ResEARCH WAtch

Immunotherapy

Major finding: Trafficking of adoptively transferred effector T cells requires CD103+ dendritic cell–derived CXCL9/10.

Concept: Tumor-intrinsic WNT signaling ablates the migration of both adoptively transferred and host CD8+ T cells.

Impact: Restoration of BATF3 dendritic cells in the TME may overcome resistance to immunotherapies.

BATF3 DENDRITIC CELLS DRIVE ADOPTIVE EFFECTOR T-CELL TRAFFICKING

Patient response to immunotherapies such as adoptive T-cell transfer and immune checkpoint blockade, which are effective in a substantial number of patients but fail in a significant subset of patients, is dependent upon the presence of a T cell–inflamed tumor microenvironment (TME). Recent evidence suggests that recruitment of CD8+ T cells to the TME is dependent on the chemokines CXCL9/10, which are CXCR3 ligands that are upregulated in response to IFNs. Having recently shown that activation of tumor-intrinsic WNT/CTNNB signaling resulted in the lack of baseline T-cell priming against tumor-associated antigens and decreased recruitment of CD103+ dendritic cells (DC) to drive resistance to immune checkpoint therapy, Spranger and colleagues evaluated the efficacy of an exogenous effector T-cell response against autochthonous mouse models of melanoma. Growth of T cell–inflamed murine melanoma tumors, but not non-T cell–inflamed Cnmb1+ mouse melanoma tumors, was controlled by adoptive T-cell transfer or endogenous memory CD8+ T cells induced by vaccination. Effector T cells exhibited greater mobility and interaction with tumor cells in T cell–inflamed tumors, which were found to be immunoedited, but not in Cnmb1+ tumors. Evaluation of chemokine receptor expression revealed that CD3+ T cells in non-T cell–inflamed tumors expressed CXCR3-expressing CD3+ T cells, whereas T cells in Cnmb1+ tumors did not express CXCR3 or CCR5. Similarly, CD103+ DCs, which were increased in non-T cell–inflamed tumors compared to Cnmb1+ tumors, produced CXCL9/10 in non-T cell–inflamed tumors but not in Cnmb1+ tumors, and the production of CXCL10 by BATF3-lineage CD103+ DCs was found to be crucial for effector T-cell recruitment to the TME. These findings provide evidence that tumor-resident CD103+ DCs are critical for the establishment of the T cell–inflamed TME and suggest a potential therapeutic strategy to overcome clinical resistance to immunotherapies.


Signaling

Major finding: YAP activates AKT signaling to promote mitotic arrest, polyploidy, and hepatocellular carcinoma.

Mechanism: AKT signaling induces cytosolic retention of SKP2 to enhance p27 stability and FOXO1/3 degradation.

Impact: AKT may be a potential therapeutic target in tumors induced by loss of Hippo signaling.

LOSS OF HIPPO SIGNALING PROMOTES POLYPLOIDY AND TUMORIGENESIS

Polyploidy can lead to genomic instability, aneuploidy, and tumorigenesis when polyploid cells do not undergo G1 arrest. Hippo signaling is highly active in polyploid cells, and overexpression of its downstream effector YAP increases hepatocyte polyploidy. However, the mechanisms by which Hippo signaling contributes to polyploidy have not been determined. Zhang, Chen, Liu, and colleagues found that YAP activation in response to loss of Hippo signaling promoted hepatocyte polyploidy in mice and synergized with p53 inactivation to induce liver tumorigenesis. Mechanistically, YAP activation induced AKT signaling that resulted in p300-mediated acetylation of the E3 ligase SKP2, promoting its cytoplasmic retention. Nuclear SKP2 targets the cyclin-dependent kinase inhibitor p27 for degradation; thus, cytoplasmic retention of SKP2 stabilized p27, preventing cell-cycle progression. In contrast, cytoplasmic SKP2 targets the proapoptotic FOXO1 and FOXO3 proteins for degradation. Consequently, YAP activation promoted FOXO1/3 degradation to enhance polyploid cell proliferation. These findings reveal a role for AKT–SKP2 signaling in inducing mitotic arrest and polyploidy, demonstrating a mechanism by which loss of Hippo signaling can enhance polyploidy and tumorigenesis. Consistent with these findings, inhibition or depletion of AKT reduced p27 levels, decreased cell polyploidy, and suppressed liver tumor formation in mice with disrupted Hippo signaling. Treatment with the AKT inhibitor MK2206 reduced tumor size and frequency, and was associated with reduced levels of cytoplasmic SKP2. In human liver tumors, YAP and SKP2 were highly expressed compared to adjacent normal tissue, and YAP and SKP2 levels were associated with advanced tumor stage. Additionally, low levels of nuclear YAP were associated with improved survival in patients with hepatocellular carcinoma. Together, these findings reveal a mechanism by which Hippo signaling may suppress polyploidy and tumorigenesis, and suggest that AKT may be a potential therapeutic target in patients with hepatocellular carcinoma.
