INHIBITION OF ERK DIMERIZATION IMPAIRS RAS–ERK-DRIVEN TUMORIGENESIS

Constitutive activation of the RAS–ERK pathway occurs in nearly 50% of human cancers. Although several pharmacologic strategies to block this pathway have yielded positive results, long-lasting efficacy has been hampered by acquired resistance mutations that reactivate ERK signaling. As an alternative approach, Herrero and colleagues sought to inhibit ERK dimerization, which specifically regulates the extranuclear function of ERK and has been implicated in tumorigenesis. Screening of small-molecule libraries identified DEL-22379, which successfully blocked ERK dimerization without affecting its phosphorylation; correspondingly, ERK cytoplasmic activity was significantly reduced, whereas its nuclear functions were enhanced. Mutation of residues within the dimerization interface of ERK disrupted the effects of DEL-22379, indicating that the compound binds directly to this interface and blocks dimer formation. DEL-22379 inhibited growth and induced apoptosis in various tumor cell lines harboring mutant BRAF or RAS, whereas wild-type cell lines were resistant. In vivo, DEL-22379 selectively inhibited the growth and metastasis of BRAF-mutant cell line–derived and patient-derived xenografts. Expression of phosphoprotein enriched in astrocytes 15 (PEA15), which retains ERK in the cytoplasm, correlated with levels of ERK dimerization and DEL-22379 sensitivity in BRAF-mutant cells, supporting the idea that the antitumor activity of DEL-22379 is dependent on ERK dimerization. Consistent with this finding, DEL-22379 was ineffective in a RAS-driven melanoma model in zebrafish, in which ERK does not dimerize. Importantly, melanoma cells with NRAS overexpression or MEK1 mutations remained sensitive to DEL-22379 treatment, indicating that the antitumor activity of DEL-22379 is not affected by drug-resistance mechanisms associated with existing inhibitors of the RAS–ERK pathway. Overall, these data describe a specific and effective treatment for RAS–ERK-driven tumors and support the development of inhibitors of regulatory protein–protein interactions, rather than catalytic activities, to prevent tumor progression.


RORC1 DRIVES CANCER-ASSOCIATED EMERGENCY MYELOPOIESIS

The rapid change in hematopoietic output that occurs in response to acute immunologic stress is known as “emergency” hematopoiesis, a process that is co-opted by tumors to enhance the generation of tumor-promoting myeloid cells. The response of T-helper cells expressing IL17A, which is controlled by retinoic acid–related orphan receptor C (RORC1), has been implicated in G-CSF–mediated emergency myelopoiesis, prompting Strauss and colleagues to investigate the role of the IL17A/RORC1 axis in cancer-related myeloid differentiation. Analysis of the myeloid compartment of tumor-bearing mice revealed that emergency hematopoiesis occurs early in tumor development and that RORC1 expression in myeloid cells is indicative of advanced protumorigenic inflammation. Genetic deletion of Rorc1 in hematopoietic cells impaired tumor growth and metastasis in multiple tumor models and resulted in a reduction in the tumor-induced expansion of undifferentiated myeloid-derived suppressor cells (MDSC) and tumor-associated macrophages (TAM) compared with wild-type mice, supporting a role for RORC1 in promoting cancer-associated myelopoiesis. Further investigation revealed that RORC1 stimulated the differentiation of early hematopoietic progenitor cells in the bone marrow into myeloid lineage cells in response to colony-stimulating growth factors by inducing the expression of CCAAT/enhancer binding protein β (C/EBPβ), a positive regulator of granulopoiesis, and inhibiting the expression of SOCS3 and BCL3, negative regulators of granulopoiesis. RORC1 regulated MDSC expansion by promoting CSF-mediated protection of immature MDSCs against apoptosis and suppressing neutrophil maturation, resulting in the survival of immature MDSCs. Concurrently, RORC1 enhanced the maturation of TAMs by inducing the lineage commitment transcription factors PU.1 and interferon regulatory factor 8 and promoted the M2 polarization of macrophages. Taken together, these results elucidate the role of RORC1 in the regulation and coordination of tumor-promoting myeloid cell expansion and differentiation and suggest targeted inhibition of RORC1 as a potential therapeutic strategy.
