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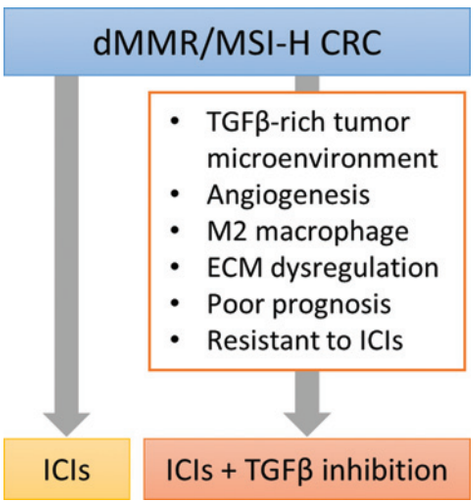
MOLECULAR CANCER RESEARCH

HIGHLIGHTS

Selected Articles from This Issue

TGFβ-Dependent Stromal Subset in dMMR/MSI-H CRC



Endo *et al.* | Page 1402

Colorectal cancer patients with defective mismatch repair and high microsatellite instability (dMMR/MSI-H) tend to be more likely to benefit from immune checkpoint inhibitors (ICI), a finding that led to the recent FDA approval of the anti-PD-1 monoclonal antibody, pembrolizumab, in this context. However, many dMMR/MSI-H patients are *de novo* resistant to current ICI interventions. In order to better understand this discrepancy, Endo and colleagues profiled the tumor microenvironment of 220 dMMR/MSI-H colorectal cancers and 1440 MMR-proficient/microsatellite-stable tumors. Comparative transcriptomics, proteomics, and immunohistochemistry identified a subset of ICI non-responders within the dMMR/MSI-H cohort that harbored a unique subset of stromal cells driven by TGFβ. Presence of these cells was linked to poor outcome and an active tumor microenvironment with high levels of angiogenesis and immunosuppressive M2 macrophages. Additionally, the TGFβ signature correlated with the presence of an extracellular matrix signature predictive of ICI resistance. The data indicate that a TGFβ-rich stromal compartment may undermine the efficacy of ICI approaches even in tumors that would otherwise be predicted to respond. The authors suggest that modulation of TGFβ signaling in combination with ICI may be a feasible way to sensitize this cohort to immuno-oncology approaches.

Transcriptional Comparisons of Common Breast Cancer Models

Ross *et al.* | Page 1278

Metastasis is a multi-step process that drives significant changes in tumor cells. Accordingly, cell transcriptomes and behaviors vary prominently between the primary tumor and its various metastases. Furthermore, different experimental models of metastasis induce different pressures on tumor cells, thus driving disparate cellular responses and making it difficult to conclusively define metastasis-specific targets. Here, Ross and colleagues report on the comparative transcriptomics of breast cancer metastasis and identify targetable gene signatures held in common across multiple models of metastatic spread. While many transcriptional signatures appeared to be differentially represented based on the model used, the authors identified the sildenafil response and nicotine degradation pathways as highly enriched across various models and routes of metastasis. Accordingly, significant reductions in metastatic spread were recorded in response to sildenafil treatment, whereas nicotine administration resulted in significantly more metastases. These data highlight crucial differences in common models of tumor metastasis, while simultaneously identifying novel targetable pathways that may be responsive to drugs that are already available.

Circadian Genes Dysregulated in Cancer Inhibit Proliferation

van der Watt *et al.* | Page 1340

Circadian rhythms (CR) are regulated by a complex interplay between transcription factors and other mediators known as "clock" genes. Their disruption has been linked to a variety of different pathologies, including cancer. However, as the clock exerts distinct functions across various tissue types, a concrete role for CR and clock genes in tumor biology has been elusive. In this study, van der Watt and colleagues describe circadian clock dysregulation in cervical and esophageal cancers with significant implications for tumor biology. Specifically, key regulators of CR—such as CLOCK, CRY1, RORα, and others—were downregulated in cancerous patient tissues and in tumor cell lines compared to normal controls, in part through promoter methylation. Surprisingly, despite reduced expression of CR genes, the cells maintained functional rhythmicity and circadian oscillation of genes controlled by the clock. These observations indicate further levels of complexity in the control and biological implications of CR in tumor cells, especially in the context of "chronotherapy," in which chemotherapeutic interventions are synchronized with CR to obtain maximal therapeutic effects.

TECs Suppress Antitumor T-cell Responses

Taguchi *et al.* | Page 1427

Tumor endothelial cells (TECs) constitute a key interface between the immune system and the tumor microenvironment. Lymphocytes homing to the site of the tumor must interface with endothelial cells in order to exit the vasculature, and TECs are known to play a passive role in immune evasion by downregulating critical adhesion molecules. Now, Taguchi and colleagues describe a new mechanism by which TECs engage in antigen-specific immune suppression via upregulation of PD-L1. Specifically, TECs from implanted mouse melanoma tumors demonstrated active tumor antigen presentation via MHC class I and II. Coupled with an increase in PD-L1 expression, TEC-mediated antigen presentation led to suppression of CD8+ T-cell cytotoxicity and induced the differentiation of suppressive CD4+ T cells. These effects were shown to be TEC/T-cell contact-dependent and were abrogated by treatment with PD-L1 blocking antibodies. The data suggest that TECs harbor a novel role as suppressive antigen presenting cells and nominate new approaches to enhancing immuno-oncology therapies.