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Cancer and the Three "E"

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Abstract

From 1909 onwards, the ***cancer immune-surveillance concept*** has undergone three distinct eras. Between 1957-1974 there was a general acceptance of the concept which was however abandoned between 1974-1996. 1996-2001 again saw the resurrection of immune-surveillance concept even-though now it had been modified to an elegant theory of tumour immunoediting proposed by Robert Schreiber. Recognition and targeting of cells by the immune system isbelieved to occur in three phases. Phase I, Elimination: cancer cells are recognized by the immune system via their antigens and targeted for destruction. In the process, some cells acquire mutations that allow them to resist immune destruction. Phase II, Equilibrium: low levels of abnormal cells persist, but their proliferation and spread are held in check by the adaptive immune response.Phase III, Escape: further mutation in the surviving cells leads to the capacity for immortal growth and metastasis. Over time, inhibitory immune responses begin to dominate and immune activity shifts from anti- to pro-. The present review aims to give a brief insight into the molecular interactions that take place during the process called **Cancer Immunoediting**.

***Index Terms*-Cancer immunosurveillance, immunoediting, equilibrium, editing, escape**

I. Introduction

Cancer cells are defined by two heritable properties: (1) they reproduce in defianceof the normal restraints on cell growth and division, and (2) they invadeand colonize territories normally reserved for other cells. While the cancer cells in a are the bearers of dangerous mutations andare often grossly abnormal, the other cells in the —especially those of thesupporting connective tissue, or stroma—are far from passive bystanders. The development of tumour relies on a three-way communication between the tumour cells, the tumour stromaand the interacting immune cells of the host.

The concept of cancer immunosurveillance was first proposed in 1909 by Ehrlich [1] who suggested that evolving tumours are constantly identified and eradicated by the host immune system even before clinical manifestations occur. This concept was refined by Burnet in 1970 with their proposal that genetic changes leading to malignancy are common in somatic cells resulting in potentially dangerous mutant cells [2].The concept was mainly supported by the immune-mediated rejection of transplanted tumours induced by chemical carcinogens or viruses in syngeneic mice[3], [4]. However,later on the concept was abandoned due to the observation that athymic nude mice did not show an increased incidence of spontaneous or chemically induced tumours compared to theirwild-type counterparts[5],[6].On the contrary research inputs during 1990s, indicated that nude

mice had NK cells and leaky T and B cell function thuscorroborating to the presence of some degree of immunosurveillance.

Interestingly two key findings between 1994–1998, raised interest in cancer immunosurveillance theory.

- First, it was demonstrated that endogenous IFN-γ could protect the host against transplanted and chemically induced tumors [7][8] and spontaneous tumors [9][10].

- The second key finding was a greater sensitivity of perforin nudemice to ***methylcholanthrene***-induced tumors compared with their wild typecounterparts [11].An increased incidence of spontaneous cancer after organ transplantation also contributed to the thought process [12].

The newer findings encouraged Robert Schreiber to propose the term ***'cancer immunoediting'*** in order to broadly describe the dual host-protecting and tumour-sculpting actions of the immune system that not only surveil for, and eliminate, nascent malignant cells but also shape neoplastic disease through equilibrium and escape mechanisms [13].

II. Immune Responses to Cancer: The 3 "E"S

Cancers are caused by the progressive growth and spread of the progeny of single transformed cell. It is likely that cells appear daily in healthy individuals but in the vast majority of instances they are removed by the immune system and do not develop into clinical malignancies. This ability of the immune system to detect cells as non-self and destroy them is called "*immunosurveillance*". It is currently thought that immunosurveillance primarily functions by immunoediting. "***Cancer immunoediting***" has been described as both the "*host protective*" and as well as the "*immunosuppressionpromoting*" ability of the nascent growing tumor mass. Three separate steps of cancer immunoediting have been proposed: **elimination**, **equilibrium** and **escape**as elaborated in **Figure.1**. However, these are not in fact separate phases, but rather represent a continuum of the interplay between tumour and immune system, shifting between elimination, equilibrium and escape depending on the state of the immune system and genuine or acquired properties of the cells.

Fig.1.The Three 'E's Of Cancer Immunoediting

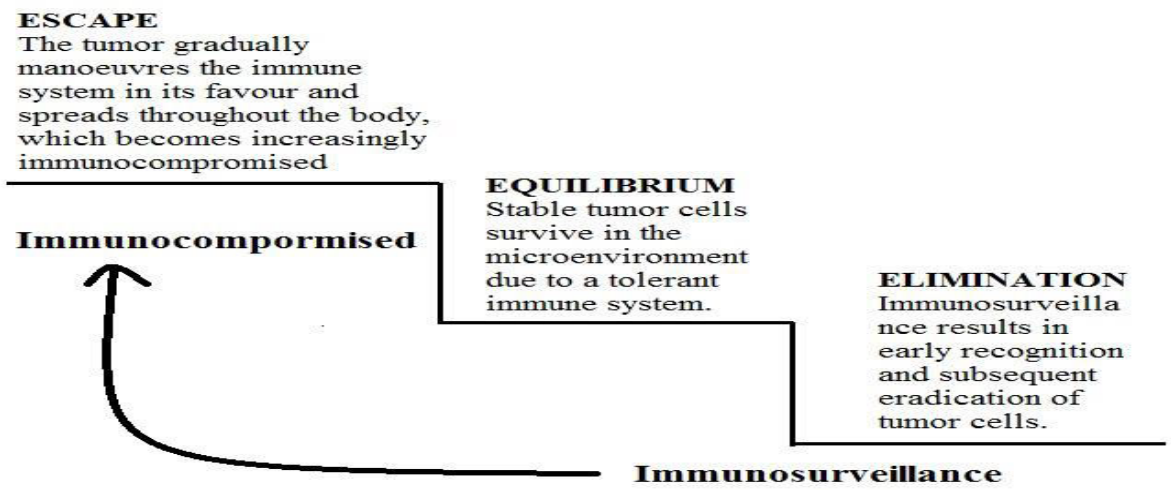

Figure. 1 The three "E" of cancer immunoediting.

During cancer immunoediting, the immune system is able to recognize and destroy the most immunologically vulnerable cancer cells because they present antigens, resulting in their elimination [14]. Nonetheless, due to genetic instability, constant cell division can generate cells with reduced immunogenicity that can evade immune elimination. This state of production of new cell variants balanced by the elimination has been dubbed "*equilibrium*", during which the cancer cells continue to divide, accumulating mutational changes by chance or in response toimmune-induced inflammation. Thus, a balance between immune control and growth is maintained, giving the appearance of *dormancy* [15].

Immune dormancy eventually enables incapacitates the immune system such that it fails to eradicate the tumor mass by immune suppressive effects or by loss of target antigen expression. It is at this stage that tumor *escape* occurs, resulting in overt clinical cancer. Nonetheless, there may also be conditions under which cells are truly dormant, for example by induction of "senescence". In this case, they would be likely to remain dormant permanently, as replicativesenescence is generally believed to be irreversible [16].

2.1. Elimination: the 1st E

The first '**E**' or "***the elimination***" represents the immunosurveillance function of host immunityin which the later is supposed to fight the tumor cells, eliminating many of them in the process.During the process evolving tumorsare successfully rejected by the innate and the adaptive immune systems by various mechanisms.For the innate immune response, several immune effector cells such as natural killer (NK), natural killer T cells (NKT), and cytotoxic T Lymphocytes (CTL) are activatedby the inflammatory cytokines, which are released by the growing tumour cells, macrophages and stromal cells surrounding the tumour cells. The secreted cytokines recruit more immune cells, thus amplifying the pro-inflammatory signals via *interleukin-12* (**IL-12**) and *interferon-γ* (**IFN-γ**). *Perforin*-(**pfp**), *Fas-ligand* (**FasL**) and *Tumor necrosis factor-related apoptosis-inducing ligand* (**TRAIL**) mediated killing of tumour cells by NK cells releases tumour antigens (**TAs**), whichlead to adaptive immune responses. In the crosstalk between NK cells and *dendritic cells* (**DCs**), [17]NK cells promote the maturation of DCs and their migration to *tumour draining lymph nodes* (**TDLNs**), resulting in the enhancement of antigen presentation to naive T cells for clonal expansion of *cytotoxic T lymphocytes* (**CTLs**). The TA-specific T lymphocytes are recruited to the primary tumor site, anddirectly attack and kill tumor cells with the production of cytotoxic interferon-γ(IFN-γ).

The 4 stages of the elimination process:

(1) **Recognition of the tumors cells by the mediators of the innate immunity:**
When a solid tumor cell has grown to more than 2–3 mm, it requires a blood supply and stromal remodelingfor progression, which in turn induces pro-inflammatory signals leading to the recruitment of innate immune cells such as NK, NKT, cytotoxic T cells, macrophages and DCs into the vicinity[18]. The transformed cells can be recognized by infiltrating lymphocytes such as NK, NKT and cd T cells, which produce IFN-γ[19].

(2) **Maturation and migration of Dendritic Cells and cross-priming for T cells**:
IFN-γ exerts a limited cytotoxicity via antiproliferative [20] and anti-angiogenic effects, [21] and induces apoptosis [22]. Some of the chemokines derived from tumors and surrounding

non-tumorous tissues, block the formation of new blood vessels even while continuing to induce tumor cell death.Necrotic cells are ingested by *immature DCs* (**iDCs**), which have matured under pro-inflammatory conditions, and have migrated to TDLNs.

(3) Generation of Tumor Antigen specific T cells:
The recently recruited-infiltrating NK and macrophages in the tumor site, produce*interleukin-12* (IL-12) and *interferon-γ*(IFN-γ), which kill more tumor cells by activating cytotoxic mechanisms such as perforin, TRAIL and reactive oxygen species [23]. In the *tumor-draining lymph nodes* (TDLNs), the migrated DCs present tumor antigens(TAs) to naive *CD4+ T helper cells* (**T_H**) that differentiate to CD4+ T_{H1} cells, which develop TA-specific *CD8+ T cytotoxic cells*(**T_C**) that lead to clonal expansion.

(4) Homing of Tumor Antigen specific T cells and elimination of the tumor cells.
Antigen-specific CD4+ T helper cells (**T_H**) and CD8+ T cytotoxic cells(**T_C**) cells home to the primary site, where the CTLs eliminate the remaining TA-expressing cells; a process enhanced by the secreted IFN-γ, which also selects for cells with reduced immunogenicity [24].

2.2. Equilibrium: the 2nd E

The second '**E**' or ***the equilibrium*** stands for a phase during which, although the developing tumor mass is still kept in check by the immune system, but is however not completely eliminated.The equilibrium phase involves - the continuous elimination of tumor cells and the production of resistant variants by immune selection pressure. It is the longest of the three ''E''s of cancer immunoediting and may occur over a period of many years [25].

In this process, lymphocytes and IFN-γ play a critical role in exerting immune selection pressure on cells. During this period of Darwinian selection, many variants from the original tumor mass are killed but new variants emerge carrying different mutations that increase resistance and survival efficiency against the immune belligerence. Since the equilibrium model persists for a long time in the interaction between cancer cells and the host, the transmission of cancer during organ transplantation can be considered.

2.3. Escape: the 3rd E

The final and the third '**E**' or ***the escape*** is the final phase characterized by generation of new variants capable of evading host immunity leading to an unrestrained growth.

In this phase, cells may escape from immune control and proliferate in an unrestricted manner, leading to clinically apparent tumors. This escape can be mediated through various mechanisms, such as reduced immune recognition, increased resistance to attack by immune cells or the development of an immunosuppressive microenvironment.

Factors that tumors exploit to avoid immune responses:

1. **Regulatory cells**:
   Immune suppression in the microenvironment, mediated by CD4+ T helper cells, CD25+ T lymphocytes and*regulatory T cells* (**T_{regs}**),or other types of suppressive cells seems to be a major mechanism of immune escape and can be a crucial hurdle for immunotherapy.

2. **Defective antigen presentation:**

   It is well established that another fundamental mechanism by which tumors evade immune surveillance is by down-modulating antigen processing machinery affecting the *major histocompatibility complex*-I (**MHC**) pathway, *proteasome subunits latent membrane protein***LMP**-2 and **LMP-7**, *transporter associated with antigen processing* (**TAP**) protein, and tapasin [26]-[31]. Effective expression of antigenic peptide is thustotally down-regulated. This leads to enhanced incidence and metastasis because cytotoxic T lymphocyte (CTL) can no longer recognize target tumor antigens on the surface of thecells [32].

3. **Immune suppressive mediators:**

   As alluded to above, tumor cells can evade immune surveillance by crippling cytotoxic T lymphocyte function [CTL] functionality via production of several immunosuppressive cytokines, either by the cancer cells or by the non-cancerous cells present in the vicinity. TGF-β is a chief mediator of this activity.In addition, necrosis factor-α**(**TNF-α), IL-1, IL-6, colony stimulating factor (CSF)-1, IL-8, IL-10, and type I IFNs can also significantly contribute to cancer growth.In addition to immune suppressive cytokines, other factors such asvascular endothelial growth factor (VEGF) produced by tumors, inhibit the differentiation of progenitors into dendritic cells (DCs) thus affecting efficient uptake and antigen presentation. VEGF and IL-10 and tumor growth factor- β (TGF-β) are also known to inhibit maturation of DCs. DCs retaining the immature phenotype are tolerogenic as they do not present antigen in the proper context with appropriate costimulation to T cells. Other factors such as gangliosides and receptor-binding cancer-associated surface antigen (RCAS1) also contribute to tumor progression.

Conclusion:

The interaction between the immune system and cancer cells is complex, and the cancer microenvironment is far from being fully understood. Accordingly, we have not covered all aspects of this complicated interplay but focused onThe 3 "E"s - **elimination**, **equilibrium** and **escape (Figure.2)**.

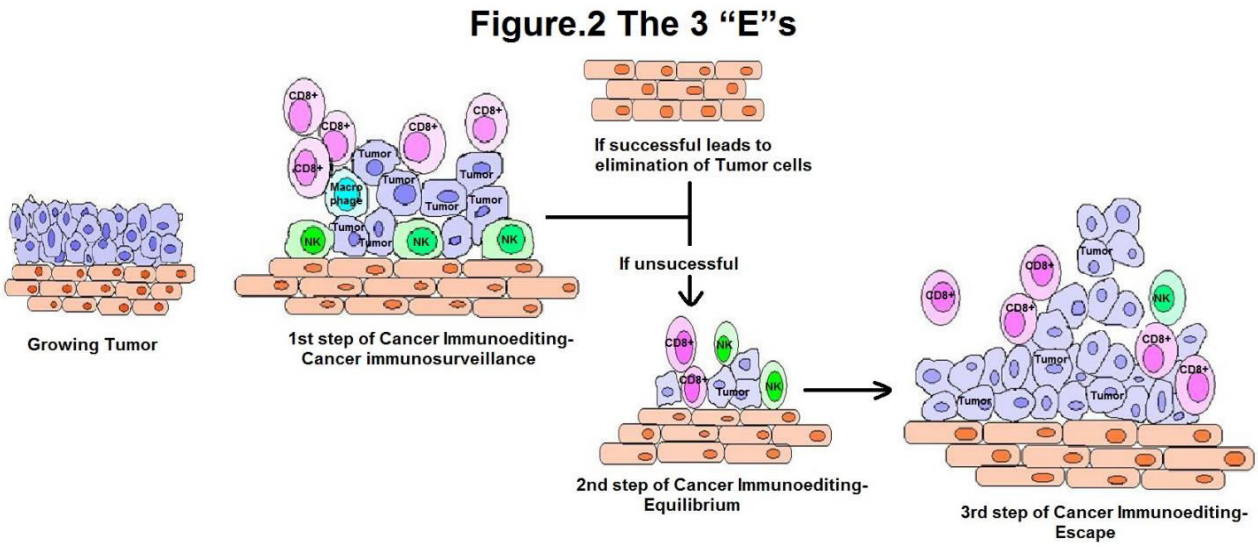

Figure. 2 The 3 "E" s

Cancer cells are gradually able to gain several mechanisms of immune evasion during tumour progression, even though they are being pursued by the initial and continuing phases of immune surveillance. Rather, immunological sculpting contributes to immune selection pressure, which produces tumour cell variants that are resistant to immune effector cells because of their low immunogenicity.

Immune escape is the final phase of cancer immunoediting process wherein cancer modulates our immune system to escape from being destroyed by it. Many cellular and molecular events govern the cancer's evasion of host immune response. The undergoes continuous remodeling at the genetic, epigenetic and metabolic level to acquire resistance to apoptosis. Cancer immune escape is sum total of plethora of immunological as well as non-immunological events both cancer-related and host-related.

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