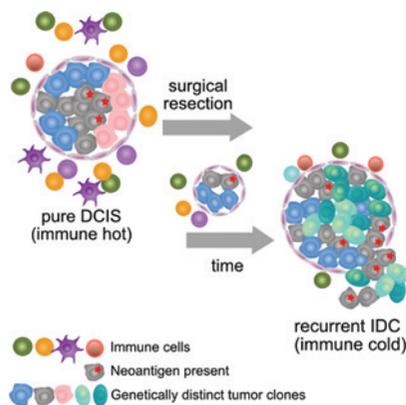


MOLECULAR CANCER RESEARCH

HIGHLIGHTS

Selected Articles from This Issue

Matched DCIS and Recurrent Invasive Breast Cancer

Trinh *et al.* | Page 623

Ductal carcinoma *in situ* (DCIS) breast cancers are non-invasive but can progress to invasive ductal carcinoma (IDC) through tumor intrinsic and -extrinsic factors that are poorly understood. In this study, Trinh and colleagues model interactions between DCIS/IDC tumors and their respective immune cell infiltrates using integrated molecular analyses. The authors find that IDC tumors are often genetically related to their DCIS precursors despite long periods of latency between the two stages, and that features of the tumor immune microenvironment are established early in tumor development and could shape the progression to IDC. In particular, recurrent *TP53* and *PIK3CA* mutations were associated with sustained inflammatory immune cell activity across the DCIS-IDC transition. The authors argue that, despite their status as neoantigens, these mutations and others could be retained through immune editing of the tumor. While in-depth study in a diverse cohort is needed, these data suggest a key role for the immune system in shaping the progression of certain DCIS tumors to IDC based on their constellation of genomic alterations.

CF10, A Potent Next-Generation Flouropyrimidine for PDAC

Haber *et al.* | Page 565

Patients diagnosed with pancreatic ductal adenocarcinoma (PDAC) face a dismal prognosis, and clinical management of PDAC is limited to cytotoxic regimens. 5-fluorouracil is a key component of these regimens, but its use is hampered by systemic toxicity due to the off-target effects of its metabolites and inefficient conversion to the active metabolite, FdUMP. Here, Haber and colleagues report a novel flouropyrimidine agent, CF10. Consisting of a capped polymeric chain of FdUMP molecules, CF10 displayed enhanced efficacy, increased stability, and reduced toxicity in preclinical models compared to precursor compounds such as 5-fluorouracil. While CF10 was shown to be effective as a single agent in preclinical models of PDAC, combination with an experimental Poly (ADP-ribose) Glycohydrolase (PARG) inhibitor or PARG ablation resulted in synergistic induction of DNA damage and PDAC cell death. Taken together, the data nominate CF10 as a promising candidate that could significantly improve the efficacy of standard-of-care regimens for PDAC.

AKT1 E17K Inhibits Cell Migration via β -Catenin SignalingGao *et al.* | Page 573

Mutations in the PI3K/AKT pathway are common in cancer and have significant implications for cell metabolism, proliferation, and survival. Despite its central role in cell biology, pharmacological agents targeting this pathway have met with limited success in the clinic. Now, using CRISPR to model specific genetic lesions, Gao and colleagues have uncovered differential functions of mutations in AKT isoforms: E17K mutations in AKT1 and AKT2 both conferred survival and proliferation advantages, but AKT1 E17K had the additional effect of suppressing invasion. Specifically, AKT1 mutation prevented nuclear localization of β -catenin, thereby repressing ZEB1 expression and impeding migratory capacity. This effect on cell migration was not observed in the context of AKT2 activation nor in the context of PIK3CA or PTEN mutations, which activate both AKT1 and AKT2. The authors therefore suggest that the use of pharmacological inhibitors of the AKT pathway may paradoxically drive disease progression in certain genetic backgrounds by releasing an AKT1-mediated brake on cell migration and epithelial-mesenchymal transition.

Heme-Sensing Pathway Dictates Apoptotic Response

Smith *et al.* | Page 636

BH3-mimetic compounds such as venetoclax have potent pro-apoptotic effects in leukemic B cells, but tumors frequently amplify their expression of anti-apoptotic BH2 domain-containing proteins, such as MCL-1, to circumvent pro-apoptotic therapeutics. In this study, Smith and colleagues employ a genome-wide CRISPR screen to identify pathways involved in regulating MCL-1 expression, and thereby identify the heme-regulated inhibitor (HRI) as a key target. The authors show that, in the absence of heme or when the interaction between heme and HRI are pharmacologically disrupted, HRI initiates the cellular stress response and suppresses MCL-1 expression. These effects were not observed when HRI expression was genetically ablated, suggesting that HRI represents a control node for the modulation of MCL-1 expression in leukemic cells. These data nominate HRI and the heme-sensing pathway as a potential candidate for development of combinatorial regimens to enhance the efficacy of BH3-mimetics in certain subsets of leukemia patients.

Molecular Cancer Research

Selected Articles from This Issue

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