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Oncoimmunology or Immunoncology- Is the Concept of Immunotherapy Applied Globally in Cancer?

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Abstract

Cancer has for long been classified as having origin in a type of cell or tissue and has for ages been considered as a result from a single tumor cell. With the advances in genomics, transcriptomic and epigenetic research, cancer has now been recognized as a heterogeneous disease within itself. This enables clonal survival and resistance to therapies. However, cancer and inflammation have walked side by side for decades. The real knowledge of its interactions between the immunological system and carcinogenesis is yet to be wholly understood. Much has been discovered on how these interactions occur, how they differ in an intratumoral context and with the direct influence of the micoenvironment.

Key-Words

Oncoimmunology; Personalized Medicine; Quality of Care

Core Tip

Since Rudolph Virchow's time in 1863, has cancer and the immune system has been walking side by side. In fact, it's due to the host immune system that a haemostatic environment is maintained, with a continuous surveillance leading to an innate or adaptive immune response. This process has been defined as immunoediting. Scientists are aware that the tumor as well as the immunological status of the patient, are always suffering dynamic and active changes. There are no static genetic, immunological or environmental "signatures" in an oncological patient.

Introduction

Since long, more precisely since Rudolph Virchow's time in 1863, has cancer and the immune system been walking side by side [1]. Even by that time it had been observed by Pathologists that in places were chronic inflammation occurred, lymphoreticular infiltrate or as more recently named, Tumor Infiltrating Lymphocytes (TILs), were observed. The possibility of cancer to emerge was greater when compared to other non–inflamed areas. The rationale behind is that, when tissues are injured associated to some classes of irritants, together with an inflammatory reaction, cell proliferation is consequently induced. However we all know that cell proliferation *per si*, does not induce cancer. Owing to inflammatory environment, growth factors, stromal activation and DNA-damaging promoter agents (oncogenes), all together can potentiate the effect and risk of carcinogenesis.

Immune Surveillance

However the concept of immune surveillance must not be neglected. When a tumor cell is presented to the immune system, one of two pathways can be chosen. First, the immune system recognizes tumor neo-antigens as "foreign", and leads these tumor cells to elimination. This is the innate immune response. On the other hand, tumor cells may gain immune resistance and induce immune "Tolerance" and the immune system favours or becomes pro-tumorigenic. In other words: tumor survival and immune evasion. We may have two types of response: an inhibitory interaction between antigen presenting cells (APCs) and T cells which dampen the T cell immune response. Or, the opposite may happen where stimulatory signal from the T cells activating APCs. In fact it's due to the host immune system that a haemostatic environment is maintained, with a continuous surveillance leading to inflammatory reactions by the immune cells coordinating an innate or adaptive immune response. So, when a normal tissue is transformed into a neoplastic cell, the tissue will induce an immune response which will eliminate the tumor cells. On the other hand, if the elimination is badly succeeded, tumor cells may escape immune control and tumor growth may occur. This process has been defined by many authors as immunoediting, and travels through three main phases: elimination, equilibrium and escape [2].

Does the Mutational Load of the Tumor Have Any Influence?

The stimulation of T cell response by APCs needs the presentation by the Major of Histocompatibility Complex (MHC)- associated proteins. These may be tumor derived

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pepetides or by neoantigens. Tumors with a low mutational load, or low intratumoral heterogeneity, are considered as having a good correlation with T cell checkpoint inhibition. Heavy mutational load makes it more difficult for antigens recognition as well as neoantigens [3].

What Do Pathologists Observe?

When a pathologist is evaluating a frozen section of neoplastic tissue, many areas may be observed: the tumor area, the intratumoral stroma; tumor cell mass, the contiguous peri-tumoral area and the lymphoid aggregate. TILs can be evaluated in many areas. Stromal TILs have been shown to be predictive of response to neoadjuvante chemotherapy as well as improved outcome after adjuvante chemotherapy. This has been shown to be the best parameter for characterization of TILs. The evaluation of TILs in an intratumoral environment is more difficult to evaluate and do not have predictive or prognostic value compared to stromal TILs [4].

Efforts have been done to organize a grading system according to the immunological host response, in relation to areas involved, attribute a grade for TILs and determine its importance [5]. Pathologists have more than ever tried to characterize the tumor microenvironment: TILs density, distribution, characterization of APCs, neutrophils, myeloid derived suppressor cells, tumor associated macrophages and fibroblasts. Define inflamed *vs* not-inflamed tumors. Many studies have described that tissues with abundance of the lymphoid aggregates are those that are more responsive to all types cancer therapies, having been described as "hot" tumors more easily controlled. As opposed to tumors with fewer T-cell infiltrates –known as "cold" tumors [6]. Gallon J *et al.* Have worked in the direction of introducing immunoscore as an essential prognostic and also as a predictive tool with relevant impact in clinical practice [7]. Attempts are being made in implementing the immunoscore in the TNM classification of cancer (TNM-I).

But How Are T Cells Regulated?

Tumor cells produce different types of cytokines which attract different types of leukocytes. The presence of $CD4^+$ regulatory T cells (Treg) have been classified in a "good" population (Th1) and a "bad" population (Th2). We may have a pro-inflammatory response (Th1 cytokines) such as IL-1, TNF-α, IFN-γ or an anti-inflammatory response (Th2 cytokines) such as IL-1, IL-10, IL-13. From this balance, the outcome of the tumor survival will be decided (Figure 1). If an extreme response of chemokines favouring a pro-inflammatory response occurs, inflammation followed by neovascularization will lead to rapid tumor growth. On an opposite type of immune response, few chemokines are released, a limited degree of inflammation and scarce vascular response, limiting tumor growth. On a balanced type of immune response, pro and anti-inflammatory chemokines are produced into the mico-environment and inflammation occurs leading to tumor regression. Concluding, Th1 favours a good clinical outcome, while Th2 does not favor an anti-tumor response. Concerning IL-1, it is considered, as already mentioned an inflammatory cytokines and plays a role in initiating the inflammatory response. However, in a tumorigenic process, neoplastic cells can divert cytokines functions to subvert the natural immune response, in favour of tumor growth, migration and differentiation [8].

Nevertheless, the presence of CD8+ T cells are well correlated to patient's survival, in other words favors tumor suppression. In fact, it's owing to this immunological balance which will drive the cells via a pathway of anti-tumor activity or through a pathway in favouring tumor development. Nevertheless, it always depends on the micro-environment response. There will always be an attempt for tumor cells, as cell's with a scientific intelligence, to subvert the host immune cell response in its favour. Nevertheless, lymphocyte response can also be counterproductive and suppress tumor development [8].

How Does Checkpoint Inhibition Work?

Given the success of checkpoint inhibitors which have been developed in many oncological areas, there is a rationale to investigate the role of these agents and its effect in the outcome of our patients. But how do they interact between each other?

Programmed cell death protein-1 (PD-1) and cytotoxic T lymphocyte protein 4 (CTLA-4) and are immune checkpoints. Their action is to inhibit the T-cell response, providing an escape pathway for tumor cells to T-cell antitumor activity [9].The B7-H1, also known as PD-L1, positive tumours interacts with its receptor PD-1 inhibiting T-cells migration, proliferation, resulting in an anti-apoptotic signal. It prevents over-activation of the immune system, escaping from destruction [10]. The immune-detection of PD-L1 was significantly associated with tumour size, invasion, lymph node metastasis and survival time of patients [11].

The direct clinical application, of these concepts, of immunologic checkpoint blockade with antibodies that target CTLA-4, PD-1 and PD-L1 have shown to be challenging strategies, which may eventually improve the outcome in cancer patients and improve quality of care (Figure 2).

What Is the Influence of the Immune Status?

The host immune status has an enormous importance as it can define upfront the treatment strategies for each individual patient in its own clinical setting. Factors considered with poor outcome when treated with immunotherapy are: decreased lymphocytes count the neutrophil/lymphocyte ratio as well as myeloid-derived suppressor cell count. Increased inflammatory markers such as reactive protein C (CRP) and erythrocyte sedimentation rate (ESR) and also hypoxia, increased lactate dehydrogenase (LDH) and low pH has been associated with poor outcome. With improved outcome elevated eosinophil count has been considered [3].

Is the Future of Immunoncology or Oncoimmunology?

Scientists are aware that neither the tumor itself is a static

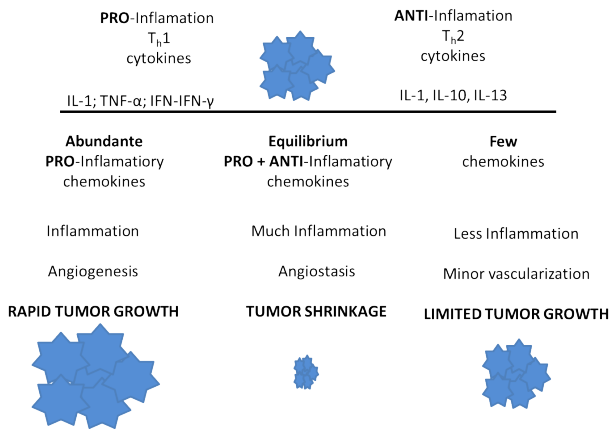

Figure 1: Equilibrium between PRO and ANTI-Inflammation

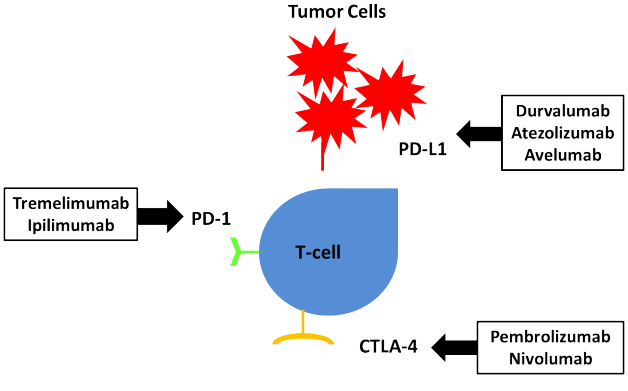

Figure 2: Checkpoint Inhibition

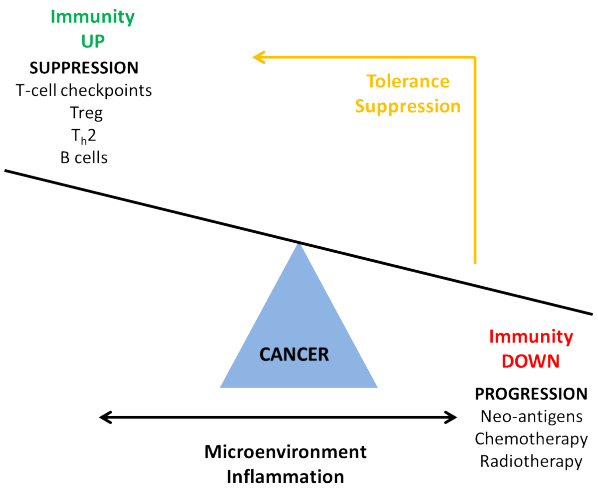

Figure 3: The balance between tumor, immunology and microenvironment

disease as well as the immunological status of the patient, which suffers changes according to the "immunological aggressions" performed. Science is in a constant turnover. There are no static genetic, immunological or environmental signatures in cancer. There is a dynamic interaction in between each other, in each individual patient (Figure3). Which one prevails first or together, depends on the determination of biomarkers, the performance status of the patient, its co-morbidities and finally, its preference according to side effects and quality of live.

Therefore, treatment discussion for each tumor in an individual patient has more than ever, been more refined and personalized having as first priority, the overall survival of our patients with the best quality of care.

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