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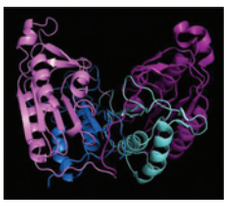
CANCER RESEARCH

BREAKING INSIGHTS

Highlights from Recent Cancer Literature

An Unexpected Prosurvival Function for Caspase-8

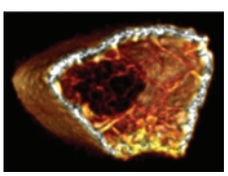


Caspase-8 is a key apoptotic mediator and its expression is lost in many tumor types. Paradoxically, caspase-8 is highly expressed in a subset of tumors. Müller and colleagues identified a novel prosurvival function for nuclear caspase-8 that facilitates bypass of a p53-dependent G_2-M checkpoint. Expression of caspase-8 in the nucleus was associated with a poor prognosis and therapeutic resistance. DNA damage increased nuclear caspase-8, and caspase-8 knockdown enhanced p53-dependent apoptosis during the G_2-M phase. Nuclear caspase-8 led to p53 degradation through cleavage of the p53 deubiquitinase, USP28, preventing apoptosis and allowing progression through G_2-M.

Expert Commentary: This study suggests caspase-8 inhibition may be an effective therapeutic strategy in p53 wild-type tumors. *(Image courtesy of Wikimedia Commons.)*

Müller I, Strozyk E, Schindler S, Beissert S, Oo HZ, Sauter T, et al. Cancer cells employ nuclear caspase-8 to overcome the p53-dependent G2/M checkpoint through cleavage of USP28. Molecular Cell; Published online January 13, 2020; doi:10.1016/j.molcel.2019.12.023.

Senescence Contributes to Therapy-Induced Bone Loss

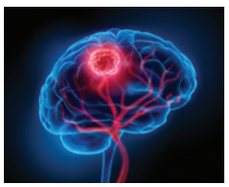


Although chemotherapy-induced bone loss has been ascribed to estrogen deficiency resulting from ovarian failure, substantial data suggests the existence of an estrogen-independent mechanism of bone loss. Bone loss correlates with increased risk of fractures that significantly impact quality of life. Using clinically relevant mouse models, Yao and colleagues demonstrated that senescence and its senescence-associated secretory phenotype (SASP) contributed to chemotherapy-induced bone loss and can be rescued by depleting senescent cells. Chemotherapy-induced SASP could be limited by targeting the p38MAPK-MK2 pathway, which resulted in preservation of bone integrity in chemotherapy-treated mice.

Expert Commentary: These data identify senescent cells as major drivers of bone loss and the p38MAPK-MK2 axis as a putative therapeutic target that can preserve bone and improve quality of life. These data combined with the authors' recent findings that inhibiting p38MAPK and MK2 can significantly reduce metastatic breast cancer growth suggest that inhibition of these key signaling pathways will benefit patients treated with chemotherapy. *(Image from cited article courtesy of publisher.)*

Yao Z, Murali B, Ren Q, Luo X, Faget DV, Cole T, et al. Therapy-induced senescence drives bone loss. Cancer Res 2020;80:1171–82.

Rational Therapeutic Modeling of Human Group 3 Medulloblastoma



To model genetic events leading to Group 3 medulloblastoma, Ballabio and colleagues performed *in vivo* transfection into the cerebella of wild-type mice. Twenty-four combinations of somatic events were observed in human Group 3 medulloblastoma. Combining cMYC +/− Otx2 or Gfi1 led to robust formation of tumors. The authors next leveraged human cerebellar organoids, electroporating both cMYC +/− Otx2 or Gfi1 combinations and observing tumor formation. Analysis of human sequencing data revealed that cMYC/Otx2 overexpression was enriched for loss-of-function mutations in SMARCA4. Expression of SMARCA4 inhibited tumor formation in both human and murine cMYC/Otx2 models due to elevated levels of other SWI/SNF complex proteins. Methylation analysis classified transformed human organoids as Group 3 medulloblastoma. Treatment of cMYC/Otx2 overexpressing organoids with EZH2 inhibitors resulted in growth inhibition.

Expert Commentary: A barrier to progress in medulloblastoma has been a paucity of models recapitulating the heterogeneity within each molecular subgroup. This study provides a rapid and rational approach to validating somatic events in a human model and identification of personalized new therapies.

Ballabio C, Anderle M, Gianesello M, Lago C, Miele E, Cardano M, et al. Modeling medulloblastoma *in vivo* and with human cerebellar organoids. Nat Commun 2020;11. DOI: 10.1038/s41467-019-13989-3.

Twisted Talks of MYC, Cancer, and Immunity

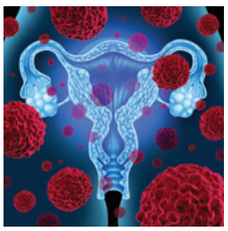
Together, MYC and TWIST1 activate or repress thousands of genes and are key regulators in normal cells. TWIST1 controls the movement and spread of cells in the embryo. To address how MYC and TWIST1 regulate metastasis, Dhanasekaran and colleagues used a transgenic model of hepatocellular carcinoma, where conditional expression of *MYC* and *Twist1* resulted in metastasis. *MYC* and *TWIST1* together activated the innate immunity through secretion of cytokines that in turn recruited and polarized tumor-associated macrophages. Treatment with CCL2 and IL13 led to metastasis, whereas inhibition of these cytokines prevented the spread of cancer cells. Analysis of 10,000 human patients with 33 different cancers showed that the expression of MYC and TWIST1 proteins correlated with high levels of CCL2 and IL13 and with poor survival.

Expert Commentary: *MYC* and *TWIST1* cooperate to induce expression of cytokines that in turn drive cross-talk between cancer and immune microenvironment, promoting spread. Targeting these cytokines may prevent metastasis. *(Image by Basile Morin courtesy of Wikimedia Commons.)*

BREAKING INSIGHTS

Dhanasekaran R, Baylot V, Kim M, Kuruvilla S, Bellovin DI, Adeniji N, et al. MYC and Twist1 cooperate to drive metastasis by eliciting crosstalk between cancer and innate immunity. Elife 2020;9. DOI: 10.7554/eLife.50731

Kinome Profiling in Ovarian Carcinoma

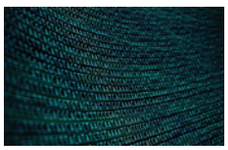


High-grade serous ovarian carcinoma (HGSOC) is among the most lethal of gynecological cancers. Kurimchak and colleagues initiated studies to identify druggable kinases required for HGSOC viability. Using multiplexed pan-kinase inhibitor beads, mass spectrometry, and HGSOC patient samples, they identified a number of known HGSOC drivers, including kinases not previously implicated in HGSOC. Among newly identified driver kinases, myotonic dystrophy kinase–related CDC42-binding kinase alpha (MRCKA) was overexpressed in HGSOC patient tissues and required for viability of a number of HGSOC cell lines. They found that MRCKA regulated HGSOC cell viability by controlling the cell-cycle checkpoint, focal adhesions, and actin remodeling. Furthermore, examining two previously described MRCKA inhibitors, they found that BDP9066 specifically inhibited MRCKA in HGSOC cell lines, reducing levels of MRCKA biomarkers and attenuating cell viability.

Expert Commentary: The identification of a novel, druggable, kinase driver of HGSOC represents an important step towards developing much needed targeted therapies for patients harboring this cancer.

Kurimchak AM, Herrera-Montávez C, Brown J, Johnson KJ, Sodi V, Srivastava N, et al. Functional proteomics interrogation of the kinome identifies MRCKA as a therapeutic target in high-grade serous ovarian carcinoma. Sci Signal 2020;13. DOI: 10.1126/scisignal.aax8238.

CD8$^+$ T-cell Gene Signatures Dictate Response to Immune Checkpoint Therapies



Although immune checkpoint inhibition has provided significant benefit in the treatment of metastatic melanoma, the reasons for the variable therapeutic response is largely unknown. Fairfax and colleagues have uncovered gene signatures in peripheral CD8$^+$ T cells that are associated with durable clinical benefit. Early gene changes revealed overexpression of T-cell receptor-encoding genes in patients who went on to have long-term responses. This was associated with a greater number of large clones, which correlated with effector memory T-cell percentage and overexpression of associated genes.

Expert Commentary: These findings provide valuable insight into the response to immune checkpoint inhibition and highlight the potential benefit of transcriptomic profiling in providing information on long-term response and patient stratification.

Fairfax BP, Taylor CA, Watson RA, Nassiri I, Danielli S, Fang H, et al. Peripheral CD8$^+$ T cell characteristics associated with durable responses to immune checkpoint blockade in patients with metastatic melanoma. Nat Med 2020;26:193–9.

Note: Breaking Insights are written by *Cancer Research* editors. Readers are encouraged to consult the articles referred to in each item for full details on the findings described.

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Cancer Res 2020;80:1369-1370.