Hypoxia-Inducible Factor-1α and Immunosuppressive Macrophages

Solid tumors are infiltrated by large numbers of immune cells derived from both the innate and adaptive lineages. In breast cancers, macrophages represent an abundant subset of leukocytes in these tumors. Macrophages are also associated with regions of low oxygen tension, or hypoxia. Doedens and colleagues evaluated the role of the inflammatory hypoxic response during tumorigenesis via genetic deletion of the hypoxia-inducible factor-1α (HIF-1α) transcription factor in macrophages and other myeloid cells. Loss of myeloid-derived HIF-1α resulted in smaller tumors at end stage in multiple models of tumorigenesis. The investigators used three-dimensional coculture models to evaluate the relationship between macrophages and neoplastic cells. This evaluation revealed that tumor cells directly affect the arginase/inducible nitric oxide synthase (iNOS) axis in an HIF-1α-dependent fashion. Because this pathway is known to suppress T-cell activation, T cells isolated from wild-type tumors were suppressed by macrophages in an HIF-1α-dependent manner. Together, these findings demonstrate that—in addition to their protumoral role in regulating angiogenesis, tissue remodeling, and invasion by providing cytokines and cathepsins proteases—macrophages infiltrating solid tumors also suppress proliferation of T cells via the HIF-1α pathway generating localized, hypoxic immunosuppression of T-cell function. Thus, therapeutic strategies that relieve hypoxia-induced immunosuppression of the adaptive immune response may provide a survival advantage.

Image courtesy of Randall Johnson, University of California at San Diego.


siRNA Targeting of Stat3

Signal transducers and activators of transcription (STAT) are important intracellular signaling molecules that mediate many effects of T helper (Th1) and Th2 cytokines. Activation of myeloid Stat3 limits antitumor immunity; thus, therapies that block Stat3 would be anticipated to direct cell responses toward Th1 immunity and foster tumor rejection. Herrmann and colleagues developed a novel siRNA delivery platform by conjugating a TLR9 agonist with siRNA that efficiently targets myeloid and B cells resulting in silencing of Stat3 alleles in following CpG triggering. Moreover, administration of the CpG-Stat3siRNA conjugates enhanced effector functions of adoptively transferred CD8+ T cells accompanied by increased presence of dendritic cell and CD8+ T-cell engagement in tumor draining lymph nodes, with concomitant upregulation of effector molecules including perforin, granzyme B, and IFN-γ. This novel strategy to selectively silence important protumor mediators indicates that use of siRNA-based platforms could be considered to enhance adjuvant therapy by improving T-cell activity.


Macrophage Subsets in Tumors

The bioactive state of macrophages and some other myeloid cells (including neutrophils) correlates with Th1 and Th2 nomenclature, referred to as M1 (classical) or M2 (alternative) activation, respectively. M1-type macrophages are typically regulated by Th1 cytokines and granulocyte monocyte colony stimulating factor (GM-CSF/CSF1), which, in part, enhance macrophage cytotoxic activity. In contrast, tissue macrophages exposed to Th2 cytokines common to tumors instead manifest an M2-type phenotype that can be potentiated by multiple mediators. M2-type macrophages are more commonly found in solid tumors. Macrophages can be immunosuppressive, proangiogenic, and pro-tissue remodeling and can also serve as expressers of high levels of growth factors and immune suppressive molecules including arginase 1 and inducible nitric oxide synthase. A conundrum regarding macrophage biology is that solid tumors often maintain multiple "types” of macrophages. Movahedi and colleagues have developed a strategy to isolate distinct populations of tumor-associated macrophages (TAM) to identify which subpopulations are associated with distinct bioactivities. They show that tumor-monocyte pools represented by Ly6C<sup>hi</sup>CX3CR1<sup>−/−</sup> monocytes both seed tumors and renew nonproliferating macrophage subsets. By gene and protein expression profiling, they were also able to segregate TAMs and reveal that the more M2-like TAMs were enriched in hypoxic tumor areas, had elevated proangiogenic activity, and increased in numbers as tumors progressed. These TAMs also were poor antigen presenters but could suppress T-cell activation, albeit by using different suppressive mechanisms. Together, these data help to unravel the complexities of macrophage biology and begin to provide insight into
which subpopulations should be targeted with anticancer therapeutics.


Neural Regulation of Breast Cancer Metastasis

Although the major cause of cancer-related death remains metastasis to distant organs, little is known regarding physiologic programs that regulate the process. Nerve fibers from the sympathetic nervous system (SNS) are present in organs that are often targets for breast cancer metastasis, including the lymph nodes, lung, and bone. Sloan and colleagues investigated the possibility that activation of neuroendocrine programs might also play a role in cancer progression by using a novel in vivo bioluminescence imaging modality to track development of metastasis. Whereas stress-induced neuroendocrine activation had no effect on primary tumor development, a 30-fold increase in metastasis to lymph nodes and lung was observed. Activation of β-adrenergic signaling was found to induce infiltration of CD11b+F4/80+ macrophages into primary tumor stroma that could be blocked by treatment with propanolol in a similar manner to colony stimulating factor 1 receptor kinase blockade. These findings are intriguing, as they reveal a previously overlooked pathway regulating breast cancer metastasis mediated by the SNS and indicate that antimetastatic therapies targeting β-adrenergic signaling may relieve aspects of macrophage-mediated protumor immunity now well recognized as fostering breast cancer metastasis.


Stromal Hyaluronan Regulates Macrophage Recruitment

Key mediators important for monocyte/macrophage recruitment into tissue include colony stimulating factor 1 and interleukin 34, as well as the chemokines CCL2/MCP1 and CCL8/MCP2. Kobayashi and colleagues report that, in addition to these well-described soluble factors, tumor-associated macrophage (TAM) recruitment into tumor stroma is dependent on hyaluronan. Macrophage recruitment into tumor stroma was abolished in chimeric tumors where the hyaluronan synthase 2 gene (Has2) was disrupted in stromal fibroblasts. Similarly, tumor-associated angiogenic and lymphangiogenic vasculature were impaired in chimeric mice. These data indicate that stromal hyaluronan serves as a microenvironmental signal for recruitment of TAMs and for development of vascular programs that support tumorigenesis.


Dosage-Dependent Role for PTEN in Pancreatic Ductal Adenocarcinoma

Approximately 90% of human pancreatic ductal adenocarcinomas (PDAC) contain KRAS mutations; however, mice genetically engineered to express KrasG12D from its endogenous locus develop PDACs only after a prolonged latency. In later stages of PDAC, PTEN-controlled phosphatidylinositol 3-kinase (PI3K)/AKT signaling axis is dysregulated. To determine if PDAC latency was regulated by PTEN/PI3K/AKT signaling subsequent to KrasG12D, Hill and colleagues generated conditional Pten-null mice (Ptenlox/lox) where activation of KrasG12D was conditionally regulated. Compound heterozygous mice had a significantly accelerated development of acinar-to-ductal metaplasia, malignant pancreatic intraepithelial neoplasia, and PDAC where mice with KrasG12D activation and Pten homozygous deletion succumbed to cancer by 3 weeks of age. These data reveal a dosage-dependent role for PTEN, and the resulting dysregulation of the PI3K/AKT signaling axis in both PDAC initiation and progression.


Note: Breaking Advances 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.
Highlights from Recent Cancer Literature

Cancer Res 2010;70:7735-7736.

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