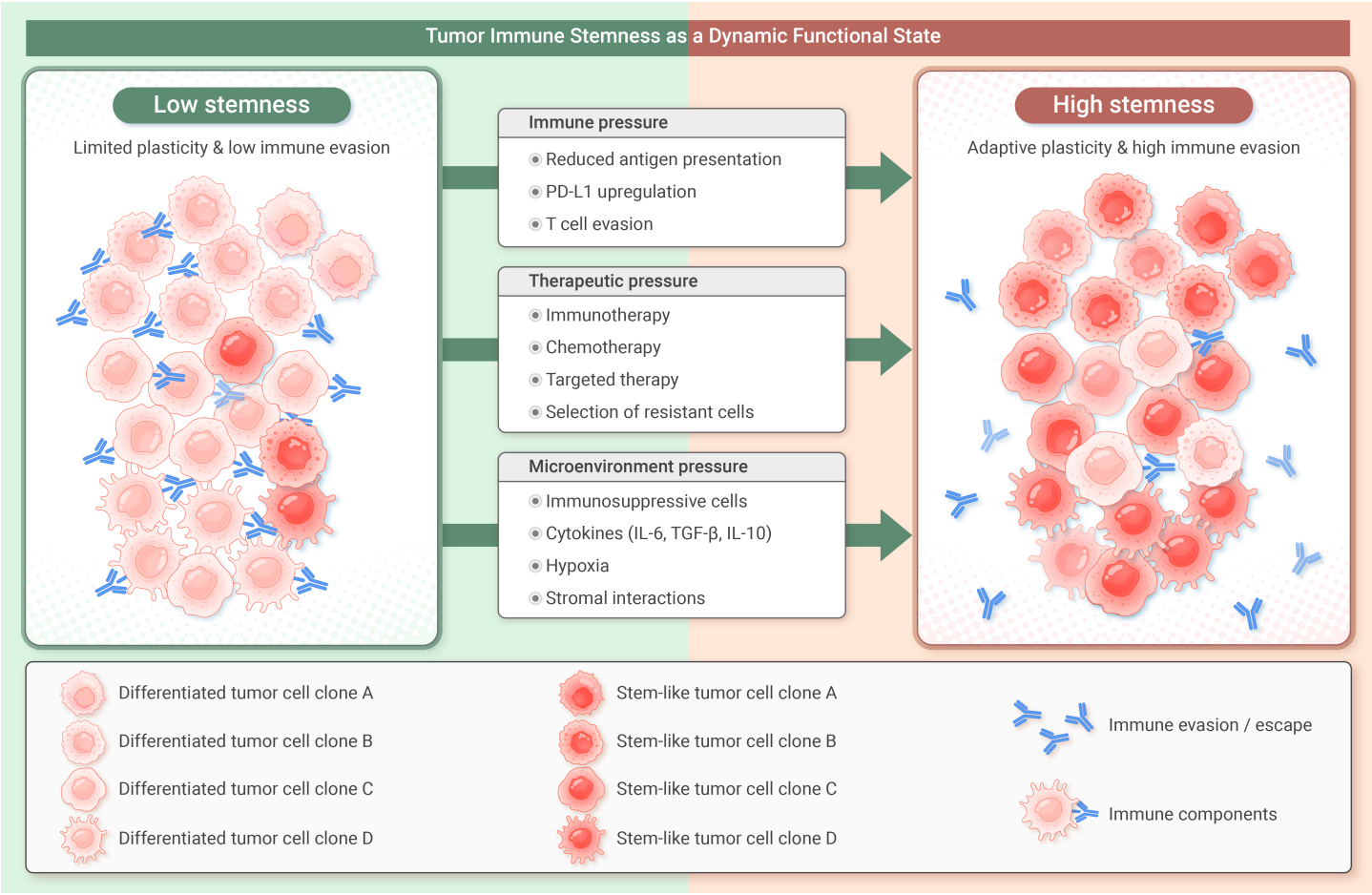

Figure 1. Tumor immune stemness as a dynamic functional state This schematic illustrates tumor immune stemness as a reversible state emerging from the interplay between cancer cell plasticity and immune evasion. Under immune or therapeutic pressure, non-stem tumor cells can transition into a stem-like, immune-evasive condition. Signals from the tumor microenvironment further stabilize this state by creating an immune-privileged niche, thereby promoting tumor persistence, immune escape, and relapse.

This degree of plasticity quietly undermines the traditional idea that therapy can simply eliminate a small, pre-existing stem-like fraction, and instead points toward a shifting reservoir of tumor cells that can adopt immune-resistant states as needed. Within this context, immune checkpoint signaling sits at a central crossroads. A number of studies published after 2020 report that PD-L1 is preferentially enriched within cancer stem–like compartments across multiple solid tumors, including hepatocellular, pancreatic, breast, and colorectal cancers. What matters here is that PD-L1 in these cells acts beyond its familiar role in dampening T cell activity. Importantly, PD-L1 is not an isolated example of this convergence. Other core regulatory pathways that govern cancer stemness also play well-documented roles in immune evasion. Wnt/β-catenin signaling, a central driver of stem-like transcriptional programs, has been repeatedly linked to impaired dendritic cell recruitment and T cell exclusion, thereby coupling self-renewal capacity with immune ignorance. Similarly, TGF-β signaling operates at the interface of tumor cell plasticity and the microenvironment, where it promotes stem-like phenotypes while simultaneously suppressing cytotoxic T cell and natural killer cell activity. Transcriptional regulators such as SOX9 further exemplify this dual functionality, as stemness-associated factors can directly engage immune checkpoint–related pathways, reinforcing both immune escape and tumor persistence. Cell-intrinsic PD-L1 signaling appears to feed directly into stemness-associated pathways, engaging β-catenin, PI3K–AKT–mTOR, and Notch-related circuits, and in doing so, creates reinforcing loops that help lock in both immune evasion and self-renewal potential. In this context, immune checkpoint molecules behave less like surface shields and more like core regulators of tumor cell identity.

The tumor microenvironment further amplifies this immune stemness state. Cancer stem–like cells actively reshape their surrounding niche by drawing in immunosuppressive myeloid populations, biasing macrophage polarization, and encouraging the accumulation of regulatory T cells. Importantly, accumulating evidence suggests that the surrounding niche is not uniform across tumor cell states, but instead differs between cancer stem–like cells and their more differentiated counterparts. Stem-like tumor cells tend to reside in spatially and functionally distinct microenvironments characterized by enhanced immunosuppression, altered stromal interactions, and preferential engagement with myeloid cells, regulatory T cells, and inhibitory cytokine gradients. In contrast, non-stem tumor cells are more frequently exposed to immune-infiltrated regions with higher effector T cell activity and less stringent immune privilege. These niche-level differences not only stabilize stem-like states but also bias immune pressure in a manner that favors the persistence and re-emergence of immune-evasive, plastic tumor populations. Cytokines such as IL-6, TGF-β, and IL-10 come up repeatedly in this setting, not only for their role in blunting antitumor immune responses but also for their ability to sustain stem-like transcriptional programs. Through these reciprocal exchanges, a localized immune-privileged space begins to take form, where ongoing immune pressure, somewhat paradoxically, favors tumor cells with greater plasticity and an enhanced capacity for long-term survival. In such settings, immune escape is no longer a secondary consequence but a selective force shaping tumor evolution.

Resistance to immunotherapy may offer the most clinically tangible evidence for tumor immune stemness. Immune checkpoint blockade can produce striking initial tumor regression, yet recurrent lesions often show an enrichment of stem-like transcriptional signatures alongside pronounced immune exclusion. Single-cell and spatial profiling studies from the past few years suggest that cancer stem–like cells are able to endure therapeutic pressure and later serve as the foundation for immune-refractory regrowth, even in settings where the bulk of the tumor remains largely sensitive to treatment. These observations help explain why durable responses remain limited despite robust immune activation in many patients.

Interestingly, there are some clear parallels between tumor immune stemness and stem-like states that arise within the immune system itself. Stem-like exhausted $CD8^+$ T cells, sustained within specialized dendritic cell niches, are now appreciated as key responders to immune checkpoint blockade.[3] In tumors enriched for immune-evasive, stem-like cancer cells, these T cell populations are often spatially displaced or excluded, which hint that tumor stemness and immune stemness may represent opposing states, subtly competing for control within the same tissue landscape.[4] This spatial and functional tension may ultimately determine therapeutic outcome.

From a therapeutic standpoint, these observations make it difficult to justify approaches that focus on stemness or immune modulation in isolation. Strategies that integrate immune intervention with disruption of pathways that support stem-like states seem more likely to be effective. Recent preclinical work suggests that concurrently targeting PD-L1–linked signaling, metabolic vulnerabilities, or signals derived from the niche can render cancer stem–like cells more susceptible to immune-mediated elimination and, in some cases, lower the likelihood of tumor relapse. While clinical translation remains challenging, such integrative strategies align more closely with the biological reality of tumor immune stemness.

In summary, tumor immune stem cells are perhaps best viewed not as a stable or well-defined cell type, but as a dynamic state that arises from the interplay between stemness plasticity and immune escape. Framing the concept this way subtly shifts how resistance, relapse, and therapeutic failure are interpreted. Instead of focusing on whether immune stem cells exist as a discrete entity, it may be more useful to ask how readily tumors can enter and maintain this state, and whether clinical interventions can be designed to interrupt that transition before it becomes entrenched.

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AUTHOR CONTRIBUTIONS

The author solely conceived, drafted, and revised the manuscript.

DECLARATION OF INTERESTS

The author declares no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.