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Anti-Tumour Treatment

The ambitious role of anti angiogenesis molecules: Turning a cold tumor into a hot one

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ABSTRACT

In renal cancer emerging treatment options are becoming available and there is a strong need to combine therapies to reformulate and adjourn clinical practice. We here highlight and discuss the need to take advantage of the common immune targets to design combined strategies to increase clinical responses.

Personal view

The introduction of immune checkpoint inhibitors (ICIs) in clinical practice has revolutionized the scenario and the outcome of cure in oncology. The immune system is a complex network where the several mechanisms and interactions involved are continuously discovered. More than ever translational scientists are close to the clinicians to better understand patients immune response to cancer in order to potentiate possible avenues of cure. Several if not all standard therapies that represent today the gold standard in oncology need to be characterized from an immunological point of view for a necessary integration process that must be done to optimize protocols of cure.

From this point of view we want to discuss and share some of the critical points in the clinical management of anti angiogenic drugs, particularly Tyrosine Kinase Inhibitors (TKIs) and immunotherapy.

TKIs are important drugs that target receptors involved in the neoangiogenesis of tumors, such as the Vascular Endothelial Growth factor (VEGF) pathway, and they have contributed to changing life expectancy particularly of renal cancer patients [1,2]. In renal cancer, the activation of genes of the hypoxic response results in the downstream activation of pro-angiogenic growth factors like VEGF. Together with sunitinib, sorafenib, pazopanib, axitinib, most recently drugs targeting possible pro-angiogenic resistance mechanisms, lenvatinib and cabozantinib are also available.

The increase in treatment options including ICI has added complexity to clinical questions on how to choose first-line treatment and treatments after recurrence [2].

Tumor associated angiogenesis and immune system

Tumor progression is characterized by a number of mutational events that confer to the initially transformed cells a number of distinctive and functional features associated with invasive potential and expression of tumor associated antigens. A class of these, the neoantigens are not essential for tumor progression, but are important in generating an immune response in the patient. Indeed the presence of a relevant anti-tumor immune infiltrate is associated with an increased mutational tumor burden; moreover these tumors have been shown to respond better to ICI [3,4]. Despite immune activation, tumors are able to evade immunological control and after a phase of equilibrium that can also be prolonged in time, they finally enter in the escape phase characterized by several immunosuppressive traits and independence from any kind of immune control.

In this scenario the tumor microenvironment appears to have an important role and a number of studies are now focalizing in understanding the dynamics of these interactions during tumor progression.

The growing tumor establishes from the beginning a complex network of cross-talk between tissue resident stromal cells and immune cells, which are also resident but more frequently recruited ad hoc from the bone marrow and circulation. Tumor directed vascularization or tumor angiogenesis appears to involve several molecules, cells and signaling pathways. One of the main leaders in this crucial step, the angiogenic switch, which allows the tumor to acquire the invasive behaviour and a fully metastatic potential is the VEGF. Hypoxic cancer cells are able to secrete VEGF which engages the specific receptor on the endothelial cells that in turn proliferate, gradient guided to generate

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new blood vessel sprouts characterized by impaired vascular maturation, poor functionality and defects in endothelial architecture [5]. The immaturity of the new generated tumor associated vasculature results in excessive permeability, poor perfusion and imperfect blood flow. This has direct impact on anticancer treatment efficacy [6].

Moreover angiogenesis has an important influence on the immune system and these processes appear to be intimately linked. The vascular network with its specific components, endothelial cells, pericytes, growth factors and receptors is fundamental in the inflammatory response, in wound healing and in immune surveillance [7]. T cells, particularly antigen primed T cells, need a healthy endotelium for the trafficking to tissue districts and the cell to cell cross-talk that is established during the priming and effector phase of the immune response.

This is the basic principle of immune surveillance that relies on an efficient vascular-lymphatic circulation and endothelia that can be viewed as "critical non-hematopoietic components of the immune system" [8].

The access of immune cells into the tumor becomes a critical issue for the outcome of immunotherapeutic strategies such as adoptive cell transfer and expansion of tumor specific T cells with ICIs. Moreover also classical chemotherapeutic drugs have been shown to benefit for optimal efficacy of an intact immune system thus suggesting a synergy between cancer cell death and immune activation [9]. A normalized endothelium is preferred assuring the correct trafficking of T cells to the tumor bed since it is now well established that the presence of tumor infiltrating lymphocytes correlates with improved prognosis for most tumors [10]. The process of T cell infiltration is regulated by several variables. The type of T cell repertoire that can be described in the tumor depends on tumor released factors, on the cytokine/chemokine secreted and relies during the tumor growth, on the first encounter between the initial transformed cells and resident antigen presenting cells. Dendritic cells (DCs) as first sentinel cells are empowered to deliver the correct Th1 signalling to generate tumor specific T cells by endocytating dead neoplastic cells or cellular debris, transporting tumor antigen to the draining lymph nodes and cross-presenting antigens to T cells. Expression of an array of receptors and molecules on the surface of DCs is required to deliver the correct non tolerogenic signaling (DC maturation) [11]. Activated T cells can now expand and home to the tumor to exert the effector functions. This whole process, theoretically simple and smooth, is tightly regulated and can be perturbed by a number of factors and variables. These include all the well described immune tumor evasion mechanisms such as phenotypic changes in DCs induced for example by VEGF, PGE2, IL-10, tumor hypoxia. The T cell tumor infiltrate can also be populated by a variety of immunosuppressive cells usually attracted by the tumor and with the ability to counteract immune anti tumor activity: Regulatory T cells (Tregs), Myeloid Derived Suppressor cells (MDSCs) and Tumor associated macrophages (TAMs) [12]. So in the end the balance between immune activation and immune suppression will determine or at least influence significantly the outcome of any cancer treatment that relies or utilizes immunity networks.

The distinction between "hot" and "cold" tumors is relatively new. Some tumors have been defined as naturally "hot" such as melanoma characterized by a high mutational load in cancer cells associated with neoepitope expression and induction of tumor specific T cells [13–15]. For these tumors the possibility that ICI immunotherapy would work is relatively high since it is believed that the tumor microenvironment already has a repertoire of exhausted PD-1$^+$ T cells ready to be expanded. Responder patients are probably these, in which the immune-balance was in equilibrium and activation just needed to be unleashed to take over. A "cold" tumor has little or no T cell infiltration like prostate cancer, and therefore the efficacy of an ICI treatment can be null or very limited. Cold tumors are also those where a T cell infiltration can be observed but is localized in the periphery of the tumor suggesting a sort of limited access probably due to the tumor stroma including the vasculature network [16,17].

Tumor associated angiogenesis and anti cancer therapies

The efficacy of most of the anti cancer therapies is severely impaired by the imperfect newly generated blood vasculature. The interruption of a regulated blood flow will not allow sufficient drug delivery in the tumor particularly in all the different areas. Therefore efficacy of the treatment will be compromised. It should be emphasized that this effect is highly variable among patients and between tumors and can explain why patients respond only initially to treatment. The other important finding is that we know today that anti-angiogenic drugs can reduce dramatically cancer induced immunosuppression, simply because the targets such as VEGF and its receptors are the main actors in this process.

The initial idea that led to the generation of anti-angiogenesis drugs was to operate a pruning effect of the tumor associated blood vessels to induce tumor starvation. The dosing and schedule of antiangiogenic drugs has been revolutionized by Jain's hypothesis demonstrated in animal models that the "judicious" use of antiangiogenic agents could transiently normalize tumor vasculature, diminish hypoxia, reduce immunosuppression and improve efficacy of different therapies [18]. This hypothesis puts the basis for using anti angiogenic therapies and immunotherapies in combination more than as single agents. Clinical data confirm and sustain the validity of this thesis i.e chemotherapy and immune therapy require functional blood vessel for optimal efficacy [19]. The recent outstanding results from the combinations of ICI and chemotherapy in lung cancer strengthens furthermore this rationale and encourages the design of novel combination and /or sequential clinical trials using drugs targeting different mechanisms (tumor cell death, endothelium, immunity).

In the last few years we have also learned that chemotherapy can influence immunity and is able to target and normalize cancer endothelium, when given in a metronomic fashion [8]. The real innovative and relevant application of metronomic chemotherapy is the combination with immunotherapy by directly affecting the immunosuppressive tumor microenvironment. Cyclophosphamide, with its well known effect in depleting the Treg population, is one of the most used drugs in a variety of cancer vaccine protocols as a tool to make space for the newly activated specific T effector cells, which would be liberated by the immunosuppressive milieu [20].

Targeting angiogenesis and the immune system: Learning from patients' immune system

Endothelium is recognized as a major contributor in the efficacy of the immune response and several receptors are shared between participant cells. Research efforts have been directed in understanding the immune effects of anti angiogenic drugs. The interest is becoming urgent since with the possibility to introduce the ICIs during or combined with the anti angiogenic treatments in several cancers it is mandatory to consider these drugs from the point of view of their impact on the patient's immune system. The important question is: can we use the normalization effect induced by the anti angiogenic drugs to potentiate immunotherapeutic strategies? Moreover how are the shared receptors among immune cells, i.e. VEGFR, influenced by the therapy? Can we use anti-angiogenetic drugs to turn a "cold" tumor into a "hot" one and prepare the cancer patient for a successful ICI therapy?

The best readouts are of course the patients. Each of them has its own immune system, which has been shaped during life starting from host genetic factors and modulated in time by history of infectious diseases, environmental and lifestyle factors, stress and microbioma repertoire [21]. When the patient arrives to our attention with a diagnosed cancer, we need to consider not only the nature (histotype, genomic portrait, etc.) of the malignancy but also the immunological "fitness" of the patient, particularly at the tumor level. This is a novel