

RESEARCH WATCH

Melanoma

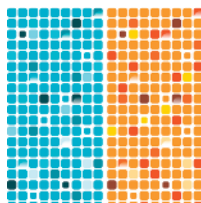
Major finding: IFN α/β enhances the cytotoxicity of MEK inhibition in melanoma cells with low basal STAT1 activity.

Approach: A biclustering algorithm identified context-specific MAPK target genes that contribute to resistance.

Impact: System-wide computational analyses of perturbations can predict drug response in patients.

TYPE I IFN ACTIVITY PREDICTS RESPONSE TO MEK INHIBITION IN MELANOMA

The majority of melanoma tumors exhibit perturbation of the MAPK signaling pathway, which has been shown to be an effective therapeutic target. However, individual patients display variable phenotypic responses to MAPK pathway inhibition due to mechanisms that are poorly understood. Litvin and colleagues developed a computational tool called context-specific regulation (COSPER) to characterize alterations in the transcriptional responses to MEK inhibition. Melanoma cell lines displayed phenotypic and transcriptional heterogeneity in response to MEK inhibition, with most genes regulated by MAPK signaling only in a subset of cell lines. Analysis of pre- and post-inhibition transcriptional data using COSPER identified context-specific gene clusters directly regulated by the MAPK pathway. Notably, the expression of a cluster containing several genes of the type I IFN pathway correlated with the cytotoxic response to MEK inhibition. This IFN cluster was split into two groups of cell lines delineated by low or high IFN-STAT1 activity. Cell lines with low STAT1 activity were sensitive to the cytotoxic response of MEK inhibition and exhibited increased



cytotoxicity in response to combined treatment with IFN α/β ; in contrast, cell lines with high STAT1 activity were resistant to both MEK inhibition and dual treatment, indicating a fundamental difference in therapeutic response between the two groups. Interestingly, although all cell lines underwent cytochrome *c* release following MEK inhibition, only cell lines with low STAT1 activity exhibited activation of the caspase pathway and induction of apoptosis. Furthermore, low IFN-STAT1 activity correlated with deletion of the IFN locus on chromosome 9p22 and low expression of IFN genes, whereas cell lines with high STAT1 activity harbored two or three copies of the 9p22 locus. These data suggest that the IFN pathway plays an important role in the cytotoxic response to MAPK-directed therapy in melanoma and demonstrate the utility of this approach for system-wide analyses of transcriptional programs to predict therapeutic response. ■

Litvin O, Schwartz S, Wan Z, Schild T, Rocco M, Oh NL, et al. Interferon α/β enhances the cytotoxic response of MEK inhibition in melanoma. Mol Cell 2015;57:784–96.

Prostate Cancer

Major finding: GATA2-induced expression of IGF2 promotes chemotherapy resistance and aggressive CRPC.

Mechanism: GATA2-IGF2 upregulation stimulates IGF1R/INSR and activation of downstream kinase signaling.

Impact: Combined inhibition of IGF1R/INSR may increase chemotherapy sensitivity and improve survival in CRPC.

GATA2-IGF2 MEDIATES CHEMOTHERAPY RESISTANCE IN LETHAL PROSTATE CANCER

Although patients with disseminated castration-resistant prostate cancer (CRPC) initially respond to treatment with taxane chemotherapy such as docetaxel, progression to lethal chemotherapy-resistant tumors often occurs. However, the mechanisms underlying chemotherapy resistance remain poorly understood. Vidal and colleagues found that GATA2, a transcription factor that regulates androgen receptor (AR) transcriptional activity, was upregulated in both docetaxel-resistant CRPC cell lines and during progression to disseminated chemotherapy-resistant disease in human prostate cancer. Depletion of GATA2 in chemotherapy-resistant CRPC cells and patient-derived xenograft models resulted in increased sensitivity to taxanes, induction of apoptosis, and diminished tumorigenicity *in vivo*, implicating GATA2 as a determinant of aggressiveness in CRPC. Transcriptional profiling of chemotherapy-resistant CRPC cells identified a signature of 28 GATA2-regulated genes that was enriched in patients with lethal prostate cancer and was independent of AR. In particular, GATA2 directly induced the expression of insulin-like growth factor 2 (IGF2), which was upregulated during disease progression and in patients treated with taxane chemotherapy and

was required for GATA2-mediated chemotherapy resistance and tumorigenicity. Depletion of IGF2 resulted in reduced taxane resistance and tumor growth, whereas the addition of recombinant IGF2 was sufficient to rescue the effects of GATA2 depletion in chemotherapy-resistant cells. Mechanistically, GATA2-driven IGF2 expression stimulated IGF1 receptor (IGF1R) and insulin receptor (INSR), resulting in activation of effector kinases, including PI3K-AKT and JNK; combined inhibition of these downstream pathways abrogated chemotherapy resistance and soft-agar growth. Importantly, treatment with a dual inhibitor of IGF1R/INSR restored sensitivity to taxane chemotherapy in xenograft models and improved overall survival in preclinical models of disseminated disease. These findings identify GATA2-IGF2 signaling as an important mediator of chemotherapy resistance and aggressiveness in lethal prostate cancer and suggest that IGF1R/INSR may be an effective therapeutic target. ■

Vidal SJ, Rodriguez-Bravo V, Quinn SA, Rodriguez-Barrueco R, Lujambio A, Williams E, et al. A targetable GATA2-IGF2 axis confers aggressiveness in lethal prostate cancer. Cancer Cell 2015;27:223–39.

CANCER DISCOVERY

GATA2–IGF2 Mediates Chemotherapy Resistance in Lethal Prostate Cancer

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