Review

Epithelial immune cell-like transition (EIT): A proposed transdifferentiation process underlying immune-suppressive activity of epithelial cancers☆

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ARTICLE INFO

ABSTRACT

The immune system plays a key role in eliminating cancer cells in the body. However, even in fully immune-competent bodies cancers can evade anti-tumor immune action. There is increasing evidence that epithelial cancers can *actively* suppress anti-tumor immune responses by creating an immune-suppressive micro-environment. It has been reported that epithelial cancers can express immune genes/proteins not normally expressed by their parental tissues, including a variety of cytokines/receptors, immune transcription factors and Ig motifs in cell surface molecules. Recently we observed increased expression of immune genes, including immune-suppressive genes, by prostate epithelial cancers. In view of the above, we propose that immune-suppressive activity of epithelial cancers may stem from their acquisition of immune properties via a transdifferentiation process, we term "Epithelial Immune Cell-like Transition" (EIT), similar to neuroendocrine-like transdifferentiation of prostate adenocarcinoma cells. We propose that the acquired immune properties enable the cancer cells to "communicate" with immune cells, leading to suppression of anti-cancer immune activity in their micro-environment and facilitation of the expansion and malignant progression of the disease. Acquired immune properties of epithelial cancers, which might be quite common, could provide novel targets for reducing cancer-generated immune-suppressive activity and enhancing anti-tumor immune activity. This proposed paradigm shift could lead to novel therapeutic approaches with improved efficacy and broad application.

Contents

1. Introduction

The immune system plays a key role in surveying and eliminating cancer cells in the body, as indicated by a vast amount of data from animal models and human patients (Dunn et al., 2004). Nonetheless, cancers can still develop in immuno-competent individuals (Dunn et al., 2002). Recent evidence has indicated that the immune system plays a dual role in the interactions between tumors and the host. In

addition to eliminating cancer cells, it can facilitate tumor progression, at least in part, by sculpting the immunogenic phenotype of tumors as they develop. This realization has led to the concept of "cancer immunoediting" to emphasize the dual host-protective and tumor-promoting actions of immunity (Dunn et al., 2004). While failure of a functional immune system to eradicate cancer growth can stem from the dualistic nature of the immune response, there is compelling evidence that it also involves an ability of cancer cells to evade immune action. Thus cancer cells can circumvent the anti-tumor immune response by a variety of mechanisms, including down-regulation of self-antigen expression and desensitization to immune cell-induced apoptosis (Hamai et al., 2010). Importantly, there is increasing evidence that cancers can *actively* suppress the immune system in their micro-environment by generating immune-suppressive activity. This ability of cancer cells can lead to down-regulation of anti-tumor activity of immune effector cells and enhance local tolerance in favor of their survival; as well, cancer cells can enhance their survival by coopting immune cells to promote tumor growth (Whiteside, 2008; Hamai et al., 2010). A recent upgrade of the hallmark characteristics of cancer includes "evasion of immune destruction", indicating that the interaction between cancer cells and the immune system is recognized as critical for cancer growth and progression (Hanahan and Weinberg, 2011). As such, elucidation of the molecular and cellular mechanisms by which cancer cells can suppress/modify the immune response in their micro-environment may lead to identification of novel therapeutic targets and improved therapeutic approaches.

As technologies such as genome/transcriptome sequencing continue to advance, it has become increasingly possible to identify novel cancer subtypes and hence refine cancer categories, with the eventual aim of providing effective personalized treatment options via more informative diagnosis (Podo et al., 2010). However, as cancer is more and more subdivided into distinct "diseases", each subtype-targeting therapy becomes more restricted to subsets of patients and less suitable for general application. Rather than continuing this "divide and conquer" approach, focusing on a therapeutic target that is common to a variety of cancers may lead to more generally applicable therapeutic regimens. In this context, it is of interest that the mechanisms by which cancer cells can generate immune-suppressive activity in their micro-environment could be common to a variety of cancers, including their subtypes. If so, elucidation of these mechanisms could lead to new, more generally applicable therapeutic approaches.

As outlined below, recent studies have indicated that epithelial cancer cells can express immune genes and their products, such as cytokines and immune-inhibitory molecules, that are not normally expressed by their parental tissues. Similarly, we have demonstrated expression of immune genes by prostate epithelial cancers. On the basis of these observations, we propose that the immune-suppressive activity of epithelial cancers may stem from their acquisition of immune characteristics, in particular immune-suppressive properties, generated via a transdifferentiation process we coined "Epithelial Immune Cell-like Transition" (EIT). Such acquired immune properties could enable the cancer cells to "communicate" with immune cells, suppress the activity of tumor-associated immune effector cells and also coopt immune cells to promote tumor growth. This proposed paradigm shift could have major implications. Novel therapeutic strategies may be developed that are specifically aimed at immune properties adopted by cancers to favor their growth. Such strategies could have superior efficacy.

Here we review reports that epithelial cancers, regardless of their tissue of origin or subtype, can harbor immune-suppressive activity in their micro-environments, thus favoring their survival. Furthermore, the growth and malignant progression of epithelial cancers can be associated with the acquisition of immune

properties by the cancer cells – evidence in support of the proposed EIT concept.

2. Association of cancers with immune cells and lymphoid tissue

Human tumors are generally infiltrated by inflammatory cells (Whiteside, 2008). In addition to malignant cells, tumors contain a dynamic combination of immune cells, such as macrophages, lymphocytes, dendritic cells, and endothelial cells, fibroblasts and perivascular cells. While the presence of inflammatory cell infiltrates (e.g., ectopic lymphoid structures) can represent anti-cancer immune action (Coppola and Mule, 2008), it can also represent tumor growth-promoting activity by, for instance, M2 tumor-associated macrophages (Hagemann et al., 2005).

Lymphoid organs and the bone marrow are frequent organ sites of cancer metastasis (Nathanson, 2003; Sikes et al., 2004). The presence of cancer cells in regional lymph nodes has long been used for cancer staging and is often associated with unfavorable prognoses and poor patient outcomes (Yokota et al., 2004). It is thought that lymphangiogenesis plays a critical role in facilitating the migration of cancer cells to local lymph nodes by providing a direct connection (Hirakawa, 2009). Expression of the VEGF family of lymphangiogenic factors by cancer cells can result in the induction of lymph vessel formation either intratumorally or near the tumor periphery, enhancing the flow of tumor antigen-presenting cells as well as tumor-associated immune cells into the tumor-draining lymph nodes (Lund and Swartz, 2010). However, there is evidence that such local lymph nodes undergo profound alterations due to the presence of the upstream tumor. Not only does the presentation of tumor antigens by host cells fail to elicit a protective immune response, but a systemic tolerance is actively created (Munn and Mellor, 2006).

3. Immune suppressor cells in tumors

It has long been known that certain cells of the immune system are responsible for maintaining self-tolerance and regulating the severity of the immune response through immune-suppressive mechanisms. The presence of many immune-suppressive cell types in the tumor microenvironment, such as regulatory T (T_{reg}) cells, plasmacytoid dendritic cells (pDCs), M2 macrophages and myeloid-derived suppressor cells (MDSCs), has been correlated with poor patient outcomes for a variety of cancers (Zou et al., 2001; Curiel et al., 2004; Sica et al., 2006; Zhang et al., 2009; Kurahara et al., 2011). Immune-suppressive molecules secreted by immune suppressor cells, such as TGFβ, IL10, IDO, and arginase, can diminish the activity of effector cells (Sica et al., 2006; Beyer and Schultze, 2009). Moreover, suppressor cells can use cytotoxic cell products, such as reactive oxygen species, granzyme B and perforin, to induce effector cell death (Beyer and Schultze, 2009; Gabrilovich and Nagaraj, 2009). Further details on the mechanism of action of immune suppressor cells have been extensively reviewed elsewhere (Beyer and Schultze, 2009; Gabrilovich and Nagaraj, 2009; Biswas and Mantovani, 2010; Matta et al., 2010). Regulatory NK and regulatory B cells may also suppress the immune response. Regulatory NK cells can negatively regulate the immune response by inducing lysis of immune effector cells, such as mature dendritic cells (Chiesa et al., 2003; Zhang et al., 2006), through, for instance, the release of IL-10 (Bouaziz et al., 2008; Deniz et al., 2008). While a role of NK cells in cancer development has not yet been confirmed, there is increasing evidence that both regulatory NK and B

cell types are involved in the control of autoimmune diseases (Lund and Randall, 2010; Yoshida et al., 2010).

Escape of cancers from anti-cancer immune action may in part be accomplished by their recruitment of immune suppressor cells. The propensity of immune-suppressive cell types to associate with cancer (Zou et al., 2001; Curiel et al., 2004; Sica et al., 2006; Zhang et al., 2009; Kurahara et al., 2011) raises the possibility that tumors are able to attract immune suppressor cells to their micro-environment, leading to suppression of the local immune response and enhancement of cancer growth. This suggestion is supported by a recent finding that secretion by breast cancer cells of CCL22, a ligand for CCR4, a chemokine receptor expressed by virtually all peripheral blood T_{reg} cells (Hirahara et al., 2006), led to recruitment of immune-suppressive T_{reg} cells (Faget et al., 2011). A similar finding was made with melanoma cells that express the chemoattractant CCL21. The secretion of CCL21 by melanoma tumors in mice led to recruitment of T_{reg} cells to the tumor sites and a shift in the host immune response from immunogenic to tolerogenic (Shields et al., 2010). These observations suggest that cancer cells, by altering their micro-environment (to attract T_{reg} cells for example), can shift the host immune response from immunogenic to tolerogenic. The mechanisms involved in such processes will need to be interrupted in order for clinical anti-tumor immunotherapy to be successful (Munn and Mellor, 2006).

4. Immune-suppressive cytokines in tumors

The micro-environment of tumors is known to be significantly different than that of normal tissue. Local expression of anti-inflammatory cytokines in, for example, certain skin cancers, leads to the development of a T_H2 type cytokine pattern in their micro-environment that favors humoral immunity with concomitant immune-suppression of cell-mediated immune responses (Yamamura et al., 1993). Similar immune-suppressive tumor micro-environments have been observed in ovarian and liver cancer (Pang et al., 2009; Yigit et al., 2010). Importantly, anti-inflammatory cytokines are released not only by suppressive immune cells, but also by cancer cells, indicating an active role for cancer cells in immune-suppression (Bellone et al., 2006; Gross and Walden, 2008). There is no doubt that alteration of the tumor micro-environment by immune-suppressive cytokines greatly perturbs immune cell functions. The prominence of, for example, TGFβ in the tumor micro-environment has wide-ranging effects on the functions of many immune cell types, including attenuation of IFN-γ production by NK cells, inhibition of normal tasks of cytotoxic T lymphocytes and induction of regulatory T cell differentiation from CD4 T cells (Flavell et al., 2010; Yang et al., 2010). An immune-suppressive cytokine environment also alters the cytokine production by macrophages and impedes the maturation of DCs (Pinzon-Charry et al., 2005; Stout et al., 2005). Taken together, the build-up of immune-suppressive cytokines in the tumor micro-environment can cause immune cells to become significantly deficient at generating the appropriate tumor-eliminating response and appears to constitute one of the ways by which cancers can create an immune-suppressive micro-environment.

5. Epithelial-immune cell-like transition (EIT)

Major characteristics of regulatory immune cells are their ability to control various aspects of the immune response and to be fully mobile in the human body. As described above (and below), epithelial cancers can, although they are not related to the immune system, suppress the anti-tumor immune response in their micro-environment via mechanisms normally applied by immune cells; furthermore, cancer cells are mobile in the metastatic form. As such, epithelial cancer cells can mimic properties of regulatory immune cells. We hypothesize that epithelial cancers can acquire immune-regulatory properties following activation or enhancement of immune genes via a transdifferentiation process. The gene products generated would not only include immune-suppressive cytokines and cytokine receptors, but also transcription factors and other proteins thought to play important roles in immune processes. The acquisition of immune-suppressive properties by cancers would markedly enhance their ability to survive and thrive. We have coined the term "epithelial-immune cell-like transition" (EIT) to describe this acquired expression of immune cell-like properties by epithelial cancer cells (Gout et al., 2009). It may represent a transdifferentiation process as reported for prostate adenocarcinoma cells that acquire a neuroendocrine (NE) phenotype complete with expression of NE markers (Yuan et al., 2007).

There is a growing body of evidence supporting the EIT hypothesis. An analysis of publicly available microarray data obtained from microdissected normal and cancerous human epithelial cells indicates a significant upregulation in the cancer cells of genes that play major roles in immune processes and apparently are not expressed by normal epithelial cells (Table 1). They include *FCGR*1*A,B* and *FCGR*2*A* (encoding high affinity receptors for the F_c region of gamma-immunoglobulins), *GZMA* and *GZMB* (encoding T cell- and NK cell-specific serine proteases), and *IL7R* (encoding the IL7 receptor).

Transplantable metastatic LTL313H and non-metastatic LTL313B prostate cancer xenograft lines have recently been established in our laboratory from one patient's prostate cancer specimen (Watahiki et al., 2011). Using next generation transcriptome sequencing, and mapping to the human transcriptome database using stringent criteria, we have demonstrated the presence, and upregulation in the metastatic line, of human-specific immune genes that have immune-suppressive properties (Table 2). They include *CD83* (soluble CD83 promotes immune suppression) (Ge et al., 2010), *CD200* (CD200 suppresses NK cell function and inhibits anti-tumor response in acute myeloid leukemia) (Coles et al., 2011), *FOXP3* (encodes a transcription factor which mediates negative regulation of immune suppression) (Josefowicz et al., 2012), *IDO1* (IDO1 can induce immune tolerance) (Ferdinande et al., 2012), and *IL23A* (IL23A can promote tumor incidence and growth) (Langowski et al., 2006).

Furthermore, expression of immunoglobulins by human epithelial cancer cells has been reported (Zhenga et al., 2007; Zheng et al., 2009). Increased expression of PAX5, considered to be an essential transcription factor for B cell development (Nutt et al., 1999), has been observed in a number of carcinoma cell lines (Norhany et al., 2006; Kanteti et al., 2009). Epithelial cancer cells showed elevated expression (relative to normal tissues) of a variety of chemokines (e.g., CXCL, CCL and CX3CL series) and chemokine receptors (e.g., CXCR, CCR, CX3CR series) (Lazennec and Richmond, 2009). As already mentioned, a tolerogenic response can result from recruitment of T_{reg} cells by epithelial cancers via secretion of chemoattractants such as CCL21 (by melanoma cells) (Shields et al., 2010) or CCL22 (by breast cancer cells) (Faget et al., 2011), or by secretion of anti-inflammatory cytokines (Bellone et al., 2006; Gross and Walden, 2008).

The evidence presented here indicates that epithelial cancers can express immune genes that are apparently not normally expressed by epithelial cells (see Table 1). Furthermore they can also show elevated expression of genes that have a role in immune processes but are not confined to immune cells, such as genes encoding chemokines and their receptors that are also expressed by the epithelial and endothelial cells (Lazennec and Richmond, 2009). Of special interest is the human-specific expression in prostate cancer xenograft lines, in particular in the metastatic line, of genes known to

Table 1
Immune genes upregulated in various epithelial cancers. Analysis based on publicly available microarray data of microdissected samples found on Oncomine[a].

Cancer type	Immune genes	Fold-increase (cancer vs. normal)	Gene product function	GEO dataset
Breast (Invasive lobular and ductal carcinoma)	FCGR1B	6.83	Binds to the F_c region of immunoglobulins gamma with low affinity. May function in the humoral immune response.	GSE5764
	FLT3	3.18	Regulates differentiation, proliferation and survival of hematopoietic progenitor cells and dendritic cells.	
Cervical (Carcinoma)	GZMA	2.65	Necessary for target cell lysis in cell-mediated immune responses.	GSE6791
	GZMB	2.42	Necessary for target cell lysis in cell-mediated immune responses.	
	FCGR2A	1.75	Binds to the F_c region of immunoglobulins gamma. Promotes phagocytosis of opsonized antigens.	
	FCGR1A	1.59	High affinity receptor for the F_c region of immunoglobulins gamma. Functions in both innate and adaptive immune responses.	
Oral Cavity (Oral squamous cell carcinoma)	GZMA	3.71	Necessary for target cell lysis in cell-mediated immune responses.	GSE3524
Ovarian (Various carcinomas)	BLNK	1.85	Regulates biological outcomes of B-cell function and development.	GSE6008
Pancreatic (Ductal adenocarcinoma)	BLNK	1.98	Regulates biological outcomes of B-cell function and development.	Supplementary Data, PMID 16103885
	FCN1	1.79	Involved in serum exerting lectin activity. Binds GlcNAc.	
	LRMP	1.66	Expressed in a developmentally regulated manner in lymphoid cell lines/tissues.	
Tonsillar (Carcinoma)	IL7R	4.46	Plays a critical role in the V(D)J recombination during lymphocyte development.	GSE6791

[a] Only data sets originating from microdissected cells were included in the cancer vs. normal cell analysis. The data were then refined using a filter of 1.5x fold difference and p-value $\leq 10^{-3}$. The immune functions of genes were taken from UniProt and NCBI gene summaries. The genes presented are apparently not expressed by normal epithelial cells.

Table 2
Gene expressions showing upregulation of typical immune genes in a human metastatic prostate cancer xenograft line relative to its non-metastatic counterpart[a].

Genes	Non-metastatic line (LTL313B)	Metastatic line (LTL313H)	Fold increase	Typical cellular expression	Gene product function
CD83	0.32	0.98	3.04	Dendritic cells	Cell surface glycoprotein, dendritic cell marker. Soluble CD83 promotes immunosuppression. (Ge et al., 2010).
CD200	0.30	1.34	4.45	Macrophages and dendritic cells	Cell surface ligand suppresses NK cell function and inhibits anti-tumor response in acute myeloid leukemia (Coles et al., 2011).
FOXP3	0.30	1.40	4.59	T_{reg} cells	Transcription factor: negative regulation of immune suppression (Josefowicz et al., 2012).
ICOSLG (B7H2)	1.78	2.13	1.20	Monocytes and dendritic cells	Costimulatory molecule with regulatory role in T-cell cytokine production (Nagamatsu et al., 2011).
IDO1	0.38	0.71	1.86	Monocytes, dendritic cells, macrophages	A tryptophan-catabolising enzyme inducing immune tolerance by modulating T-cell responses (Ferdinande et al., 2012).
IGHA1	0	0.90	high	B cells	Major immunoglobulin.
IGHA2	0	0.88	high	B cells	Major immunoglobulin.
IL23A	1.03	4.19	4.08	Dendritic cells and macrophages	IL23A increases angiogenesis, matrix metalloprotease production and can promote tumor incidence and growth (Langowski et al., 2006).

[a] Relative human-specific immune gene expression was established in transplantable metastatic LTL313H and non-metastatic LTL313B prostate cancer xenograft lines (4th generation), developed from one patient's prostate cancer specimen in immuno-deficient NOD-SCID mice (Watahiki et al., 2011). To this end, Illumina transcriptome sequencing was used, coupled to stringent mapping to the human transcriptome database. Sequence reads for each transcriptome library were aligned to the ALEXA reference sequence database using MAQ 0.7.1 (Li et al., 2008; Griffith et al., 2010) allowing no more than 2 mismatches. The expression levels using RNA-Seq reads were quantified as previously described (Lapuk et al., 2010) and normalized using quantile normalization. Gene expression was estimated using the average of all exon and junction expressions from a gene. Fourth generation xenografts, developed over a 2 year period in NOD-SCID mice, do not contain human immune cells.

have immune-suppressive abilities (Table 2). Taken together, the data support the EIT concept, namely the acquisition by epithelial cancer cells of immune cell-like properties, via activation or enhancement of immune genes, leading to immune-suppressive activity in their micro-environment and immune evasion. The increase in immune-suppressive activity found for metastatic prostate cancer cells suggests that EIT has an important role in metastasis.

6. Cancer-induced immune imbalance

It has been suggested that joint inflammation in rheumatoid arthritis is the result of a disturbance of the balance between pro-inflammatory and anti-inflammatory immune cell types (Mauri and Carter, 2009). A similar disturbance may underlie the development of epithelial cancers following their initiation. The evidence presented above indicates that such cancers can tip the balance of the immune system in their micro-environment in favor of immune tolerance by actively promoting immune-suppressing activity. The reduced anti-tumor immune response obtained would then allow survival of cancers as well as their expansion and malignant progression. Viewing cancer outgrowth this way could have significant implications for cancer therapy development, particularly with regard to cancer immunotherapies. Such therapies, focusing on enhancing the anti-tumor immune response either through tumor antigen vaccination or through introduction of effector cells, have had

only limited success (Copier et al., 2009; Antonarakis and Drake, 2010). The major barrier to these approaches appears to be the immune-suppressive environment of most tumors (Burgents et al., 2010). Therapeutic approaches may therefore be more effective by targeting the mechanisms driving the EIT that result in cancer-induced immune suppression in the tumor micro-environment rather than focusing on enhancement of immune effector cell functions, although a combination of the two approaches could be beneficial.

7. Conclusions

There is increasing evidence that the generation of an immune-suppressive micro-environment is a fundamental trait of epithelial cancers, allowing their development and progression/metastasis in spite of an active anti-tumor immune response. If this process is based on EIT-mediated cancer-immune cell crosstalk, it would render EIT the major hallmark of human epithelial cancers. As well, targeting of the acquired immune cell-like properties of the cancers could likely lead to effective therapeutic approaches. Their identification may be achieved via molecular analysis. While the acquired immune properties are likely to vary for the different types of epithelial cancers, they are confined to the immune system and could, for certain cancers, provide common therapeutic targets. The proposed paradigm shift could therefore lead to novel therapeutic approaches with improved efficacy and broad application.

Conflict of Interests

The authors declare that they have no conflicting interests.

Acknowledgments

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