

# Integrating Role of Immunity in Cancer: Journey from Immune Surveillance to Tumour Escape.

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## ABSTRACT

**Introduction:** Cancer immunoediting is crucial to understand the success or failure of a tumor. Immune system plays dual roles in tumor development and progression, promoting or suppressing tumor depending on tumor microenvironment and the events that lead to initiation of carcinogenesis. The immune system has potential to recognize and destroy tumors, and thus function as a primary defense mechanism against cancer. On the other hand, unresolved immune responses can result in the growth and progression of cancer.

**Objectives:** The host immune system determines tumour fate in three phases (Elimination, Equilibrium and Escape) and according to this theory, it blocks adaptive and innate tumour responses or promotes conditions that favour tumour progression.

**Conclusion:** The purpose of this review is to emphasise the importance of immunity in tumour promotion and suppression.

**Keywords:** Cancer immunity, Immunology in cancer, Immune surveillance, Immunoediting

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## INTRODUCTION

The immune system has the capacity to either block tumour development and deter established tumours, or to promote carcinogenesis, tumour progression and metastasis, the prevalence of which depends on the balance between the pro- and anti-tumour mediation of both innate and adaptive immunity. There are unifying mechanisms that orchestrate immunity towards tumour promotion vs. tumour destruction.<sup>1</sup>

“The study of the interaction between a human host and a neoplasm is complex and if not treated adequately can cause death of the host.” This defines Tumour Immunology and the inability of the host’s immunologic responses to limit tumour growth and spread led to the understanding that immunologic and nonimmunologic variables may interact to influence carcinogenesis.<sup>2</sup> To prevent tumours, the immune system has three main roles.

1. The immune system can protect the host from tumours caused by the virus by removing or suppressing viral infections.
2. Rapid elimination of pathogens and rapid resolution of inflammation can prevent the establishment of a tumour-prone inflammatory environment.
3. The immune system can specifically identify and eliminate tumour cells based on their expression of antigens or tumour-specific molecules induced by cell stress.

The third process is called tumour immune surveillance, which allows the immune system to identify cancer and/or precancerous cells and rule them out before they cause harm. Despite tumour immune surveillance, development

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of tumours occur in the presence of a functioning immune system.<sup>3</sup>

The tumour immunoediting concept works on the principle that T-cell recognition of tumour antigens drives the immunological elimination or sculpting of a developing cancer and have set the foundations for understanding the dual host protective and tumour sculpting actions of immunity on cancer and establishing the basis for novel individualized cancer immunotherapies. The cancer immunoediting is to control and shape cancer and for that the three phases are called as the three E’s of cancer immunoediting.<sup>4</sup>

During cancer immunoediting, the tumour’s fate is shaped by the host immune system in the three phases by innate and adaptive immune mechanisms activation.

a. First phase, **Elimination**, the cells that are transformed are destroyed by a competent immune system. Immunosurveillance is the notion that this phase is based on.

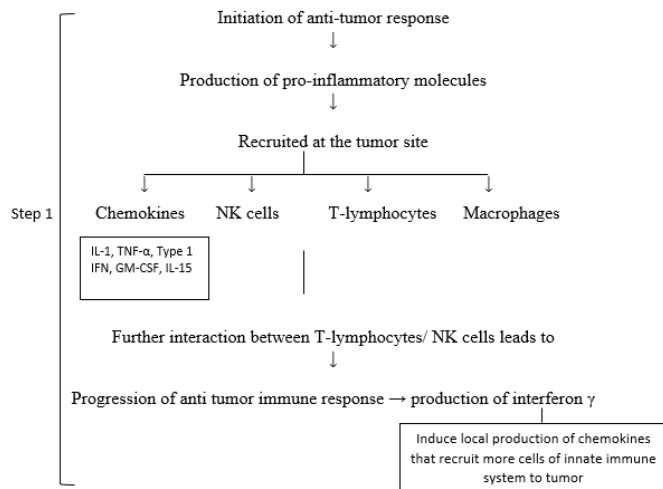
b. Second phase, **Equilibrium**, is the immune-mediated latency period after incomplete tumour removal.

c. The Third and final phase of the process is **Escape**, in which immunologically shaped tumours begin to develop, become clinically visible, and form an immunosuppressive tumour microenvironment.<sup>4</sup>

**a. Elimination**

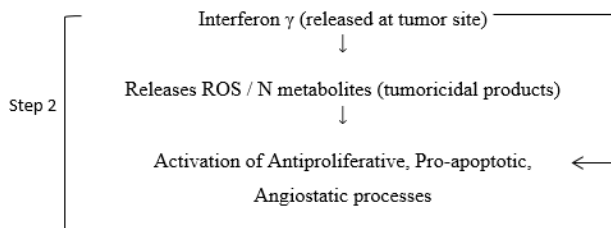
Elimination phase is the hallmark of the original concept in cancer immunoediting for successful eradication of developing tumour cells, the process of elimination includes innate and adaptive immune responses. The proposed four steps are explained by structured flow chart<sup>5</sup>:

Step 1: Tumour cell recognition<sup>6</sup>



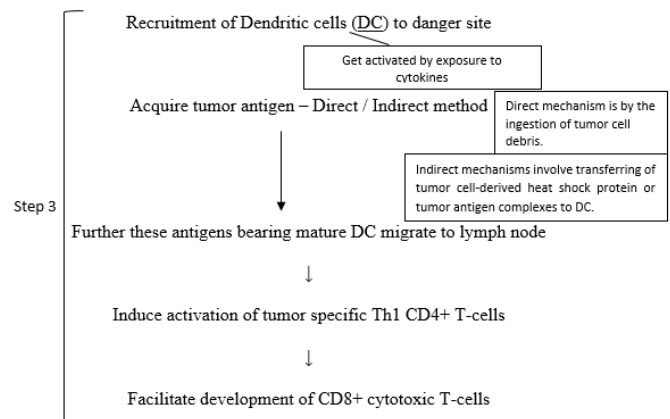
On initiation of anti-tumour response once tumour cells are detected, pro-inflammatory molecules production and their recruitment at the tumour site occurs where they interact with t-lymphocytes or NK cells and progress towards anti tumour immune response. This leads to the production of interferon  $\gamma$ .

Step 2: Dendritic cells maturing<sup>7</sup>



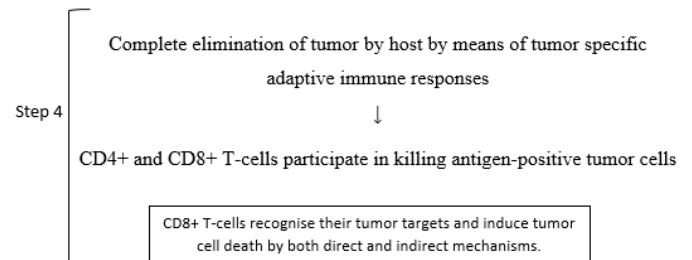
Interferon  $\gamma$ , produced in the first step are released at the tumour site and this in turn releases tumouricidal products. Their release activates all the tumour cell death related processes.

Step 3: T cell generation specific to tumour antigen.<sup>8</sup>



Dendritic cells are recruited to tumour site and acquire tumour antigen by direct or indirect methods. Now antigen bearing mature DC migrate to lymph node and induce activation of tumour specific T-cells (Th1 CD4+) which facilitate development of cytotoxic T-cells.

Step 4: Locating tumour antigen-specific T lymphocytes to the tumour site.<sup>9</sup>



Finally, these tumour-specific adaptive immune responses eradicate the tumour from the host, and T- cells kill antigen-positive tumour cells. As a result of the expression of antigens or tumour-specific chemicals generated by cell stress, the immune system can selectively detect and suppress tumour cells. Tumour immune surveillance is the term for this procedure. The concept of Cancer Immunesurveillance has been formulated based on the hypothesis that cancer cells are recognized as non-self and are capable of inducing a rejection reaction. Despite strong evidence supporting this process, immunocompetent individuals still develop cancer because the immune system can facilitate tumour progression by sculpting the immunogenic phenotype of tumours as they develop.<sup>10</sup>

Thus, the phase of elimination of cancer immunoediting (the cancer immunosurveillance phase) is an ever-ongoing process and is repeated each time antigenically distinct neoplastic cells arise. As a result, it's worth noting that cancer is more common among the elderly, when the immune system's functioning and cancer immunosurveillance begin to deteriorate (Figure 1).<sup>11</sup>

**b. Equilibrium**

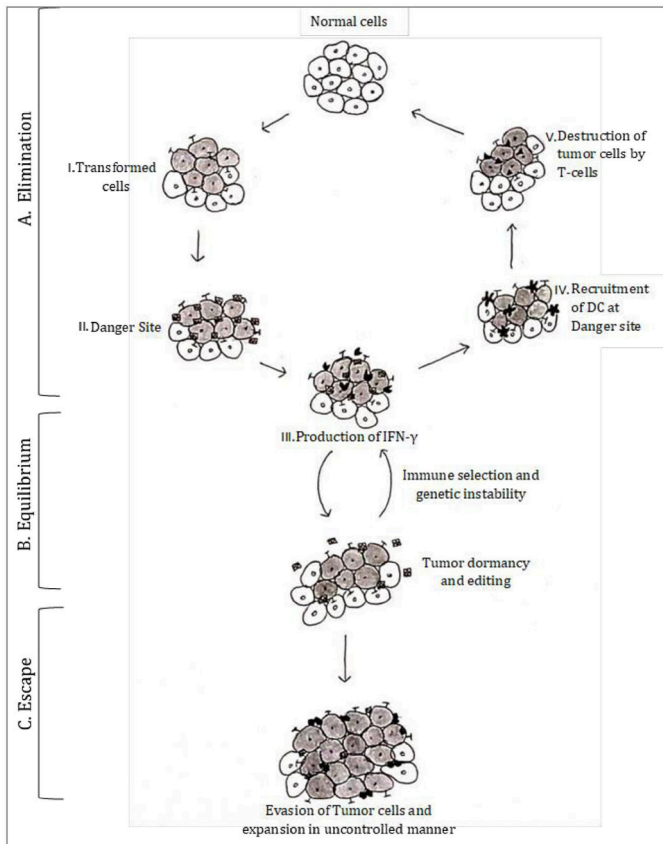
The previous phase's tumour cell variations that survived, enter the equilibrium phase. Out of the three phases (elimination,



equilibrium and escape), Equilibrium phase is the longest and is expanded over a period of many years in humans. Original tumour cell variants are destroyed in this phase and are replaced by new variants arising from mutations.<sup>12</sup> Increased resistance is provided by these new variants and hence the end result of this phase is tumour clones new population with reduced immunogenicity.

Tumour transmission from an organ donor to a recipient has provided evidence for the equilibrium phase of cancer immunoediting, demonstrating that the tumour in the donor

© Tumor cell; & IFN- $\gamma$ ; @ Dendritic cells; A T- cells; « M2, B-cells, MDSC, CD4+ T-cells, T-regs; & TNF  $\alpha$ , CD8+, M1, NK, IL-1.



**Fig. 1:** Schematic representation of the concept of cancer immunology: **A. Elimination-** cancer immune surveillance **i.** Due to immune instability normal cells are transformed **ii.** Pro inflammatory molecules which are recruited at the tumor site (i.e. danger site) **iii.** Produce interferon- $\gamma$  which in turn **iv.** Recruit dendritic cells at tumor site and help in **v.** Destruction of tumor cells by T-cells. **B. Equilibrium-** due to immune selection and genetic instability either the cells are sculpted by immune editors to produce new population of tumor cells or their outgrowth is prevented by immunologic mechanisms. **C. Escape-** immunosuppressive state where immune effector mechanisms don't work and tumor cells outgrow and promote tumor progression.

was controlled by an immunologic mechanism and that tumour growth was allowed by transplanting the organ into an immunosuppressed host. This provided clinical evidence which supported the equilibrium phase of cancer immunoediting (Figure 1).<sup>13</sup>

The relative balance of immunosuppressive cells and immune cells capable of exhibiting antitumour effector actions in the tumour microenvironment is connected with maintaining tumour cells in a state of immune induced dormancy.

### c. Escape

The escape phase represents the failure of the immune mechanism to do away with or manage converted cells, which further permits tumour cell variants to develop in an immunologically unrestricted manner. To acquire modern growth, the tumour cells must evade both or atleast one of the hands of the immune system, i.e., innate and adaptive immune responses (Figure 1).<sup>14</sup> Tumours can obstruct the development of anticancer immune responses, either directly or indirectly, by expressing immunosuppressive cytokines and T-lymphocytes with immunosuppressive properties, which target the immune system to achieve tumour escape. The unresponsiveness of these malignancies could be due to aberrant IFN- receptor signalling component function.

Tumours possess tumour rejection antigens, capable of escaping destruction by host immunity, indicating occurrence of immune evasion. There are three different strategies to get over tumour immunity.

- Lack of recognition
- Lack of susceptibility
- Induction of immune dysfunction.<sup>15</sup>

Tumours in two circumstances confront the adverse environment. The developing tumours must first get nutrition and then avoid the host immune system's attack in order to grow rapidly.<sup>16</sup>

Cancer immune evasion is a major hindrance in designing effective anticancer therapeutic measures. Although considerable progress has been made in understanding tumour evasion, measures to counteract it has not kept pace. As there are number of contributing factors for tumour persistence, despite having effective immune system, immunoediting is one of the key aspects why tumours evade surveillance causing the tumours to lie dormant for years through equilibrium and senescence before reemerging.

## CONCLUSION

The cancer immunoediting concept attempts to integrate the diverse effects of the immune system on tumour development and outgrowth. With elucidation of the molecular and cellular mechanisms that underlie the elimination, equilibrium, and escape phases of this process, it should be possible to develop new cancer immunotherapies that are safer and more efficacious in a substantial percentage of cancer patients. Given the well-established effects of immunity on cancer development and outgrowth, escape from immune control can now be viewed as one of the "Hallmarks of Cancer". The scope of cancer immunology in coming years will be to introduce elegant combinational treatments involving novel immunotherapeutic strategies which are expected to induce improved clinical responses and eventually cancer prevention.

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