Trends in Immunology

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Review

Inflammation-Induced Plasticity in Melanoma Therapy and Metastasis

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Phenotype switching contributes to nongenomic heterogeneity in melanoma and other cancers. These dynamic and in part reversible phenotype changes impose diagnostic and therapeutic challenges. Understanding the reciprocal coevolution of melanoma and immune cell phenotypes during disease progression and in response to therapy is a prerequisite to improve current treatment strategies. Here we discuss how proinflammatory signals promote melanoma cell plasticity and govern interactions of melanoma and immune cells in the tumor microenvironment. We examine phenotypic plasticity and heterogeneity in different melanoma mouse models with respect to their utility for translational research and emphasize the interplay between melanoma cells and neutrophils as a critical driver of metastasis.

Phenotypic Coevolution in Tumor Tissue

Heterogeneity is a hallmark of human cancers that complicates both diagnosis and treatment [1]. The rapid progress of high-throughput genome-sequencing technologies allows us to disentangle the genetic heterogeneity of human malignancies and to explore the genetic evolution of tumors in the context of therapy resistance and disease progression [2,3]. However, there is an emerging notion that nongenomic changes of tumor and immune cells are just as critical, particularly in view of the recent clinical success of cancer immunotherapy [4]. Restoring antitumoral immunity by blocking the PD-1/PD-L1 negative immune checkpoint molecules achieves remarkable response rates in patients with various types of cancer including malignant melanoma, which has become a paradigm disease for the development of new immunotherapies [5,6]. Ligation of the PD-1 surface receptor on T cells by its ligand PD-L1 promotes an exhaustion phenotype and thereby inhibits the elimination of tumor cells by cytotoxic T cells. PD-1 signaling is also involved in metabolism and, in addition to PD-L1, subsets of melanoma cells apparently also express PD-1 [7,8]. Consequently, there is a growing interest in the reciprocal interactions between melanoma and immune cells in the tumor microenvironment [4,9]. For example, a thorough understanding of this phenotypic coevolution in tumor tissues is needed to optimally combine or sequence inhibitors that target mutant $BRAF^{V600E}$ or MEK1/2 kinases [collectively named mitogen-activated protein kinase inhibitors (MAPKis)] with immunotherapy in melanoma patients [10,11]. Proinflammatory cytokines released in response to therapy-induced tumor tissue injury are critical signals that induce phenotypic plasticity of melanoma and immune cells [12]. In recent years, several studies have started to shed light on this dynamic interplay, paving the ground for a growing interdisciplinary research field that involves tumor biologists and tumor immunologists as well as clinician–scientists [12–16]. Technological advances in intravital imaging [17], genome editing, and sequencing as well as new mouse models [18] and computational tools [19–21] (Box 1) will strongly accelerate research in this exciting field and provide valuable knowledge to improve patient care.

Trends

Phenotypic coevolution of melanoma and immune cells emerges as an important determinant for rational combinations of MAPK and immune checkpoint inhibitors in patients.

An interplay of melanocyte lineage and cellular stress signaling pathways orchestrates the inflammation-induced plasticity of melanoma cells.

Melanoma cell states shape the immune cell composition of the tumor microenvironment.

UV irradiation strikes twice in melanomagenesis by causing both transforming mutations and metastasis-promoting neutrophilic inflammation.

Neutrophils exert pro- and antitumoral functions in a context-dependent manner.

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Box 1. Immunogenomics and Melanoma

Bioinformatics approaches can strongly support experimental efforts to explore the interplay between inflammation and tumor cell plasticity. Projects like The Cancer Genome Atlas (TCGA) (http://cancergenome.nih.gov/) and integrative analysis platforms provide comprehensive genomic profiling of large cancer patient cohorts as valuable resources. Improved computational tools for digital deconvolution and enumeration of immune cell subtypes based on gene expression signatures from complex tumor tissue samples will accelerate experimental and translation studies [20,21]. Integration of clinical annotations like patient survival data will help to identify interesting immune cell subpopulations that warrant further investigation for patient stratification and innovative therapeutic interventions. These bioinformatics approaches will be particularly informative when applied to patient cohorts treated with cancer immunotherapy, ideally including samples before treatment in addition to biopsies under treatment or at disease progression. This will allow precise characterization of the dynamic coevolution of tumor and immune cell phenotypes in the context of cancer therapy.

Plasticity of the Melanocyte Lineage in Development

Malignant melanoma is an aggressive type of cancer that originates from the pigment-producing melanocytes in the skin. UV light exposure due to excessive sun tanning causes genomic aberrations in melanocytes and represents a major etiologic risk factor for this disease with a growing incidence. Phenotypic plasticity is a characteristic of the melanocyte lineage, which derives from the neural crest during embryonic development [22,23]. The neural crest is a multipotent cell population that gives rise to several cell lineages including melanocytes, Schwann cells, and peripheral neurons [24,25]. During embryonic development melanocyte precursors migrate long distances in the body, following blood vessels to ultimately reach the skin and fully differentiate into pigment-producing melanocytes. Consequently, mice with genetic defects in genes required for melanocyte differentiation exhibit typical spot-like pigmentation defects [26,27]. These *in vivo* models provided essential insights into the molecular mechanisms that govern the temporospatial control of melanocyte migration and differentiation during development. Hence, phenotypic plasticity and a high migratory potential are characteristics of the melanocyte lineage that can be traced back to its neural-crest origin. These features are likely to explain the propensity of melanoma cells to metastasize early in the course of the disease [28,29].

Plasticity in Melanoma Mouse Models

The histologic appearance of melanoma is highly heterogeneous and dermatopathologists have described numerous morphological variants [30,31]. As an example, typical melanomas with heavily pigmented epithelioid tumor cells strongly differ from desmoplastic melanomas comprising amelanotic spindle-shaped tumor cells that abundantly express markers of neural crest precursors like the nerve growth factor receptor (NGFR) [32]. Morphological heterogeneity further increases in metastatic melanoma, indicating that phenotypic evolution accompanies disease progression. Occasionally, metastatic melanomas even recapitulate histologic features of malignant peripheral nerve sheath tumors (MPNSTs)–neural crest-derived malignancies that originate from the nerve sheath-forming Schwann cells [33]. Recently, we systematically investigated this underappreciated aspect of melanoma cell plasticity, which has been documented repeatedly in the literature in clinical case reports. We incidentally found that *Cdk4*^{R24C} mutant mice simultaneously develop highly pigmented immune cell-poor and amelanotic immune cell-rich melanomas on melanocyte-specific conditional activation of the *Braf*^{V600E} oncogene in conjunction with a single application of the carcinogen DMBA [18]. Amelanotic melanomas showed prominent morphological and molecular features of MPNSTs and MPNST-related benign neurofibromas. Curiously, amelanotic MPNST-like melanomas were densely infiltrated with mast cells, a histological finding that is frequently seen in human neurofibromas and, to some extent, in MPNSTs [34]. Using a transplantable cell line established from a MPNST-like mouse melanoma, we demonstrated that this cell state directly governs mast cell recruitment and MPNST-like histological appearance driven by a clearly discriminable gene expression program. A cross-species comparison identified the relatively rare cases of human MPNST-like