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Review Article

Cancer immune resistance: can theories converge?

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Immune oncology (IO) is challenged to expand its usefulness to a broader range of cancers. A second generation of IO agents acting beyond the realm of Checkpoint Inhibitor Therapy (CIT) is sought with the intent of turning immune-resistant cancers into appealing IO targets. The published literature proposes a profusion of models to explain cancer immune resistance to CIT that largely outnumber the immune landscapes and corresponding resistance mechanisms. In spite of the complex and contradicting models suggested to explain refractoriness to CIT, the identification of prevailing mechanisms and their targeting may not be as daunting as it at first appears. Here, we suggest that cancer cells go through a conserved evolutionary bottleneck facing a Two-Option Choice to evade recognition by the immune competent host: they can either adopt a clean oncogenic process devoid of immunogenic stimuli (immune-silent tumors) or display an entropic biology prone to immune recognition (immune-active tumors) but resilient to rejection thanks to the recruitment of compensatory immune suppressive processes. Strategies aimed at enhancing the effectiveness of CIT will be different according to the immune landscape targeted.

Immune oncology (IO) is urged to expand the usefulness of Checkpoint Inhibitor Therapy (CIT) to a broader range of refractory cancers [1–3]. In spite of the variety of models proposed to explain cancer immune resistance, the identification of prevailing mechanisms and their targeting may not be as daunting as it at first appears [4] as long as answers are sought following a well-designed and systematic strategy; to quote Jonas Salk: '*the answer to biological problems preexists, it is the question that needs to be discovered*' [5]. A survey of open access data from The Cancer Genome Atlas (TCGA) comprising four histotypes (breast, lung, colon carcinoma and melanoma) indicated that cancer cells go through a conserved evolutionary bottleneck facing a Two-Option Choice (TOC) to evade immune recognition by the immune competent host: they can either adopt a clean oncogenic process devoid of immunogenic stimuli (immune-silent tumors) or display an entropic biology prone to immune recognition (immune-active tumors) but resilient to rejection thanks to the recruitment of compensatory immune suppressive processes [3]. We refer to the first option as Primary Immune Resistance (PIRes) and to the second as Compensatory Immune Resistance (CIRes). These two landscapes may influence refractoriness to *CIT* through entirely distinct mechanisms. In addition, Secondary Immune Resistance (SIRes) may ensue as an escape mechanism following originally successful treatment. Finally, we refer to False-Immune Resistance in those cases in which treatment could not be completed due to limiting toxicity.

To explain the distinct landscapes and the respective reasons determining immune refractoriness to CIT, a wealth of observational and/or experimental models has been advocated that largely outnumber the three phenotypes of human cancer (Table 1). The current series presents some of the salient models that propose a targetable mechanism regulating the growth of cancer in the immune competent host, primarily focusing on immune regulatory control of cancer within the immune-active landscapes. However, this review will lean toward the discussion of potential strategies to immune convert silent tumors into immune-active ones, therefore, offering a window of opportunity for IO agents that would otherwise be unlikely to affect an immune-silent environment where innate resistance dominates.

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Table 1 Salient models explaining cancer immune landscapes and pertinent literature

	References	*ICR group*
WNT/β–Catenin	[6,7]	Depleted
MAPK hypothesis	[8]	Depleted
Immunogenic cell death	[9,10,11]	Active
Regulatory T cells	[12,13]	Active
IL23-Th17 axis	[14–18]	Active
Myeloid suppressor cells	[19]	Active
PI3K-γ signature	[20–24]	Depleted
IDO/NOS signature	[25–27]	Ubiquitous
SGK1 signature	[28,29]	Depleted
Shc1 signature	[30]	Depleted
Barrier molecules	[31,32]	Depleted
Mesenchymal transition	[33–35]	Depleted
Cancer-associated fibroblasts	[36–40]	Ubiquitous
TAM receptor tyrosine kinases	[41–45]	Active
Hypoxia/adenosine suppression	[46,47]	Active
TREX1 clearance of cytosolic DNA	[48–50]	NA
Checkpoint cluster	[51,52]	Active
Oncogene addiction	[53,54]	Depleted
Epigenetic regulation	[55–58]	Depleted
Regulatory B cells	[59]	Active
NF-κB activation	[60]	

We recently proposed a theory that unifies current models of cancer immune resistance into a Theory of Everything (TOE) assigning each of them to a specific immune landscape according to their transcriptional expression pattern [3]. This conclusion was based on a survey of two open access datasets comprising ∼3000 cases of breast cancer [3,8,61]. A nomenclature was proposed to define cancers according to their immune contexture ranking them according to the transcriptional expression of genes associated with Immune-mediated Tissue-specific Destruction (ITD). ITD is a conserved mechanism responsible for destructive flares of autoimmunity, acute allograft rejection, and graft-versus-host disease, clearance of pathogen-infected cells and rejection of cancer [62,63]. A signature representative of the ITD was selected from a larger set of interferon (IFN)-γ-induced transcripts named the Immunologic Constant of Rejection (ICR) [62]. The ICR bears both predictive and prognostic implications within a continuum of anticancer immune surveillance [64] and includes four functional categories: CXCR3/CCR5 chemokines (CXCL9, CXCL10 and CCL5), Th1 signaling (IFNG, IL12B, TBX21, CD8A, STAT1, IRF1 and CD8B), effector (GNLY, PRF1, GZMA, GZMB and GZMH) and immune regulatory (CD274, CTLA4, FOXP3, IDO1 and PDCD1) functions. The expression of the 20 representative genes is highly correlated with the extended ICR signature that includes ∼500 genes [62,63,65]. It has been conclusively shown that responsiveness to CIT is observed almost exclusively in the immune-active landscape and is predetermined by a conducive microenvironment [35,66,67]. However, while the immune-active landscape is a prerequisite, it is not sufficient alone to predict immune response.

This concept was described originally by our group in 2002 in the context of other types of immunotherapy, including response to antigen-specific vaccination administered in combination with systemic interleukin-2 [68], and subsequently validated in the context of systemic interleukin-2 administration [69] and the adoptive transfer of tumor-infiltrating lymphocytes [70]. Therefore, immune responsiveness is promiscuous to treatment and it is multifactorial with the tumor microenvironment, playing a permissive but not exclusive role [71].

The 20-gene ICR signatures bear strong analogy with other IFN-γ-dependent signatures predictive of immune responsiveness to interleukin-2-based therapies [68–70] and CIT [66]. Thus, we used these 20 genes as surrogate biomarkers to define immune landscapes more or less likely to be susceptible to CIT. The expression pattern of the 20 ICR genes defined four cancer immune landscapes that were segregated from ICR1 to ICR4 according to the crescendo of expression of ICR transcripts. ICR1 and ICR2 represent various degrees of immune depletion, while ICR3 and ICR4 demonstrate rising levels of expression of ICR genes. For the purpose of discussion, the four landscapes were conflated conceptually into immune-silent or immune-active clusters.

Subsequently, a selection of transcripts reported in association with various cancer immune resistance models was collated into a signature meant to unify within a single study the hallmarks of cancer immune biology (Table 1). We refer to this collection as the TOE signatures of resistance (sRes) and used it to define the geographical distribution of each model within immune landscapes.

We observed that most transcripts representative of immune regulatory mechanisms tightly correlated in expression with the ICR and TIS (tumor inflammation signature), suggesting that immune suppression goes hand-in-hand with immune activation [3].

Based on this analysis of breast cancer data, we hypothesized that immune-silent tumors evolve by employing a strictly essential interface of interactions with the host's stromal cells that exclude immune cell recognition. This may be due to the development of a cancer cell cycle that avoids Immunogenic Cell Death (ICD) or by the downstream induction of biochemical or mechanical barriers that hamper immune infiltration. Thus, these 'clean' tumors evolve through the promotion of cancer cells that adopt refined growth mechanisms reduced to the bare necessities of life. Indeed, similar observations could be corroborated by the analysis of another three cancer histotypes including lung, colon carcinomas and melanoma (Figure 1).

This hypothesis is corroborated by the observation that these tumors (1) are transcriptionally dormant compared with the immune-active ones and (2) bear low prevalence of mutations in oncogenes suggesting a more orderly growth process [8]. It is, therefore, reasonable to suppose that clean tumor growth is dependent on a stepwise oncogenic mechanism that avoids immune recognition [72–74]. Thus, we propose that the natural history of cancer is shaped at the cross-road of two biologies by a 'TOC' or Hobson's predicament: (1) immunogenic tumors can only survive in the host when immune suppressive mechanisms balance the reaction of the host and (2) silent tumors can grow undisturbed.

Here, we suggest that interference of a clean oncogenic pathway may result not only in cancer cell death but also in the disruption of its biology leading to less pristine processes conducive to ICD and allowing, therefore, a window of opportunity for IO agents [9–11,75–95].

This concept is based on the premise that cancer is fundamentally a cell biology problem with cancer cells orchestrating and directing their surroundings. Therefore, efforts aiming at altering the tumor microenvironment should primarily be directed toward the disruption of intrinsic cancer cell processes. A best example of the central role played by cancer cells in determining their surroundings is the Patient-Derived Xenograft (PDX) model; after three passages in immune-deficient mice, the mouse stromal cells completely replace the human, yet the original architecture of the cancer is maintained [96–98]. A second premise is that the immune environment of cancer is driven by a cascade of innate mechanisms (first signal), while the adaptive immune response requires signals initiated by the innate immune system that inform about the origin of the antigen and the type of response to be induced as described by Charles A. Janeway and by Polly Matzinger's Danger Model [83,99–108].

The leading role played by ICD in driving the immune landscape of cancer is counteracted by lines of thought that promote priming of adaptive immune responses by non-self-antigens (neo-antigens) generated by the translation of missense mutations into novel protein domains. This hypothesis is based on several experimental [109,110] as well as the clinical observation that cancers with high mutational burden are more frequently associated with the immune-active landscape and consequently with responsiveness to CIT [33,98,109]. This concept has been, however, questioned by recent observations by our [8] and others' groups [111]. Moreover, basic understanding of immunologic processes confutes the primary role that adaptive immunity plays in the rejection of cancer in the absence of a first initiating signal [99–104,107]. The conditionality of adaptive immune responses is suggested by experimental evidence that they are not an essential requirement for the rejection of cancer as exemplified by the transferrable anticancer innate immunity model [112–115] and by oncotropic virus-mediated immune rejection of xenografts in immune-deficient mice [116,117]. From the clinical standpoint, the secondary role played by adaptive immunity could also explain

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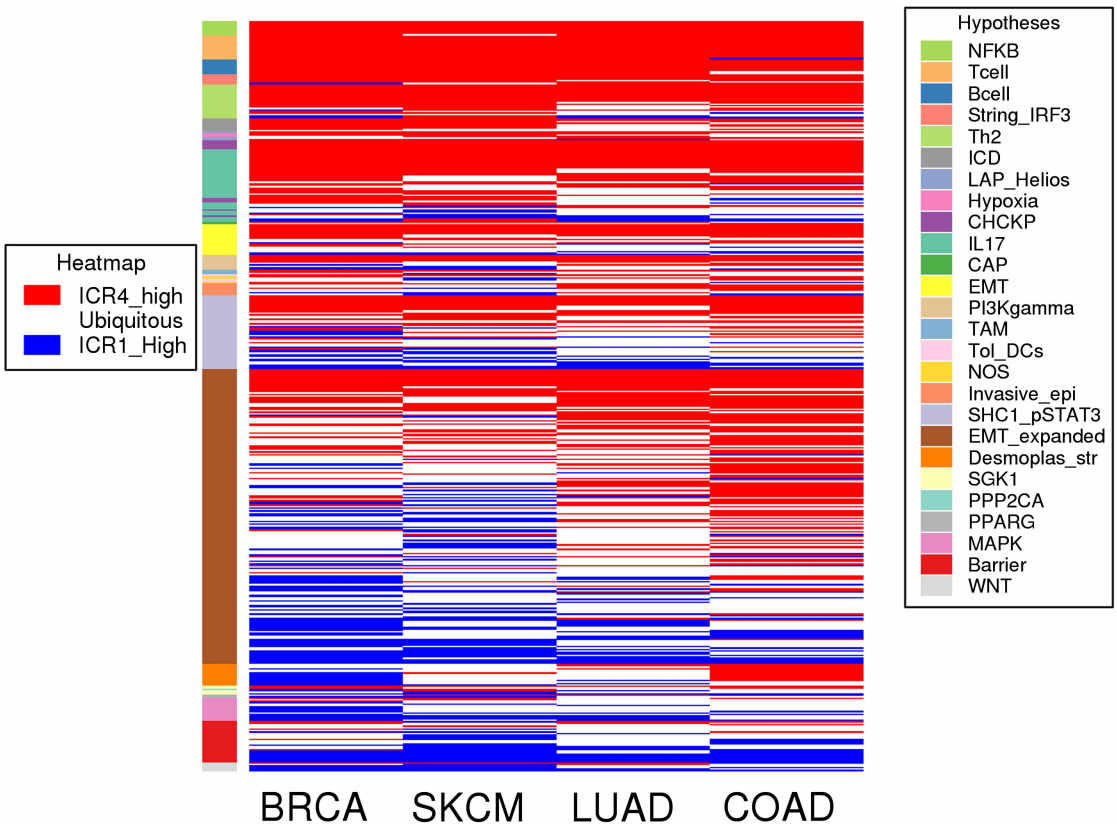

Figure 1. Consistency of immune resistance signature expression across different.

Mapping gene signatures according to their expression in different immune landscapes of breast (BRCA), lung (LUAD) and colon (COAD) carcinoma, and melanoma (SKCM); in red are signatures selectively expressed in the immune-active (ICR4) landscape, in blue those selectively expressed in the immune-silent (ICR1) landscape and in white those that are ubiquitously expressed independent of immune landscape.

the paradoxical observation that vaccines aimed at priming adaptive immune responses can consistently elicit systemic immunity, which, however, does not correlate with tumor rejection [118,119]. It could be postulated that because of the adjuvants used in vaccine administration, at the site of vaccination the afferent loop of the adaptive immune response can be initiated stimulating chemoattraction and antigen presentation. However, at the tumor site, in the absence of a strong innate immunity-mediated chemoattraction, the efferent loop languishes mostly because of lack of trafficking on vaccine-induced cancer-specific T cells to the target tissue. It should also be pointed out that seminal studies done on the effectiveness of tumor-infiltrating lymphocytes demonstrated that their homing at the tumor site is necessary, though not sufficient, to induce tumor regression, emphasizing the critical role that chemoattraction plays in immune responsiveness [120]. In turn, chemoattraction of circulating T cells is tightly dependent on the expression of CXCR3- and CCR5-binding chemokines that are expressed in response to innate immune activation as a component of the ICR signature. Finally, it has been recently shown that the intra-lesional injection of oncolytic virus can turn an immune-silent tumor into an immunogenic one with activation of innate signals that secondarily attracts adaptive immune responses [121].

Thus, we believe that the prospect for IO therapy is to segregate future efforts according to immune landscapes and respective cause for refractoriness to CIT. It is likely that cancers displaying immune-activated landscapes and associated CIRes will benefit from combination of various IO agents that could shift the balance in favor of immune-effector over immune regulatory mechanisms. On the other hand, silent cancers will need to be primed to stir ICD and subsequent recruitment of innate and adaptive immune cells that could become suitable targets for IO agents including CIT.

Summary

- Immune suppression goes hand-in-hand with immune activation.
- Immune-active tumors include almost exclusively all the immune regulatory mechanisms to counterbalance their immunogenicity.
- Immune-silent tumors are enriched of signatures that reflect activation of oncogenic mechanisms and exclude immune regulatory mechanism.
- Human cancers go through a conserved evolutionary bottleneck facing a two-option choice to evade immune recognition by the immune competent host: they either adopt a clean oncogenic process devoid of immunogenic stimuli or display an entropic biology prone to immune recognition but resilient to rejection thanks to the recruitment of compensatory immune suppressive processes.
- Immunotherapy agents including check point inhibitors work only on the immune-active tumors enriched of immune regulatory mechanisms.
- Immune-silent tumors need to be targeted with agents that can disrupt their lean biology and induce immunogenic cell death.

Abbreviations

CIRes, compensatory immune resistance; CIT, checkpoint inhibitor therapy; ICD, immunogenic cell death; ICR, Immunologic Constant of Rejection; IFN, interferon; IO, immune oncology; ITD, immune-mediated tissue-specific destruction; TCGA, The Cancer Genome Atlas; TLR, Toll-like receptor; TOC, Two-Option Choice; TOE, Theory of Everything.

Competing Interests

All authors are employees of AbbVie. The design, study conduct, and financial support for this research were provided by AbbVie. AbbVie participated in the interpretation of data, review, and approval of the publication.

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