Tumor-Marrow Axis: Myeloid Reprogramming from Suppression to Activation

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Myeloid-based therapeutics are emerging as a distinct pillar of cancer immunotherapy, both as an independent modality and as a means to improve the durability and safety of T cell–based approaches (immune checkpoint blockade, CAR-T cells, and T-cell–engaging bispecific antibodies). In both solid tumors and hematologic malignancies, the myeloid system acts as a gatekeeper of therapeutic immunity by controlling antigen handling, cytokine milieu, immune-cell trafficking, and the balance between productive inflammation and immune paralysis. Tumor- and host-driven shifts in myelopoiesis and macrophage/dendritic cell networks frequently bias toward immunosuppressive states that limit T and NK cell function, highlighting that resistance can be systemic and bone marrow linked rather than restricted to the tumor niche, a bidirectional tumor–marrow axis that shapes therapy response.

Mechanistically, these programs arise through three convergent layers. First, type-2 polarization circuits in the tumors and chronically inflamed tissue that bias macrophages/monocytes toward repair-oriented, anti-inflammatory states with heightened scavenging and efferocytosis, dampened antigen presentation, and chemokine programs that recruit additional suppressive myeloid cells, Second, progenitor-level rewiring of marrow output (“stress” or emergency myelopoiesis) that shifts hematopoiesis toward expanded, immature suppressive trajectories and couples to stress-response modules (including NRF2-linked antioxidant/metabolic adaptation) that stabilize a tolerant, low-inflammatory phenotype. Third, myeloid checkpoint pathways, especially ILT3/LILRB family inhibitory receptors, which reduce DC maturation and inflammatory cytokine production and reinforce tolerogenic signaling loops. Together, these mechanisms induce and sustain immune suppression and propagate T-cell dysfunction.

However, suppressive myeloid states are not permanent that especially macrophage circuits remain reprogrammable, creating opportunities to convert the tumor microenvironment into one that supports antigen presentation, chemokine-guided trafficking, and effective adaptive immunity. Tissue-resident macrophages (TRM) are increasingly recognized as architects of local immune “set points” through regulation of vascular and extracellular-matrix programs and inflammatory thresholds, suggesting a critical function not only for treatment but also for intercepting early lesions in high-risk tissues. Early clinical experience with engineered macrophage approaches (e.g., HER2- CAR-M) provides proof-of-concept for feasibility, tumor trafficking, and tumor microenvironment remodeling, motivating next-generation strategies that pair myeloid reprogramming with checkpoint blockade or other immune modulators and apply integrated systemic and local tissue microenvironment immune monitoring to distinguish beneficial activation from pathologic inflammation and to guide rational combinations and patient selection.