**Immunology**

**Major finding:** Natural killer (NK) cells recruit conventional type 1 dendritic cells (cDC1) to the tumor microenvironment.

**Concept:** NK cells produce the chemokines CCL5 and XCL1 to recruit cDC1, which is blocked by tumor-derived PGE2.

**Impact:** Chemokines may represent therapeutic targets to enhance cDC1 recruitment and antitumor immunity.

**NATURAL KILLER CELLS RECRUIT DENDRITIC CELLS TO PROMOTE ANTITUMOR IMMUNITY**

Conventional type 1 dendritic cells (cDC1) promote antitumor immunity and are linked to response to immunotherapy. However, cDC1 are rarely found in the tumor microenvironment (TME) of human tumors, and the mechanisms that control their abundance are not understood. Strategies to increase cDC1 abundance might potentially enhance the antitumor immunity and suppress tumor progression. Prostaglandin E2 (PGE2) suppresses antitumor immunity and is secreted by many tumors, and Böttcher and colleagues found that cDC1 accumulate in the tumor microenvironment in BRAFV600E melanomas when the cyclooxygenases (COX) required for PGE2 production (Pgs1 and Pgs2) are deleted from tumor cells. This finding suggested that tumor-derived PGE2 may disrupt cDC1 accumulation. The accumulation of cDC1 in the tumor microenvironment required natural killer (NK) cells in COX-deficient BRAFV600E melanoma cells, and NK-cell depletion accelerated tumor growth. Mechanistically, NK cells produced the chemokines XCL1 and CCL5, thereby facilitating the recruitment of cDC1 to tumors, as cDC1 express both the XCL1 receptor XCR1 and the CCL5 receptors CCR1 and CCR5. Conversely, PGE2 reduced NK-cell production of CCL5 and XCL1, and reduced NK-cell survival, thereby preventing cDC1 recruitment. Similarly, blocking CCL5 and XCL1 reduced cDC1 accumulation in vivo, whereas expressing CCL5 and XCL1, in tumors that do not express PGE2, increased cDC1 accumulation in the TME and suppressed tumor growth. However, expression of CCL5 and XCL1 was not sufficient to recruit cDC1 in PGE2-producing tumors, in part due to a PGE2-mediated downregulation of XCR1. Analysis of data from The Cancer Genome Atlas revealed that the NK cell and cDC1 gene signatures were associated with expression of XCL1, XCL2 (a human paralog of XCL1), and CCL5, and these signatures were linked to extended patient survival. Altogether, these findings reveal a mechanism by which NK cells facilitate cDC1 recruitment to promote antitumor immunity, and suggest the potential for therapeutic targeting of cDC1-attracting chemokines and PGE2.


**Structural Biology**

**Major finding:** KSR-MEK complexes allosterically activate BRAF, which then phosphorylates a second MEK molecule.

**Concept:** BRAF and KSR interact via the BRAF N-terminal BR5 and KSR coiled-coil sterile α motif domains.

**Impact:** Disrupting BRAF N-terminal regulatory regions may suppress allosteric activation and oncogenic signaling.

**MEK BINDING TO KSR PROMOTES ALLOSTERIC ACTIVATION OF BRAF**

The RAF family kinases (ARAF, BRAF, and CRAF) have emerged as potential therapeutic targets in cancer as they are activated by oncogenic RAS signaling and in turn phosphorylate MEK to activate downstream MAPK signaling. The pseudokinases KSR1 and KSR2 have been reported to act as scaffolds, promoting the interaction between RAF and MEK. However, the structural mechanism by which KSR1/2 interact with and regulate the activity of RAF proteins has not been fully elucidated. Lavoie, Sahmi, Maisonneuve, and colleagues identified a mechanism by which KSR promotes allosteric activation of BRAF. Binding of MEK to the kinase domain of KSR induced heterodimerization of the BRAF and KSR1 kinase domains independent of MEK catalytic activity, and this event was sufficient to promote BRAF activation. The KSR-MEK interaction was also required for KSR-mediated BRAF activation. Further, the BRAF-KSR association required the side-to-side dimerization surface of the BRAF and KSR kinase domains. Specifically, the BRAF–KSR interaction occurred through the N-terminal coiled-coil-sterile α motif of KSR1 and the N-terminal BRAF-specific (BR5) domain of BRAF. Determination of the BR5 domain crystal structure to 2.1 Å revealed that it is comprised of two antiparallel α-helices connected by an α-hairpin. Mechanistically, MEK1 binding to KSR1 via the helix αG facilitated KSR1 side-to-side dimerization with BRAF, thereby allosterically activating BRAF and allowing it to phosphorylate a second MEK substrate molecule bound to the BRAF helix αG. Collectively, these findings reveal a role for KSR in promoting MEK-dependent allosteric activation of BRAF, and suggest the potential for targeting MAPK signaling by disrupting the BRAF N-terminal regulatory region.
