

Self or Not Self: The Autonomy of the Immune System

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This article is the second of a series by Dr William Barnes which explore the structure and function of the immune system, and how it fits into the changing medical paradigm.

Introduction:

The immune system and its function still provide plenty of opportunity for investigation. Since Collie's first endeavours described in my previous article, cancer therapies and researchers have tried to tease out the instruments that make up the orchestra of the immune system. The music being the immune system's response.

Cytokines namely interleukins and interferons (chemicals that communicate and coordinate the immune response) have been used with limited success in the fight against cancer. However the shroud of mystery surrounding the structure and function of the immune system is lifted more promising therapies will emerge.

In everyday language and in popular lay press, the strengthening of the immune system has become the catch cry. Many products are marketed on such a cry. However the intricacy of the response and the specific therapy that truly enables the immune system to do its job will yield far greater rewards.

The common belief is that the immune system is too weak to conquer the cancer. This in most cases could not be further from the truth. The scientific evidence and the work of researchers such as Collie, suggest that the immune system if properly provoked and directed can have devastating effects on tumours even in the late stages of cancer. Trials with the interleukins 2 and 12 have shown that tumours can be destroyed but the toxicity with these substances has been too great.

The use of Radiotherapy and Chemotherapy are universally seen as destructive to the immune systems capabilities, requiring rejuvenation during and after these therapies. However the biggest problem in my opinion is the inability of our immune systems to recognise the cancerous cells as foreign.

The task therefore in therapy is to not only enhance the response, but to provide a means of direction and identification.

Structure:

The immune system is a name given to a collection of molecules, cells and organs whose complex interactions protect the host from an invasion from external and internal organisms and foreign cells. I will describe the actions of the immune system mainly in its surveillance and destruction of cancer.

The main cell types in this process are which are all under the collective name of white cells.

1. Phagocytes
2. T lymphocytes (T cells)
3. Natural Killer Cells (NK cells)

Phagocytes:

These are also described as non-specific effector cells. They are white blood cells and are most important in surveillance.

The Phagocytes are mainly neutrophils, macrophages and dendritic cells. Neutrophils and Macrophages roam through the blood vessels looking for foreign material, dendritic cells are fixed in strategic places and catch foreign substances as they pass.

The first action of the most important cell, the macrophage, is phagocytosis, a multi-step process that involves the complete engulfment of the foreign substance. Through a digestive action the macrophage

processes the foreign substance. Parts of this substance are then secreted onto the cell surface. This substance is called MHC (major histocompatibility complex). This substance along with protein bits from the foreign substances is responsible for activating circulating T cells. These activated T cells trigger a whole cascade of immune responses. T cells develop into different forms and cytokines are released both from the T cells and the macrophages.

T Cells:

T cells are lymphocytes in the general family of white cells. They mature and function under the influence of the Thymus, a gland in the front of the chest cavity, hence the name T cell. During the foetal development the original T cell called the T stem cell moves from the marrow to the Thymus where it matures and learns the concept of self. Mature T cells leave the thymus and circulate in the blood stream where they can be identified as T helper cells (CD4) or T suppressor cells (T8). The AIDS virus attacks and destroys the T Helper cells thus destroying the arm of the immune system.

Activated T cells, after contact with macrophages, produce a wide range of cytokines, which in turn activate more T cells coordinating a cascading immune response, appropriate to the threat. The T cells divide into 3 types: those that produce cytokines as already discussed, Effector cells which are killing machines, the most potent of all the killing cells in the immune system. The third is memory cell, which stays dormant until the same threat presents itself at a later date promoting a much faster response by T cells a second time around. When a new foreign substance is first met it can take up to ten days to get a full-blown immune response.

Cytokines:

Cytokines are chemical compounds produced by the cells of the immune system. As discussed previously these chemicals act powerfully as growth activators of T cells, enabling rapid growth of T cells stamped with the code given to it by the macrophage (MHC). They also direct the type of response the immune system will make, as some organisms are better dealt with by one response than another. This effect may account for variable response by the immune system to cancer. If the wrong arm of the immune system is activated then the response may be inadequate or ineffective.

Interleukin 12 is a cytokine currently under investigation for its potential in fighting cancer. To date it has shown promise but too much toxicity, however better systems of delivery, under investigation, may improve its performance.

Interferon another cytokine, which was discovered earlier, is currently used in treating renal cancer and melanoma with some success, however it has been most successful in treating a rare form of leukaemia called hairy cell leukaemia. The blocking of the enzyme Tyrosinase in melanoma is a treatment being examined to enhance the effect of interferon therapy. This is discussed further in Problems of Immune Response,

Natural Killer Cells:

As previously described the whole process of the T cell immune response can take some time. NK cells can activate very quickly providing a more immediate response. The NK cells are not as specific or effective as killers as the T effector cells but can respond immediately. Not only do they kill but they also produce cytokines often different from those produced by the macrophage giving a more complete immune response.

NK cells are particularly important in the surveillance against cancer. Cancer cells for reasons that will be explained invariably go undetected by the phagocytes (macrophages). They do not present differently enough from normal cells, so often get past macrophage surveillance. NK cells however do not require the presence of MHC or an antigen on the surface of the macrophage to be activated. This provides the immune system with an early response to cancer cell invasion.

NK cells are lymphocytes but are different in structure from CD4 and CD8 cells (T cells), they can make up to 5 to 30% of the total lymphocyte numbers in the blood. Total lymphocyte numbers are often reduced during and after chemo and radiotherapy.

Problems of Immune Response in Cancer:

There are three main reasons why cancer goes undetected by the immune system.

1. Insufficient numbers of white blood cells as discussed.
2. Shielding:
 - A) The inability of the immune system to recognise the cells as foreign.
 - B) The production by cancer cells of enzymes called proteases.

German researcher named Dr Nieper described a process of camouflage used by cancer cells he called shielding. A cancer cell he claimed produced a form of protective coat around its cell wall made of mucous. The coat he described as similar to a coat human embryo produce to protect against being aborted by mother. This coat on the cancer cell reduces the ability of detection by the surveillance cells namely phagocytes and NK cells. Nieper claimed this mucous could be reduced by the use of Beta-carotene and a plant enzyme called bromelaine as oral supplementation.

More recent research suggests that this shield may contain protein-eating enzymes. In particular an enzyme called tyrosinase. Tyrosinase activity has been shown to be increased over six fold in the blood of patients suffering from advanced malignancies, melanoma and breast cancer featuring in the highest group.

Suitable methods of tyrosinase inhibition are being researched with possibility of an improvement in immunotherapy's ability to challenge cancers looking promising,

In my clinic I used Venus Fly Trap both orally and intravenously. This has been described as a protease inhibitor. Clinical observations suggest an increase in immune response in our treated cases.

Immune Privilege:

Many lines of tumour cells have been found recently to have a process which enables them to evade surveillance and destruction by T cells, this process is described as immune privilege.

It has been known for sometime that certain organs such as the eyes and testis can resist a full immune response from the immune system. The reason for this lies in the delicate nature of the tissue. A full response could have a very destructive effect on these delicate tissues. To accomplish this, the cells of the eyes and testis produce a substance called FAS Ligand which when met by a T cell causes the T cell to spontaneously die. This process is called programmed cell death or apoptosis. Cunningly, tumour cells can produce an identical substance thereby resisting an attack by the immune system. As the activated T cell approaches the cancer cell it is instructed by the FAS L produce by the cancer to apoptose (die). Currently there is considerable research going into nullifying this resistive process. The ability to turn off the cancer's defence will greatly enhance the immunological approach to fighting cancer.

Conclusion:

Outlined above is a rudimentary description of immune function in relation to cancer. The process of applying an immunological treatment to cancer is complex. In the next paper I will outline some strategies currently available and research which is developing new advances in treating cancer, which will harness rather than hinder the body's own defence.

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