Tumor Microenvironment

**Major finding:** Neural progenitors cross the blood–brain barrier and infiltrate prostate tumors to drive neurogenesis.

**Concept:** Differentiation of DCX+ cells into adrenergic neurons enhances tumor development and metastasis.

**Impact:** These data define cross-talk between the CNS and tumor cells and suggest potential therapeutic targets.

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**CNS-DERIVED NEURAL PROGENITORS MEDIATE NEUROGENESIS IN PROSTATE CANCER**

Innervation of the tumor microenvironment is critical for tumor development and metastasis in many solid cancers. However, whether this process involves outgrowth of already-established nerves or requires de novo neurogenesis remains unclear. Mauffrey and colleagues show that, in prostate cancer, neural progenitors from the central nervous system (CNS) cross the blood–brain barrier and seed areas of local and metastasized tumors to initiate neurogenesis. The stroma of human prostate tumors contained cells expressing doublecortin (DCX), a marker of neural progenitors, and the density of DCX+ cells was associated with tumor aggressiveness and recurrence. In a murine model of prostate cancer, DCX+ cells were indeed found in neurogenic areas of the CNS, including the subventricular zone (SVZ), and also in the tumor stroma, but not in the prostates of healthy mice. These cells expressed additional markers of neural progenitors as well as genes associated with neuron differentiation and projection. Moreover, lineage tracing of these progenitor cells revealed that adrenergic neo-neurons can develop in situ within the prostate tumor microenvironment. During tumor development, DCX+ neural progenitors exited the SVZ and crossed the breached blood–brain barrier, migrated through the blood, and infiltrated prostate tumors, where they could differentiate into neurons. Selective depletion of DCX+ cells, either from the entire mouse or specifically from the SVZ, reduced the number of neoplastic lesions and impaired orthotopic engraftment of tumor cells. Conversely, transplantation of DCX+ neural progenitors purified from prostate tumors or the SVZ into established tumor xenografts enhanced tumor growth and metastasis. Taken together, these data demonstrate the role of neural progenitors in prostate tumor development and highlight DCX+ cells as potential targets to suppress primary tumors and metastases.


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**Lymphoma**

**Major finding:** A dominant-negative mutant of the transcription factor musculin was identified in ALK-negative ALCL.

**Concept:** MSC<sup>E116K</sup> disrupts canonical DNA binding, heterodimerization, and tumor suppressor expression.

**Impact:** MSC<sup>E116K</sup> sensitizes ALCL cells to BET inhibition and identifies new targets for ALCL treatment.

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**IDENTIFICATION AND CHARACTERIZATION OF A MUSCULIN MUTANT IN LYMPHOMA**

The genomic landscape of anaplastic large-cell lymphomas (ALCL), a common group of T-cell non-Hodgkin lymphomas (T-NHL), has been largely unexplored. As a result, unique targets for therapies to treat this diverse set of aggressive malignancies are lacking. To identify potential drivers of ALCL, Luchtel, Zimmermann, and colleagues performed exome sequencing of 62 T-NHLs and identified a recurrent E116K mutation within the ERXR motif of the DNA-binding domain of musculin (MSC), a transcription factor that heterodimerizes with other transcription factors to regulate lymphocyte development. Additional sequencing revealed that the MSC<sup>E116K</sup> variant occurs almost exclusively in ALK-negative ALCLs harboring DUSP22 rearrangements and was not identified in ALK-positive or TPH3-rearranged ALCL. MSC<sup>E116K</sup> significantly increased protein expression of musculin in both patient samples and cell lines. Transduction of the MSC<sup>E116K</sup> variant into CD4+ T cells and ALCL cells resulted in significant increases in cell growth compared with MSC<sup>WT</sup>. Disruption of the DNA-binding motif subsequently disrupted the ability of MSC<sup>E116K</sup> to bind to canonical target sequences and sequestered known heterodimerization partners such as E2A and HEB. Further, MSC<sup>E116K</sup> also reduced expression of E2F2, a transcription factor involved in the repression of cell-cycle progression; overexpression of E2F2 resulted in decreased expression of CD30 and MYC. Compared with MSC<sup>WT</sup>, MSC<sup>E116K</sup> upregulated the CD30–IRF4–MYC axis, increasing expression of TNFRSF8, CD30, MYC, and IRF4. As IRF4 was shown to regulate expression of musculin, this positive feedback loop is an important driver of cell-cycle progression in ALCL. Consistent with these findings, analysis of ALCL MSC<sup>E116K</sup> patient specimens revealed increased MYC expression. Treatment of ALCL cells overexpressing MSC<sup>E116K</sup> with a bromodomain and extraterminal domain (BET) inhibitor significantly decreased cell growth and reduced cell viability compared with cells overexpressing MSC<sup>WT</sup>. Collectively, these data identify a recurrent MSC mutation that drives cell-cycle progression in T-NHL and suggest a potential therapeutic strategy for patients with ALK-negative ALCL.


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