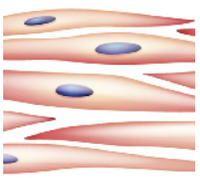
Sarcoma

Major finding: Dystrophin (*DMD*) deletions are frequent in GIST, RMS, and LMS and confer metastatic properties.

Concept: Intragenic *DMD* deletions lead to inactivation of a large dystrophin isoform but not an essential isoform.

Impact: Therapies developed for muscular dystrophies should be evaluated in myogenic sarcomas.

DYSTROPHIN IS A TUMOR SUPPRESSOR IN MYOGENIC CANCERS



Gastrointestinal stromal tumor (GIST), rhabdomyosarcoma (RMS), and leiomyosarcoma (LMS) are soft tissue sarcomas that frequently express myogenic differentiation markers. Wang and colleagues sought to identify shared factors contributing to the development of myogenic cancers using single-nucleotide polymorphism arrays and found that 63% of high-grade myogenic cancers harbored intragenic deletions in the longest human gene, dystrophin (*DMD*), which encodes a sarcolemmal protein that structurally links the actin cytoskeleton with the extracellular matrix. *DMD* deletions were not identified in nonmyogenic sarcomas and were rarely observed in nonsarcoma cell lines. Both normal myogenic tissues and benign precursors of myogenic cancers expressed high levels of several dystrophin isoforms. However, metastatic myogenic tumors specifically exhibited deletions of *DMD* exons 1 to 62, which resulted in loss of the large 427-kDa dystrophin isoform in 96% of metastatic GIST, 100% of metastatic embryonal RMS, and 62% of metastatic LMS samples assayed. Despite the loss of the 427-kDa isoform, metastatic tumors retained expression of a 71-kDa dystrophin isoform encoded by exons 63 to 79. Knockdown of 71-kDa dystrophin impaired growth of RMS cells, indicating it was essential for myogenic tumors. Reexpression of a *DMD* construct lacking exons 17 through 48, which encodes a functional 240-kDa dystrophin isoform, suppressed migration, invasiveness, invadopodia formation, and anchorage-independent growth of GIST, RMS, and LMS cells, suggesting that dystrophin inactivation promotes metastatic behavior. In addition to providing evidence that dystrophin acts as a tumor suppressor in myogenic cancers, these data suggest that muscular dystrophy therapies that aim to correct dystrophin defects should also be evaluated in myogenic cancers. ■

Wang Y, Marino-Enriquez A, Bennett RR, Zhu M, Shen Y, Eilers G, et al. Dystrophin is a tumor suppressor in human cancers with myogenic programs. Nat Genet 2014;46:601–6.

Immune Evasion

Major finding: Interactions between Tregs and antigen-presenting cells impair cytotoxic T-cell function in tumors.

Mechanism: Treg-induced CD80 and CD86 depletion in APCs increases PD-1 and TIM-3 expression in cytotoxic T cells.

Impact: Treg-induced alterations in the balance of costimulatory and coinhibitory signals prevent tumor rejection.

CYTOTOXIC T LYMPHOCYTE DYSFUNCTION IS CAUSED BY TREG–APC INTERACTIONS

Regulatory T cells (Treg) can suppress the activation of effector T cells and have been implicated in tumor immune tolerance, but the underlying mechanisms are not completely understood. To determine how antigen recognition affects immunomodulation by Tregs in tumors, Bauer and colleagues used a mouse model of adoptive T-cell therapy in which antigen-specific responses were evaluated by implanting transgenic tumor cells expressing an influenza antigen (HA) into wild-type mice at the same time as adoptive transfer of Tregs specific for HA (HA-Tregs), followed by HA-specific $CD8^+$ (HA-CD8) CTLs 1 week later. HA-Tregs prevented tumor rejection by HA-CD8 CTLs, but if the tumor expressed a mutated HA not recognized by HA-Tregs, HA-Tregs no longer prevented tumor rejection, indicating a requirement for local antigen recognition by Tregs for tumor immune tolerance. HA-Tregs induced a hyporesponsive state in CTLs marked by low effector cytokine expression and inefficient cytotoxic granule release that resembled T-cell exhaustion. Consistent with these observations, HA-CD8s expressed higher levels of the coinhibitory receptors programmed cell death-1 (PD-1) and T-cell immunoglobulin and mucin domain-3 (TIM-3) in the presence of HA-Tregs compared with non–HA-specific Tregs. Furthermore, dendritic cells (DC) pre-conditioned with HA-Tregs induced higher expression of PD-1 and TIM-3 in CTLs than DCs conditioned with HA antigen alone. Mechanistically, transient interactions between Tregs and antigen-presenting cells (APC) such as DCs in tumors led to reduced expression of the costimulatory factors CD80 and CD86, suggesting that Tregs dysregulate CTLs by simultaneously reducing costimulatory signals they receive from APCs and enhancing coinhibitory signals. Although the origin and antigen specificity of Tregs that reduce antitumor responses remains unknown, these data illustrate that antigen recognition by Tregs within tumors is required to impair CTL function and prevent tumor rejection. ■

Bauer CA, Kim EY, Marangoni F, Carrizosa E, Claudio NM, Mempel TR. Dynamic Treg interactions with intratumoral APCs promote local CTL dysfunction. J Clin Invest 2014;124:2425–40.