Butyrate Mediates Tumor-Suppressive Effects of Dietary Fiber

- Fiber protects against colorectal cancer when butyrate-producing bacteria populate the microbiota.
- Butyrate is not metabolized and accumulates in cancer cells due to the Warburg effect.
- HDAC inhibition by butyrate is associated with increased expression of tumor suppressor genes.

Whether dietary fiber intake reduces colorectal cancer risk remains controversial, possibly because epidemiologic studies have not controlled for gut microbiota composition. Bacteria in the colon convert fiber into metabolites such as butyrate, which serves as the primary energy source for normal colonocytes but also inhibits histone deacetylases (HDAC) to epigenetically regulate gene expression. To address whether butyrate and the microbiota mediate protective effects of fiber, Donohoe and colleagues fed gnotobiotic mice colonized with the butyrate-producing bacterium Butyricivibrio fibrisolvens a high-fiber diet prior to chemically inducing colorectal carcinogenesis. The combination of B. fibrisolvens and high fiber conferred a greater protective effect than either alone, whereas a mutant B. fibrisolvens strain deficient in butyrate production had a diminished protective effect that could be rescued by exogenous butyrate. Because butyrate is minimally metabolized in colorectal cancer cells due to the Warburg effect, which promotes a shift to glucose dependency through increased glycolysis and decreased mitochondrial oxidative phosphorylation, butyrate preferentially accumulates within colorectal tumors. Consistent with butyrate’s role as an HDAC inhibitor, histone H3 acetylation was significantly increased in tumor cells compared with adjacent normal colonocytes and was associated with increased expression of genes that promote apoptosis and cell-cycle arrest. Collectively, these findings provide mechanistic evidence for how dietary fiber protects against colorectal cancer that can be evaluated in future epidemiologic and microbiome studies and raise the possibility that modulation of an endogenous HDAC inhibitor by diet or microbiotic supplementation could be a chemopreventative strategy.

Genomic Profiling of PACC Identifies Potential Therapeutic Targets

- Next-generation sequencing revealed recurrent BRAF and RAFI rearrangements in 23% of PACCs.
- The SND1–BRAF fusion is oncogenic and enhances sensitivity to the MEK inhibitor trametinib in vitro.
- Fusion-negative PACCs harbor mutually exclusive inactivating alterations in DNA repair genes.

Pancreatic acinar cell carcinoma (PACC) is a rare subtype of pancreatic cancer that exhibits distinct morphologic and histologic characteristics compared with pancreatic ductal adenocarcinoma and pancreatic neuroendocrine tumors. Previous genomic studies revealed rare activating mutations and somatic inactivation of tumor suppressor genes in PACCs; however, whether PACCs harbor recurrent targetable genomic alterations remains unclear. To address this question, Chmielecki, Hutchinson, and colleagues performed comprehensive genomic profiling of 44 PACCs and related mixed acinar carcinomas. This analysis identified recurrent and diverse rearrangements of BRAF and RAF1 in 23% of PACCs, including three previously unidentified nonrecurrent BRAF fusions. The most frequently detected BRAF fusion, SND1–BRAF, was enriched in PACC and resulted in constitutive activation of MAPK signaling and oncogenic transformation, which were suppressed by treatment with the MEK inhibitor trametinib in vitro. Compared with other pancreatic cancer subtypes, PACCs were characterized by a distinct genomic landscape, including a lower frequency of mutations in KRAS, SMAD4, CDKN2A, and TP53, increased prevalence of BRCA2 mutations, and loss-of-function alterations in PRKAR1A. Furthermore, inactivating and mutually exclusive genomic alterations in DNA repair genes such as BRCA1, ATM, MSH2, BRIP1, and PALB2 were detected in 45% of PACCs and were enriched in fusion-negative tumors, implicating defective DNA repair in PACC and suggesting potential sensitivity to platinum-based agents and PARP inhibitors. These findings suggest the presence of clinically actionable genomic alterations in the majority of PACCs and may enable stratification of patients with PACC for personalized therapy.

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Hypoxic Induction of SHMT2 Is Required for Redox Homeostasis

- In MYC-amplified cancers, hypoxia triggers induction of SHMT2 in a HIF1α-dependent manner.
- SHMT2 upregulation maintains mitochondrial redox balance and prevents ROS-dependent cell death.
- SHMT2 expression promotes MYC-amplified neuroblastoma growth and is correlated with poor prognosis.

Although serine synthesis is frequently increased in many cancers, the role of serine catabolism in tumor cell growth and survival is poorly understood. Ye, Fan, and colleagues found that the serine catabolic enzyme mitochondrial serine hydroxymethyltransferase 2 (SHMT2) was overexpressed in a variety of human cancers, including neuroblastoma and breast cancer, and was correlated with expression of phosphoglycerate dehydrogenase, which catalyzes the initial step of serine synthesis. Interestingly, SHMT2 expression in cancer cells was induced by hypoxia; this transcriptional regulation was mediated by hypoxia-inducible factor 1α (HIF1α) and was dependent on elevated expression of MYC. Downregulation of SHMT2 and serine catabolism resulted in decreased production of NADPH and increased mitochondrial reactive oxygen species (ROS) under hypoxia, suggesting that SHMT2 is required to maintain redox balance. Consistent with this idea, depletion of SHMT2 in MYC-dependent neuroblastoma cells stimulated ROS-dependent cell death under hypoxia and impaired xenograft tumor growth in vivo, whereas ectopic SHMT2 expression in cells lacking MYCN amplification was sufficient to protect against hypoxia-induced cell death. Furthermore, SHMT2 expression was correlated with HIF1α levels in patients with MYCN-amplified neuroblastoma and was associated with poor prognosis and aggressive tumors. These results identify a critical role for SHMT2-driven mitochondrial serine catabolism in the regulation of redox homeostasis, cancer cell survival under hypoxia, and tumor growth and suggest that SHMT2 inhibitors may be effective in MYC-amplified cancers.

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Distinct Biochemical Properties of NRASQ61R Drive Melanoma Formation

- Endogenous expression of NRASQ61R promotes melanoma in mice more efficiently than NRASG12D.
- NRASQ61R cooperates with LKB1 loss to induce metastasis and faithfully models human melanoma.
- Increased stability and activation of NRASQ61R may explain its enhanced melanomagenicity.

Of the three RAS oncogenes, NRAS is the most frequently mutated in human melanoma, with 84% of aberrations localizing to codon 61, as compared with only 7% in codon 12. However, the mechanisms underlying this codon-specific mutation selection in melanoma remain unclear. Burd and colleagues compared the oncogenic potential of NRASQ61R, NRASG12D, and KRASG12D using three conditional knock-in mouse models in which mutant RAS was expressed from the endogenous promoter specifically in melanocytes. In the context of concomitant p16INK4a inactivation, NrasQ61R and KrasG12D mice readily developed nevi, hyperpigmented regions, and melanoma with high penetrance, whereas tumors rarely formed in NrasG12D mice, indicating that physiologic expression of NRASQ61R more effectively transforms melanocytes. NRASQ61R expression was also able to cooperate with serine/threonine kinase 11 (Shk11, also known as Lkb1) loss to induce highly metastatic disease reminiscent of human NRAS-mutant melanoma. Functional analyses revealed that NRASQ61R and NRASG12D similarly bound downstream effectors, including PI3K and RAF, and activated MAPK and PI3K signaling. However, NRASQ61R displayed increased affinity for GTP, a slower rate of GTP hydrolysis, and greater stability compared with NRASG12D. Together, these data suggest that codon 12 and 61 mutations in NRAS are biochemically distinct and that the abundance of active GTP-bound NRASQ61R, rather than preferential engagement of downstream effector pathways, explains its increased melanomagenicity and predominance in human melanoma.

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The BRCA1 tumor suppressor functions to promote error-free homologous recombination (HR)-mediated DNA repair (HRR) and to maintain genome stability. Inactivating mutations in BRCA1 have been linked to breast and ovarian cancer susceptibility, presumably due to loss of HRR; however, recent work suggests that the BRCA1–RAP80 complex may also play a role in fine-tuning HRR amplitude. To dissect the mechanisms that govern this process, Hu and colleagues characterized BRCA1-binding partners and showed that PARP1 interacted with RAP80–BRCA1 complexes and induced the poly-ADP-ribosylation (PARsylation) of a fraction of BRCA1 within a region containing its DNA-binding domain. Functionally, BRCA1 PARsylation negatively regulated its DNA-binding activity and promoted the formation and integrity of RAP80–BRCA1–PARP1 complexes after DNA damage. Blocking PARP1-mediated BRCA1 PARsylation enhanced HRR and, surprisingly, increased the frequency of certain types of chromosomal aberrations. In support of the hypothesis that HRR hyperactivation may stimulate genome instability, silencing of essential HRR components reversed or blunted the increase in radial structures and complex chromosome rearrangements in cells deficient in BRCA1 PARsylation. Furthermore, characterization of breast cancer cell lines and patient-derived xenografts revealed decreased expression of PARsylated BRCA1, RAP80, or ABRA1, suggesting that hyper-recombination resulting from defects in the BRCA1 PARsylation–RAP80 pathway may contribute to cancer development. Together, these results highlight a previously unrecognized role for BRCA1 in the negative regulation of HRR and provide evidence that excessive HRR may represent a source of genome instability that drives carcinogenesis.

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- BRCA1 PARsylation by PARP1 promotes RAP80–BRCA1 complex integrity and tunes BRCA1 function.
- Failure of BRCA1 PARsylation stimulates HR-driven repair and promotes chromosome instability.
- Decreased BRCA1 PARsylation and/or RAP80 expression are detected in a subset of breast cancers.

Follicular Dendritic Cells Provide a Proproliferative Niche for CLL Cells

Tumor–stromal cell interactions have been implicated in B-cell chronic lymphocytic leukemia (B-CLL) progression and therapeutic resistance, but the mechanisms that regulate CLL cell trafficking to protective niches in the lymphoid microenvironment are largely unknown.

Using the murine Eµ-Tcl1 CLL model, Heinig and colleagues determined that leukemic B cells express chemokine receptors and lymphotoxins (LT) that promote access to secondary lymphoid organs. In particular, chemokine (C-X-C motif) receptor 5 (CXCR5) was critical for leukemia development and conferred a proliferative advantage to tumor cells. Intravital imaging tracked leukemia cell migration across the marginal zone to gain access to the follicular dendritic cell (FDC) network within the germinal center light zones of the spleen, which was dependent on CXCR5 signaling through its ligand CXCL13. Colocalization of leukemia cells with FDCs enhanced B-cell receptor signaling in leukemia cells and provided paracrine B-cell growth factors that promoted leukemia cell proliferation. In irradiated mice, leukemia cells reciprocally stimulated mesenchymal stromal cell differentiation, resulting in rapid recovery of FDC networks with increased CXCL13 and B-cell–activating factor expression that enhanced CLL cell proliferation. In addition, inhibition of stromal LTβ receptor (LTβR) signaling with decoy receptors eliminated FDC networks and, similar to the effects of Cxcr5 deletion, delayed leukemia growth. Taken together, these results indicate that CXCR5 is critical for leukemia cell homing to a proliferative niche, which may be therapeutically exploited to prevent tumor–stroma crosstalk and inhibit leukemia growth.

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- CXCR5 induces CLL cell migration to protective FDC networks that provide proliferative stimuli.
- Activation of stromal LTβR signaling maintains FDCs and enhances CLL growth in mice.
- Targeting this tumor–stroma crosstalk via inhibition of CXCR5 or LTβR delays CLL progression.