Tumor Microenvironment

Major finding: T_{reg} cells connect hypoxia with immune tolerance and angiogenesis.

Mechanism: T_{reg} cells are recruited via CCL28-CCR10, suppress T-effector cells, and secrete VEGFA.

Significance: T_{reg} cells are critical in promoting a permissive tumor environment.

HYPOXIC CONDITIONS LEAD TO RECRUITMENT OF T_{reg} CELLS

Recent evidence has highlighted the complex interactions between tumors and the immune system. Although antitumor immunity can suppress tumor growth under some circumstances, tumors often evade the immune system, and certain types of immune cells have been shown to promote progression and metastasis. Hypoxia triggers both angiogenesis and the release of damage-associated pattern molecules, which can trigger an antitumor immune response. Facciabene and colleagues show that tumors in hypoxic conditions maintain immune escape by recruiting regulatory T (T_{reg}) cells through induction of CCL28. The authors first examined a panel of ovarian cancer cell lines and found that *CCL28* was highly upregulated under hypoxic conditions by HIF1α. CCL28 correlated with HIF1α expression in ovarian cancer samples and overexpression was associated with a poor outcome in patients. *In vitro* and mouse experiments showed that CCL28 recruited T_{reg} cells via the CCR10 receptor, and that recruitment of these cells caused a significant acceleration in tumor growth. Further, the T_{reg} cells appeared to suppress effector T-cell function in the tumors. Consistent with reports of inverse correlation between tumor infiltrating T cells and angiogenesis, increased levels of the pro-angiogenic factor VEGFA were contributed by $CCR10^{+}$ hematopoietic cells recruited into the tumors, and the authors also found that the T_{reg} cells themselves secreted VEGFA. These data show that hypoxic conditions result in recruitment of T_{reg} cells that induce a pro-angiogenic program and contribute to immune tolerance, thereby promoting tumor growth and progression. ■

Facciabene A, Peng X, Hagemann IS, Balint K, Barchetti A, Wang LP, et al. Tumour hypoxia promotes tolerance and angiogenesis via CCL28 and T(reg) cells. Nature 2011;475:226–30.

Tumorigenesis

Major finding: The tyrosine phosphatase SHP2 determines whether parafibromin is a tumor suppressor or an oncogene.

Mechanism: Dephosphorylation of parafibromin promotes complex formation with β-catenin and Wnt signaling.

Impact: Findings provide insight into mechanisms of SHP-mediated neoplasms and developmental malformations.

SHP2 CONVERTS PARAFIBROMIN/CDC73 FROM TUMOR SUPPRESSOR TO ONCOPROTEIN

SHP2 is a ubiquitously expressed protein tyrosine phosphatase encoded by the *PTPN11* gene. Mutations in *PTPN11* are associated with the hereditary developmental disorder Noonan syndrome in addition to adult and juvenile leukemia. SHP2 plays a central role in cell signaling events that promote growth and motility and is required for activation of the RAS signaling pathway. Deregulation of SHP also has been implicated in the development of multiple human malignancies. In a recent article, Takahashi and colleagues identified a unique role for SHP2 in the nucleus, as the determinant of the function of parafibromin/Cdc73, a component of the nuclear RNA polymerase II-associated factor (PAF) complex. Parafibromin has opposing functions that are context dependent. When complexed with the histone methyltransferase SUV39H1, parafibromin acts as a tumor suppressor that inhibits the transcription of *cyclin D1* and *c-myc*. However, upon binding β-catenin, parafibromin switches to an oncogene that activates the promitogenic Wnt signaling pathway. The authors discovered that parafibromin is a unique substrate of SHP2 and that dephosphorylation by SHP2 determines its binding partner and therefore its nuclear function. In the absence of SHP2, parafibromin was tyrosine-phosphorylated and complexed with SUV39H1. Upon tyrosine dephosphorylation by SHP2, parafibromin preferentially bound to and trapped β-catenin in the nucleus. The formation and nuclear accumulation of the stable parafibromin/β-catenin complex was able to override parafibromin/SUV39H1-mediated repression and led to the induction of Wnt target genes. Overall, the important finding that SHP2 activity determines whether parafibromin behaves as a tumor suppressor or an oncogene offers mechanistic insight into how the deregulation of SHP2 may play a causative role in the development of neoplasms and developmental malformations. ■

Takahashi A, Tsutsumi R, Kikuchi I, Obuse C, Saito Y, Seidi A, et al. SHP2 tyrosine phosphatase converts parafibromin/Cdc73 from a tumor suppressor to an oncogenic driver. Mol Cell 2011;43:45–56.