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How Tumor Cell Dedifferentiation Drives Immune Evasion And Resistance to Immunotherapy

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Abstract

Immunotherapy has revolutionized cancer treatment, yet most patients do not respond. While tumor antigens are needed for effective immunotherapy, a favorable tumor immune microenvironment is also critical. In this review, we discuss emerging evidence that tumor cells exploit cellular plasticity and dedifferentiation programs to avoid immune surveillance, which in turn drives metastatic dissemination and resistance to immunotherapy. A deeper understanding of these programs may provide novel opportunities to enhance the efficacy of existing immunotherapies.

Keywords

Tumor immunology; immune evasion; tumor dedifferentiation; cell plasticity

Tumor immunotherapy and resistance mechanisms

Studies over the past two decades have uncovered a crucial role for the immune system in tumor biology (1). Immune cells interact with and functionally influence tumor cells at every stage of tumor development and metastatic dissemination (1–3). Therapeutic interventions enhancing immune cell functions – including chimeric antigen receptor (CAR) T cell-based treatments and immune checkpoint blockade (ICB) – have revolutionized the clinical care of cancer patients with various types of malignancies (1,4–6). Despite these remarkable successes, most cancers are refractory to immunotherapy as a result of immune evasion of tumor cells (7–11). Moreover, immune evasion is an important step in the colonization of disseminated and dormant tumor cells in distant organs (2,3,12). Because tumor immune evasion leads to poor clinical outcomes by promoting therapy resistance and metastatic outgrowth, a deeper understanding of the underlying molecular and cellular mechanisms is needed.

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Tumor cells use various strategies to evade immune surveillance (13,14). These include: (i) down-regulation of the antigen presentation machinery (15–18), (ii) silencing the expression of tumor associated antigens (19,20), (iii) dysregulation of tumor cell intrinsic interferon signaling pathways (21–25), (iv) recruitment of immunosuppressive cells (e.g. regulatory T cells and suppressive myeloid cells) to establish an “immune-privileged” microenvironment (26–29), (v) upregulation of immune suppressive molecules (e.g. PD-L1) (30–32), and (iv) metabolic activity of tumor cells (e.g. production of prostaglandin E2) (33–38). Conveniently (for the tumor cells), many of these immune-evading adaptations are driven by the very oncogenic signaling pathways that provide tumors with their enhanced growth and proliferation properties (e.g. Wnt, mTOR, MYC, and Kras signaling) (13,14,32,39–46). This, in turn, begs an obvious question: What biological properties link oncogenic signaling with immune regulation? One answer to this question, supported by several recent studies, is that such signaling can simultaneously alter cellular differentiation states of tumor cells as well as their recognition by the immune system.

Tumor cell plasticity and dedifferentiation drives immune evasion

Cellular plasticity – defined as a dramatic shift in cellular phenotype – is commonly observed in various types of malignancies, where it contributes to tumor progression and resistance to therapeutic interventions (47–51). One manifestation of plasticity in tumors is dedifferentiation, in which tumor cells lose their specialized properties and take on less differentiated phenotypes reminiscent of early embryonic development or regenerative processes (52). Loss of differentiation is known to be associated with increased tumor cell invasiveness and drug resistance (49–51), but there is growing evidence that tumor cell dedifferentiation is also coupled to immune surveillance.

Studies in melanoma, for example, have shown that tumor cell dedifferentiation – and adoption of a stem- or progenitor-like phenotype – leads to an escape of immune recognition by adoptively transferred T cells in both preclinical mouse models and patients (20,53). Two factors contribute to this immune-privileged state: (i) a loss of differentiation-associated antigens (20,53) and (ii) dedifferentiation-associated transcriptional changes that result in the recruitment of immunosuppressive myeloid cells (54). Moreover, a study published earlier this year linked dedifferentiation of melanoma cells with resistance to ICB in both preclinical mouse models and cancer patients (55). Thus, there is ample data to support a connection between tumor cell dedifferentiation and immune evasion in this lethal form of skin cancer.

There is also evidence for such a connection in other tumor types. In squamous cell carcinoma, for example, dedifferentiated tumor cells acquire stem-like properties and express the immune modulating molecule CD80, leading to escape from immune attack (56). Similarly, dedifferentiated tumor initiating cells can evade immune surveillance by dysregulation of PD-L1 or NKGD2 (57,58). Moreover, single cell analysis has revealed that lung cancer cells possess heterogeneous differentiation states that correspond to various stages of lung development. These distinct states are associated with different sensitivities to immune surveillance and metastatic colonization capacity, a consequence of differential expression of natural killer cell and T cell recognition and regulatory molecules (59).

Interestingly, one recent study showed that metastasis-initiating colorectal cancer cells possess molecular features of regenerative epithelial cells (60). These studies highlight potential molecular connections linking tissue regeneration and immune surveillance, given that tissue damage, compensatory regeneration, and the associated inflammatory response may all promote tumor progression. Such an idea is in line with studies from multiple tumor types that epithelial mesenchymal transition or EMT (another form of altered cellular differentiation) leads to immune evasion through various molecular mechanisms, including increases in immune inhibitory molecules and decreases in the antigen presentation machinery (49,61–66). It is also important to note that dedifferentiation of tumor cells may cause increased expression of developmental antigens such as cancer testis antigens, which may have an opposing effect on immune surveillance (67–69). Together, these studies indicate that tumor cell dedifferentiation promotes immune evasion through distinct, but related, molecular mechanisms.

Conserved immune evasion mechanisms in normal cells

Why might acquisition of a stem- or progenitor-like state – the phenotypic consequence of dedifferentiation – lead to immune evasion? One possibility is that tumor cells are simply recapitulating an evolutionarily conserved program that protects stem cells from immune attack. It is known that certain quiescent tissue-resident stem cells evade detection and killing by the innate and adaptive immune system by downregulating molecules involved in antigen presentation (70). Interestingly, one recent study provided evidence that disseminated pancreatic tumor cells in the liver can evade T cell mediated immune surveillance when they reside in a quiescent state (71). Likewise, other studies have highlighted the function of slow cycling and less differentiated cancer stem cells in shaping the tumor immune microenvironments (72). Collectively, these findings indicate that dedifferentiation-associated changes in cell proliferation may regulate the interaction between tumor cells and surrounding immune cells.

Recently, an evolutionarily conserved molecular mechanism for immune invasion was described in which epigenetic regulation by the polycomb repressive complex 2 (PRC2) robustly repressed the expression of antigen presentation molecules in embryonic stem cells, tissue specific progenitor cells, and cancer cells (15). Thus, immune privilege may be a feature of cells that normally exist in a dedifferentiated state: tissue resident stem and progenitor cells. By extension, cancer cells – responding to oncogenic signals that promote dedifferentiation – may simply be exploiting such evolutionarily conserved mechanisms to evade immune surveillance.

Important questions to be answered

This concept of differentiation-associated tumor immune regulation raises several unanswered questions: (i) *How does tumor cell plasticity and dedifferentiation mechanistically lead to immune evasion?* While several possible mechanisms have been described, additional molecular links between tumor differentiation status and immune system activity remain to be elucidated; (ii) *Do epigenetic changes couple tumor dedifferentiation to immune evasion?* Epigenetic regulators have been demonstrated to drive

tumor cell plasticity and dedifferentiation (49). Given recent studies highlighting the important role of epigenetic factors in regulating antigen presentation on tumor cells (15), tumor cell identity may be directly coupled to immune escape through the action of epigenetic regulators; (iii) *Do different tumor types use distinct mechanisms to evade immune surveillance*? Studies to date have revealed divergent mechanisms of immune evasion in various tumor types, ranging from reduced antigen presentation by tumor cells to heightened immunosuppression in the tumor microenvironment. Further study is needed to determine whether tumors arising in different tissues-of-origin prefer certain immune-evasive strategies or whether a variety of mechanisms are available for a given tumor regardless of lineage. Likewise, given the fact that features of the host tissue also contribute to tumor immunity (73), tactics for immune evasion in metastases may track with either the primary tumor's lineage, or with the site of dissemination; (iv) *Does cellular plasticity associated with tissue injury-regeneration confer immune protective effects to incipient cancers?* Cellular plasticity is a feature of normal tissues subjected to injury or inflammation, as is commonly observed in premalignant states of metaplasia (49). Thus, the mechanisms underlying plasticity in these inflammatory states may provide incipient tumors with additional immuno-protective properties; (v) *Does "redifferentiation" increase the susceptibility of a tumor to immune surveillance?* The less differentiated a tumor is, the more aggressive its behavior. Hence, therapeutic approaches that promote tumor cell redifferentiation can provide clinical benefit (74). An additional benefit of such approaches might be an increased susceptibility of tumor cells to immune surveillance, thereby enhancing the efficacy of existing immunotherapies such as CAR-T cells and checkpoint blockade; and (vi) *What are the implications for stem cell biology?* A further understanding of immune-evasive mechanisms in cancer may inform strategies for preserving stem cell viability and longevity in normal tissues by protecting these self-renewing cells from aging-dependent immune-mediated attrition.

Concluding remarks

In summary, there is mounting evidence to suggest that tumor cells hijack immune evasive mechanisms from normal somatic stem and progenitor cells. As cells become less differentiated during tumor progression, they employ both cell autonomous and non-cell autonomous mechanisms to change their susceptibility to immune recognition and destruction (Figure 1). However, there are many remaining questions that need to be explored. Recent development of transcriptional and epigenetic profiling techniques that could examine molecular features of tumor cells at single cell resolution will facilitate a detailed picture of interactions between dedifferentiated tumor cells and the immune microenvironment. In addition, establishment of improved *in vitro* organoid systems will be helpful, as they could allow high throughput unbiased screens to differentiation-promoting agents which could simultaneously slow tumor growth and improve immune recognition. In conclusion, elucidation of the mechanisms by which tumor cells evade immune destruction, and their links to evasive mechanisms utilized by normal somatic stem and progenitor cells, may provide novel therapeutic opportunities for enhancing the efficacy of existing immunotherapies. At the same time, such knowledge may broaden our understanding of interactions between immune cells and stem cells in other biological contexts.

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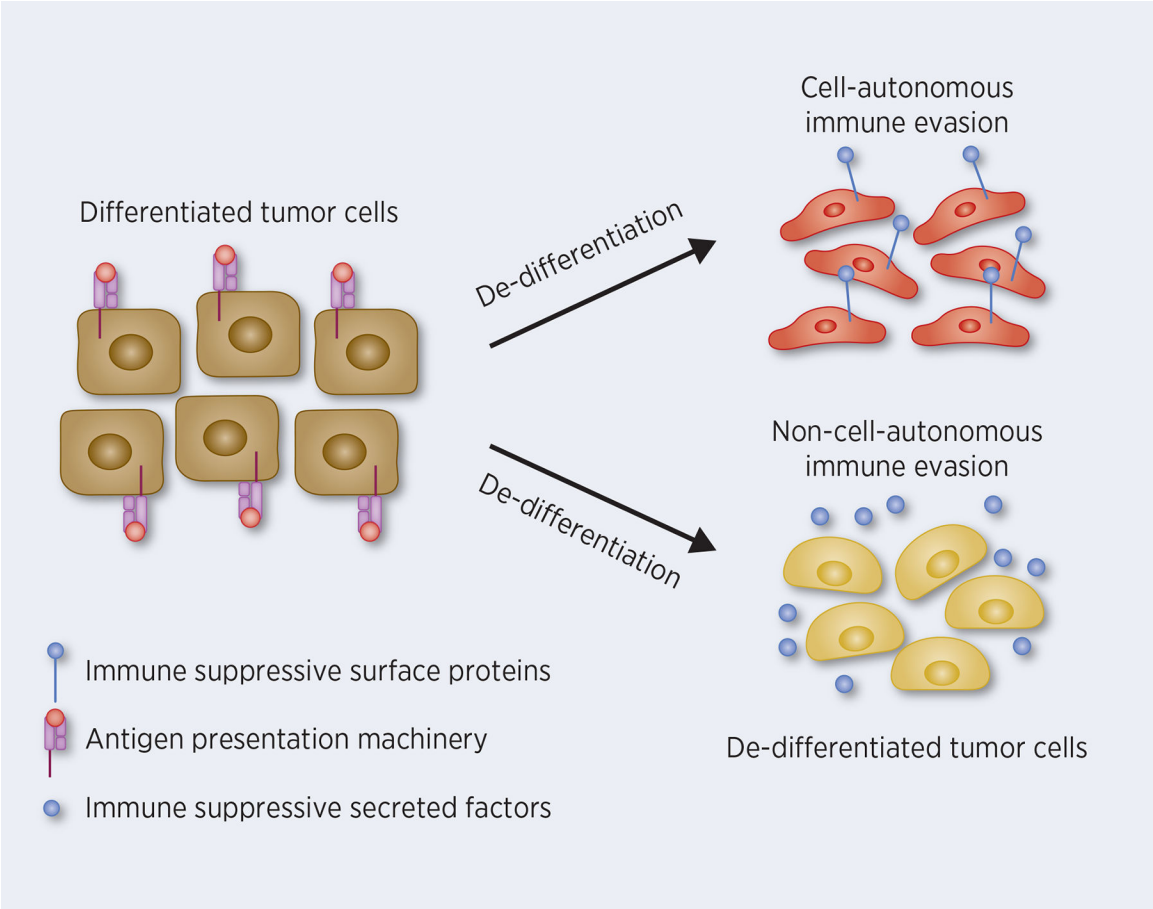

Figure 1. Dedifferentiation of tumor cells leads to immune evasion.

Diagram showing how dedifferentiation of tumor cells induces immune evasion through cell-autonomous mechanisms (e.g. loss of differentiation-associated antigens, decreased expression of antigen presentation molecules, and increased expression of immune suppressive molecules, such as PD-L1) and non-cell-autonomous mechanisms (e.g. expression of suppressive myeloid cells recruiting chemokines and growth factors).