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Review

Clinical onco-immunology: Immune reconstitution - A place to start

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ABSTRACT

The history of using the immune system as the primary weapon against cancer, intentionally or inadvertently, stretches back for at least three centuries. The probability of inducing a durable remission, when utilizing immunotherapy, depends upon three inter-related elements. They are the availability of a quantity of recognizable cancer antigens, the degree of anergy which is suppressing immunity, and the underlying structure of the immune system. Addressing the components of immune structure and function through a systematic approach of immune reconstitution will be briefly considered.

KEYWORDS: cancer, onco-immunology, anergy, antigens, immune reconstitution.

1. Introduction

Cancer and infectious diseases have long afflicted mankind. Indeed, based upon the study of hominin remains originating in Northeastern Africa, it is believed that smallpox has troubled us since at least 10,000 BC [1, 2]. Some Egyptian mummies dating back to 1570 BC show evidence of the disease [3]. By 430 BC, it had been observed that survivors of the disease were resistant to further episodes of the affliction and were thus called upon to tend to those who were currently ill [4]. It is lost to the sands of time who invented the procedure of inoculating (from the Latin *inoculare*, meaning "to graft".) the uninfected person with a small amount of pus from one suffering with smallpox to hopefully induce a limited infection and protection from a more severe case. By the 18th century the technique was introduced to Europe, likely from traders arriving from Istanbul. There was much interest in the technique and support by the aristocracy. They didn't want to get their hands dirty, and hence supported the new treatment. History records that Lady Mary Wortley Montague championed the procedure having suffered the disfiguring effects of the disease herself and hoping to spare her children from the same fate [5]. As a result of her efforts, thousands were thus treated after she convinced the court physicians of its efficacy, including a demonstration on her own children. One of those inoculated was Edward Jenner [2].

Edward Jenner was a pioneering English physician and scientist who improved the procedure of smallpox inoculation to create the smallpox vaccine in 1796 [6, 7]. In the scientific fashion, he purposely exposed people that he had vaccinated against smallpox to prove that the cowpox pus that he used did indeed confer protective resistance. Although others before him had used cowpox to provide protection from smallpox, he was the first to then demonstrate that it did in fact work, and that the effect was reproducible in subsequent patients [8-10]. Although not knowing about the intricacies of the immune system, because he applied the scientific method, as it existed in his time, he is referred to as the "Father of Immunology" [11].

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2. Early observations

Physicians then were now more interested in this observable, reproducible and useful phenomenon and began to look for ways to apply it to other diseases. In 1810 Samuel Hahnemann wrote in the first edition of his "Organon of Medicine," with several editions to follow, a very interesting observation;

> "I myself saw mumps (angina parotidea) disappear as soon as a cowpox inoculation had taken and approached its climax. Only after the pustules and their red areola had disappeared did the feverish swelling of the parotoid and submaxillary glands, caused by the mumps miasm, come back and run its seven-day course. This is the case with all dissimilar diseases; the stronger suspends the weaker,…the acute illness suspends the chronic affliction" [12, 13].

In the 1880s through the 1890s, based upon these and other observations, when physicians were faced with treating the rare cancer patient, they would occasionally attempt drastic treatments that, if the patient survived, may in fact result in a prolonged remission. One of these drastic treatment strategies included taking a large splinter of wood, dipping it in cow dung and jabbing it into the patient's thigh [14]. The resulting bacterial sepsis and fever must have been incredible but were sometimes lifesaving. Soon after these observations were made, Dr. D. M. Foubister made a medicine to try and reproduce these "beneficial effects" using a simple vaccine type approach which reportedly had some success [15]. It has also long been observed that various acute viral infections can also lead to a "spontaneous remission" of an underlying cancer including infections from Adenovirus (a cold virus), Newcastle (a chicken virus) and even Jenner's Cowpox, amongst others [16-18]. Now we know that the resulting fever and infection will generate a cascade of heat shock proteins (HSPs). Heat shock proteins have some properties that act as molecular chaperones, and can bind tumor-specific peptides and deliver them deep into the antigen-processing pathways of antigen-presenting cells (APCs), macrophages, dendritic cells and some B-cells [19]. They can activate tumor-specific immunity, trigger the proliferation of cytotoxic lymphocytes (CTLs) and stimulate the capabilities of cancer-specific CD8+ T cells, thus inhibiting tumor growth and promoting its death [20]. Further advances in HSP research has shown anticancer effects that involve improving the properties of activated CTLs, capable of penetrating the tumor milieu, tumor infiltrating lymphocytes (TILs), and specifically targeting tumor cells [21].

3. Non-specific immune activation

Without understanding the pathways and cells involved, but by being astute clinical observers, physicians pushed medical science forward. Again, observing the relationship between acute infections suppressing an underlying cancer, it was observed that erysipelas (beta hemolytic group A Streptococcus) could also lead to a cancer remission. Dr. Coley refined the procedure by extracting the Streptococcal toxins while making a sterile solution [22]. So, no longer was a life-threatening sepsis necessary to possibly obtain some of the beneficial effects of the bacterial toxin mixture. For decades Parke-Davis manufactured "Coley's Toxins", making them available to physicians to treat many different kinds of cancer with some success. Supplanted by newer discoveries, Coley's Toxins use in the United States ended in 1963 but they are still used in several other countries today [23]. As the pathways of immune activation became clearer, their interaction with bacterial toxins as an anticancer agent has become better understood. Now there is a lot of research using CpG oligodeoxynucleotides. According to the NCI drug dictionary:

> "A synthetic oligodeoxynucleotide, containing unmethylated CpG motifs derived from bacterial DNA (including Strep), with immunostimulatory activities. A CpG oligodeoxynucleotide (CpG ODN) binds to and activates a Toll-like receptor 9 (TLR9) and is taken up into cells by endocytosis; once internalized, it may activate numerous signaling transduction pathways resulting in the release of multiple cytokines. Through activation of TLR9, a CpG ODN can directly stimulate B-lymphocytes, dendritic and NK cells, resulting in an increase in innate immunity and antibody-dependent cell cytotoxicity (ADCC). Additionally, a CpG ODN

can indirectly modulate T-cell responses, through the release of cytokines (IL-12 and IFN gamma), to induce a preferential shift to the Th_1 (helper) phenotype resulting in enhanced CD8+ cellular cytotoxicity" [24].

CpG Oligonucleotides are now being used in several studies and clinical trials which are quite an advancement over Coley's toxins and represent an important, non-specific, plan of attack against cancer [25-30]. As a further advancement, CpG molecules are mixed with lysed tumor cells, to add some specificity to the anticancer response, or anti-OX40 antibodies [31-33]. The success or failure of these strategies depends upon the "intactness" of the underlying immune system to be able to follow through once stimulated in these relatively non-specific ways. Newer strategies have evolved to unleash the immune response, again, in relatively non-specific ways; this involves using monoclonal antibodies to dis-inhibit the immune response.

4. The dawn of modern immunotherapy

First approved in 2011 for the treatment of metastatic melanoma, ipilimumab's creation was made possible by a deeper understanding of how the immune system works and how it interacts with cancer cells in the tumor micro-environment. Activation of T-cells, that results in stimulated cytotoxic effector cells requires (at least) two signals [34-36]. Tumor-associated antigens attached to the major histocompatibility complex I or II activates antigen-presenting cells (APCs) causing them to express the B7 peripheral membrane protein. The B7 protein, on the APC, then binds with the CD28 receptors on the T-cell surface, initiating activation. Optimally then, activated T-cells subsequently proliferate, differentiate, target and destroy the cancer cells. Shortly after T-cell activation, cytotoxic T-lymphocyte antigen-4 (CTLA-4) is upregulated to competitively inhibit the binding of B7 to CD28 and stop T-cell activation and proliferation thus acting as one of many of the immune system's feedback loops or checkpoints [37-39]. Ipilimumab is a recombinant, human monoclonal antibody that binds to the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) molecule inactivating the suppressive response. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation but in a "shot gun" sort of manner absent the information flow from the APCs. Tumor infiltrating T-cells dis-inhibited in this way will generate a cytotoxic inflammatory effect against the nearest targets, destroying cancer cells and non-cancer cells alike. The antigen release from the damaged non-cancer cells can then trigger a new response of the APCs against them generating a toxic auto-immune cascade that accounts for the many potential side effects of Ipilimumab [40]. Still, it has proved to be very helpful in saving thousands of lives.

A refinement came in December 2014 with the approval of nivolumab, and what a Christmas present that was! This human antibody was first approved to treat Melanoma, then Lung cancer, and now it is in trials against all forms of cancer whose cells manifest the PD-1/PD-L1 marker. The programmed cell death 1 (PD-1) receptor is expressed on several cell types including activated T cells, B cells, macrophages, regulatory T cells (Tregs), and natural killer (NK) cells, and is accessed through a set of feedback pathways that normally regulate immune function. The PD-1 and/or PD-L1 protein (ligand) is also found on the surface of some cancer cells [41]. When the PD-L1 ligand, on the cancer cell, fits into the PD-1 receptor on the activated T-cell, it triggers a cascade ending in the programmed cell death of the T-cell, thus putting the brakes on the immune response [42]. Activation of the PD-1/PD-L1 pathway is a common and important mechanism by which tumors evade antigen-specific T-cell immunologic responses. Binding to and blocking this signal with anti-PD-1 or anti-PD-L1 monoclonal antibodies dis-inhibits the immune system and prevents this downregulation allowing for more robust activity but, again, does not help with the targeting or balance of the immune response [43]. More recent studies show that using both Ipilimumab and Nivolumab together allows for the activation of immune response genes on a much greater scale than the sum of their parts, allowing more patients to go into remission [44]. These monoclonals are referred to as checkpoint inhibitors because they prevent the cancer from "check mating" the immune system. Dis-inhibiting the immune response is not without consequences. As you might imagine, if you take

the breaks off of the immune system, it could and does make antibodies against anything and everything, causing toxic auto-immune reactions, some of which are potentially fatal [45-48].

5. Cellular pathways

Getting back to understanding how the immune system works on a cellular level, medicine would have to wait until 1862 when Ernst Haeckel and soon after William Osler describe specific cells and their function, along with the process of phagocytosis which was later refined and identified as an immune activity by Elle Metchnikoff [49]. The discovery of other elements of the immune system was slow to follow; mast cells by Paul Ehrlich in 1877, neutrophils, basophils and eosinophils years later and finally, as recently as 1959, James Gowans described the nature and circulation of lymphocytes for which he received the Wolf prize [50, 51]. With these and many other discoveries, doctors began to connect the dots of why certain things may help a cancer reverse course and possibly disappear.

6. Communication pathways and immune activation

In part, research on the immune system was still slow to progress due to the extraordinary complexity and intrinsic feedback mechanisms promoting homeostasis in tissue injury, repair, inflammation, and the general immune response. However, it did progress and in the early 1960s, research studies reported "activities" in leukocyte-conditioned media that promoted lymphocyte proliferation and stimulation [52]. This soluble factor produced by one cell and acting on another cell, as a "hormone" of the immune system was soon identified from cultured human cells in 1980 and called interleukin-2 [53]. Research, testing, and the development of IL-2 (Interleukin-2) continued and, in 1992, the FDA approved it under the trade name, "Proleukin" for the treatment of metastatic renal cell carcinoma [54]. Soon it was observed that IL-2 could significantly activate natural killer cells, promoting their proliferation and leading to subsequent tumor cell lysis [55-58]. It wasn't long before IL-2 was being used, off label, against other cancers with some success [59-62].

Research on cytokine-induced stimulation of the immune system didn't end with IL-2. As the pathways of immune system modulation were gradually worked out, it soon became apparent that there was another major player in the field, Interferon-g. In the mid 1960s it was discovered that if you took a culture of leukocytes and incubated them with the mitosis stimulant (mitogen) phytohemagglutinin, the culture would have potent antiviral effects [63]. Due to the many effects both as a modulator and stimulant of the immune system, by this newly discovered cytokine, it would take until 1980 for research to clearly demonstrate that all of the observed effects were from one molecule which was named Interferon-gamma (IFN-g) [64]. IFN-g can initiate an immune cascade by activating both macrophages and dendritic cells [65-67]. Once the antigen presenting cell identifies a target deemed to be foreign, it couples with the immature (CD3) Th_0 lymphocyte, which then begins the differentiation process into a mature T helper cell (CD4) and takes its place amongst the "brains" of the immune system. The interaction of the T Cell Receptor (TCR)/CD3 complex, referred to immunologically as a ligand, along with cytokines released by the macrophages, or other nearby cells, determines the maturation pathway that it follows. Helper T (CD4) lymphocytes perform most of their effector functions *via* the activity of secreted cytokines. CD4 cells can be segregated into several different mature subsets, termed Th_1, Th_2, Th_9, Th_{17}, Th_{22}, etc., based upon the array of secreted and intra-cellular cytokines that they produce. Th_1 cells uniquely produce IL-2, IL-12, IFN-g, and Lymphotoxin (TNF-b), whereas Th_2 cells uniquely produce IL-4, L-5, IL-10, and IL-13. Th cells of all types produce other lymphokines like GM-CSF. The distinction based on the intracellular and secreted lymphokines corresponds to the functional phenotype of the cells [68, 69].

Current research demonstrates that the Th_1 cells are responsible for delayed type hypersensitivity reactions and the activation of cytotoxic lymphocytes (CTL). There are three, major, known types of CTLs; Cytotoxic T (CTL)(CD8) cells, natural killer (NK)(CD16/56) cells, and natural killer T (NKT)(CD161) cells. While there are some differences in their primary targets, they can

all participate in an anti-cancer affect and are stimulated by IFN-g. The immune system is not a simple pathway but a network within which a cascade of information gets processed, forwarded, focused, and amplified resulting in the ultimate destruction of the identified cancer cells, largely with the help of IFN-g. In 1999, the FDA approved Interferon gamma 1b, Actimmune, for the treatment of Chronic Granulomatous Disease. However, since research has clearly shown the many benefits of IFN-g on the structure and function of the immune system, many promising off label studies against cancer have continued [70-74].

Learning more about immune structure and function allowed physicians to do laboratory tests to better understand where the "holes" were. It soon became evident that some of these "holes" could be bridged with cytokines that supported the flow of information from antigen processing cell, to the immature T_0 cell, to the Th_1 cell, to the cytotoxic effector cells. Various dosage models have been used and it is clear that many of the cytokines have biphasic effects. At "high" doses the anticancer effects were often dramatic but toxic to the patient, while at "low" doses the effects of single cytokines were often ineffective or even cancer promoting. However, the combination of some "low" dose cytokines can be very helpful and have a more specific, guided, anti-cancer effect. A specific antitumor immune response usually requires expression of MHC class I or II molecules on tumor cells, for targeting purposes. For most cancer cells, MHC antigen down-regulation is an apparent tumor growth promoting mechanism and a pathway for evading the immune system [75-79]. Administering low dose IFN-g subcutaneously every other day, or even weekly, can induce cancer cell MHC expression [80]. In addition to spot lighting cancer cells with increased MHC expression, it is highly supportive of the subsequent immune response. IFN-g is produced predominantly by natural killer (NK) and natural killer T (NKT) cells as part of the innate immune response, and by CD4 Th_1 and CD8 cytotoxic T lymphocyte (CTL) effector T cells once antigen-specific immunity develops [81]. As such, IFN-g is the primary cytokine that defines Th_1 cell activity. Th_1 cells secrete IFN-g, which in turn causes more undifferentiated CD4+ cells (Th_0 cells) to differentiate into Th_1 cells, representing a positive feedback loop and, perhaps more importantly, suppresses Th_2 cell differentiation and activation [82, 83]. It appears that IFN-g is responsible for the activity of most of the cells that have a direct anti-cancer effect but it doesn't initiate differentiation, for that we need IL-2.

Interleukin-2 is necessary for the growth, proliferation, and differentiation of thymic-derived lymphocytes (T cells), the first steps to becoming active effector T cells, both Th_1 and Th_2. IL-2 is normally produced by T cells during an immune response and quickly becomes an autocrine form of activation once begun [84, 85]. Antigen binding to the T cell receptor (TCR) stimulates the secretion of IL-2 and, along with IL-12 and other factors in the milieu, pushes the development of the immature lymphocytes in the Th_1 direction. IL-2 is also necessary for the development of T cell immunologic memory, which depends upon the expansion of the number and function of antigen-selected T cell clones [86, 87]. Administering low dose IL-2 subcutaneously every other day can increase a clinically beneficial immune counter attack without the attendant toxicity associated with a higher dose [88]. Together, low dose IL-2 (1MU) alternating with low dose IFN-g (1MU) can re-establish immune communication pathways, "transmit" information from the APCs, and may restore an effective, guided, and targeted anticancer response [89].

In broad terms, we have described a "non-specific" anti-cancer response using a toxin reaction, or immune dis-inhibitors, and a more "specific" immune response using cytokines to try and restore the normal immune cascade pathways. Cytokine pathway restoration may be aided by synthetically activating APCs (dendritic cells) with "cancer vaccines" [90-95]. Whereas over targeting cancer cells with CAR-T cells may miss the long-term benefit mark by not attacking all of the cancer cell lines thus allowing for recurrence [96]. All of these strategies may have their own niche for maximum benefit and minimal side effects, as yet to be clearly delineated; however they all miss the basic tenets of immune reconstitution which are to biochemically support an intact immune system and to break anergy [97].

If we're using the immune system as the primary weapon against cancer, then we have to start by supporting its infra-structure or the immune response that we generate will not be sustainable, thus leading to recurrence, side effects and treatment failure.

7. Immune reconstitution

Immune reconstitution is the evolving clinical science of restoring immune competence by correcting biochemical imbalances, augmenting cytokines, restoring cascade pathways and/or implanting specific stem cells to bridge areas of damage. All severe or chronic diseases are known to have one or more significant defects in the immune system adversely affecting the immunological imperatives of recognition, response and memory thus leading to anergy and tolerance of the cancer. Testing for and breaking anergy is the first step in immune reconstitution [98]. Correcting anergy is of critical importance because it directly correlates to the stage of cancer: over 90% of patients with Stage 4 disease are found to be anergic [99]. The immune system cannot fight something that it doesn't know is there, and that's exactly what arises with anergy. Anergy manifests when there is a failure of signal transmission at ANY point in the immune response cascade. Before we can break anergy, and wake up the immune system, we must make sure that we are dealing with true anergy as opposed to another pathology.

Of historical interest, some years ago the Mérieux Company introduced a skin test called the "Multitest Mérieux" or "CMI Multitest" system (Istituto Merieux Italia, Rome, Italy). It is used as a general test for assessing the level of the cellular immune response. It is an intradermal test of skin reactivity (similar to allergy tests) in which a control (glycerol) is used with seven common antigens of bacterial or fungal origin (tetanus toxoid, tuberculin, diphtheria, streptococcus, candida, trichophyton, and proteus). In this test, reactions are categorized according to the number of antigens provoking a response, and the summed magnitude of the skin response to all seven antigens. Based on the chart and information supplied with the simple skin test, basic anergy can be quickly assessed and quantified [100]. Unfortunately, this test cannot tell us where in the recognition/response chain of events the problem lies. However, specialized blood tests are now generally able to do that. Once this state of unresponsiveness has been confirmed, the next step in breaking anergy is with an immunotherapy protocol specific to the area(s) of immune response dysfunction.

8. Recognizing anergy

A first step in initiating an immune cascade is that of recognition of abnormal cells by the APCs. A blood test called a Phagocytic Index directly measures the activity of the macrophages and is taken as an indirect measure of the functional activity of the Dendritic Cells [101, 102]. It is calculated as the average number of bacteria ingested by each macrophage, in an individual's blood, after a mixture of the blood serum, bacteria, and phagocytes have been incubated per the protocol's period of time. Depending upon how suppressed the immune system is (and for what reasons) the elevation of the Phagocytic Index, after stimulation, can last for 1 to several weeks. To counter this level of anergy, and depending upon the availability in your country, there are several options for stimulating APCs in a relatively short period of time including:

B-1,3-Glucan [103-105].

Dendritic Cell Vaccines [106, 107, 108].

BCG [109, 110, 111].

PNEUMOVAX® 23 [112, 113, 114].

Gc-MAF [115, 116, 117].

Viscum [118, 119, 120].

Dendritic Cell Vaccines not only stimulate APCs, but have been shown to be effective against many forms of cancer. However, the only form currently available in the United States is a variation that is called Provenge® (Sipuleucel-T), and it is used for advanced Prostate cancer.

Bacillus Calmette–Guérin (historically known as Vaccin Bilié de Calmette et Guérin currently referred to as Bacille de Calmette et Guérin or BCG) is a "vaccine" that is commonly given in many countries around the world as a modicum of protection against tuberculosis, along the lines of what Jenner did for smallpox. It is prepared from

an attenuated strain of the live bovine tuberculosis bacillus, *Mycobacterium bovis*. Through a special process of sub-culturing, a less virulent strain has been created to use for this purpose. When injected intra-dermally it will form a local infection that can smolder for months, all the while stimulating APC activity systemically. BCG can be infused into the bladder to generate a local immune/inflammatory response that can stop some early, superficial bladder cancers better than the chemotherapy that it was tested against, according to the product insert [121].

PNEUMOVAX® 23 vaccine contains polysaccharides that can stimulate APCs and macrophages locally and initiate a T & B cell cascade systemically. Cooperation between the two major components of immunity, innate and adaptive, is crucial in the generation of long-term protection against cancer through antibody-dependent cellular cytotoxicity (ADCC). Innate immunity is the first part of the immune response that occurs within hours of an identified threat, and is relatively non-specific. Recognition of pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors (PRRs) found on cells such as macrophages and dendritic cells (APCs) results in a series of signaling events, leading to the release of numerous cytokines and chemokines. The chemical mediators recruit and activate APCs to kill and phagocytize the identified target. Dendritic cells (DC's), which have specialized processing abilities, will migrate from the periphery to secondary lymphoid organs and mature, resulting in their ability to efficiently prime T cells for adaptive responses. The interaction between DCs and T cells initiates the adaptive arm of the immune response, which occurs in an antigen-specific manner, resulting in an immune response cascade. Th_1 cells thus activated release their own cytokines that stimulate effector cells downstream such as NK and NKT cells that will then actively search for and destroy cancer cells. B-cells that are stimulated through this cascade of information will mature into plasma cells and make specific antibody's that can act as a targeting beacon for the NK cells completing the ADCC response. Strep pneumoniae polysaccharides can thus act as a bridge to help prime an effective immune response. Activated DC's injected intratumorally can cause an inflammatory cell response, resulting in a loss of tumor cell structure and severe local necrosis of the tumor [122, 123].

Macrophages can also be stirred into action by a glycoprotein called Group-specific Complex-Macrophage Activating Factor (Gc-MAF) that is normally produced by the body. Cancerous cells secrete several abnormal enzymes into the bloodstream such as EctoNox 2 and α-N-acetylgalactosaminidase (NaGalase). NaGalase causes the deglycosylation of serum vitamin D3-binding protein (known as Gc protein), that is a precursor for the production of macrophage activating factor (MAF). Subsequently, this blocks Gc-MAF's production and activity. Therefore, macrophages of cancer patients having deglycosylated Gc protein cannot be activated, leading to immunosuppression of these critical antigen presenting cells. This suppressive effect can be temporarily overcome by administering Gc-MAF. The Gc-MAF seems to work on several cell types to help initiate an immune response. Furthermore, studies have demonstrated the ability of Gc-MAF to decrease angiogenesis and stimulate the production of several chemokines [124].

Viscum album (VA) preparations, commonly known as European mistletoe, are frequently used to improve the quality of life of cancer patients and to reduce the tumor's growth. They are known to exert a variety of anti-cancer effects directly and indirectly through an immune response. VA stimulates the maturation and activation of dendritic cells (DCs) which in turn can trigger an effective anti-cancer cascade enhancing IFN-g production and bolstering a Th_1 immune response. Viscum also aids in switching macrophage polarization from M2 to M1 which further increases IFN-g production, Th_1 activity and the response of natural killers and cytotoxic T-cells. This is important because tumor-associated macrophages (TAMs) are typically of the M2 phenotype and are known for their pro-tumoral functions such as promotion of cancer cell motility, metastasis formation and angiogenesis. TAMs produce immunosuppressive cytokines like IL-10, TGFβ and PGE2 and low levels of pro-inflammatory cytokines (IL-12, IL-1β, TNFα, IL-6). The usual ability of macrophages to present tumor-associated antigens is decreased in TAMs

as well. As a result, they are unable to further stimulate effector cells and cannot lyse cancer cells. VA has been shown to be effective in the re-education of TAMs from a M2 to a M1 phenotype [125-134].

Cytotoxic T cells also kill virally infected cells while NKT cells are important in recognizing glycolipids from organisms such as mycobacterium. NK cells are primarily tasked with tumor cell surveillance but can also bind to cell receptors (ligands), that indicate that the cell is infected, to directly induce apoptosis [135].

The lymphocyte mitogen proliferation panel is one test that is used for *in vitro* assessment of cellular immunity in patients with immunodeficiency, autoimmunity, infectious diseases, cancer and chemical-induced hypersensitivity reactions. Normally, healthy lymphocytes have receptors for mitogens such as the plant lectin concanavalin A (Con A), pokeweed mitogen (PWM), the protein A component of Staphylococcus aureus Cowan strain I (SpA) and various chemicals. Lymphocytes respond to these mitogens (substances that stimulate lymphocytes to replicate into a large number of clones of themselves without prior sensitization) [136]. Inability of the lymphocytes to respond to mitogens is but one diagnostic sign of impaired cell-mediated immunity and a cause of anergy [137-144].

9. Antigenic targets

Any therapy that causes a rapid die off of cancer cells will cause a spike in the concentration of antigens that are shed from the cancer. Timed with an immuno-therapeutic regimen, it can lead to an effective systemic immune response, the length of which will depend upon the future availability of antigens and the underlying structure and function of the immune system. Therapies that aren't also immune suppressive have the best possibility of success and they include radio frequency ablation (RFA), electroporation, cryotherapy, focal hyperthermia, High Intensity Focused Ultrasound (HIFU), intra-tumor injections of apoptotic agents, and hypo-fractionated radiation which has been shown to potentially induce the abscopal effect.

The abscopal effect is a phenomenon in the treatment of metastatic cancer where localized treatment of a tumor causes not only a shrinking of the treated tumor but also a shrinking of tumors throughout the body. This phenomenon was first described in 1953 by Dr. R. H. Mole, of Britain's Medical Research Council. He coined the term 'abscopal effect' to characterize it. (The word "abscopal" is derived from the Latin prefix "ab-" meaning "away from", and the Greek word "skopos", meaning "target"). Initially associated with single-tumor, localized radiation therapy, the term has also come to encompass other types of localized treatments that then induce a systemic therapeutic effect. While all of the pathways for its induction are not yet known, leaving this still as an unusual phenomenon. When the abscopal effect occurs, the results are often dramatic and durable [145-150].

10. Infrastructure support

The three most common causes of functional damage to lymphocyte activation, to the point of rendering them incapable of mounting a response and thus anergic are nutritional deficiencies, virus infections (T-cell retroviruses and B-cell viruses) and toxins.

Toxins have a devastating impact on the structural and functional integrity of the immune system. They can compromise immune function to the point of anergy, on the one hand, and induce life threatening diseases like cancer, which the immune system is then ill equipped to stop, on the other (ex. The leukemia cluster from Arsenic at Falon, NV) [151]. The NIH website, (http://toxnet.nlm.nih.gov/) is devoted to warehousing studies and data on the effects of various toxins on us. If you type "immune system" into the search bar, over 40,000 articles will pop up which clearly describe the devastating effects that heavy metals, volatile organic compounds, PCBs, DES, etc., have on our immune system.

Nutritional deficiencies may be characterized as being either absolute or relative. Owing to the availability of social support programs like WIC and EBT cards, in North America, an absolute nutritional deficiency, meaning that the individual isn't getting basic nutrients in the food that they're eating, is less common. However, it is quite common, with the processed nature of North American diets, to create an environment that

shuts down enzyme systems leading to any number of problems as simple as indigestion or as serious as inflammatory processes in the digestive tract damaging the micro-villi, leading to impaired absorption (Irritable Bowel Syndrome, Enteritis, Celiac). Prolonged, incomplete or improper digestion leads to impacted feces blocking absorption potentially creating a malabsorption syndrome and causing liver toxicity because the body is trying to reabsorb what it believes to be nutrients in your colon. According to Dr. Charles B. Simone, nationally renowned Medical Oncologist and Immunologist, "nutritional deficiencies decrease a person's capacity to resist cancer, infection and its consequences and decrease the capability of the immune system in general" [152].

11. The wound that does not heal

Cancer has been described as "a wound that does not heal" [153-155]. There are several phases of wound healing which can be summarized as repairing and replacing damaged tissue and eliminating infection and abnormal cells [156]. The later part of the healing process largely involves the immune response to the damaged tissue and the chemokines and cytokines that it releases. Just as certain nutrients have been found to be essential for tissue repair, other nutrients are critical as a biochemical foundation to a healthy immune response [157, 158].

Naturally occurring substances with known, beneficial, physiological or biochemical effects are referred to as nutraceuticals and can be very helpful in the fight against cancer [159, 160]. Some of the nutraceuticals that are helpful for correcting anergy are discussed below. The only nutraceutical that has proven itself effective as a true immune system modulator, in that it activates both sides of the cytokine signaling receptors and thus is not an immune stimulant is BLC/AiE10 [161]. It can serve to re-connect critical cytokine communication pathways and can speed up the reconstitution of lymphocyte activity and response.

A brief, non-exclusive list of potentially useful nutraceuticals begins with Quercetin. Quercetin is a plant pigment, biochemically a flavonoid, that is widely distributed in nature. The name has been used since 1857, and is derived from quercetum (oak tree), the plant that it was isolated from. Its antioxidant and anti-cancer affects are derived from, amongst other things, its ability to suppress NF-kappaB [162, 163].

Fish oil has long been used as an antioxidant. Its anti-inflammatory affects are broad and deep acting, because it is lipid soluble, and are focused, like those of Viscum, on its ability to suppress the COX-2 enzyme system [164, 165]. In addition to reducing systemic inflammation and supporting lymphocyte activation, it also has protective affects against the inflammatory aspects of cardio-vascular heart disease, reduces the joint inflammation of arthritis and reduces the inflammation associated with neuro-degenerative diseases, to name but a few of its many affects [166, 167].

Vitamin E has powerful effects on the immune system. Like fish oil, and many other supplements, it has biphasic effects. In low doses, staying within the "normal" range of lab tests, it supports lymphocyte activation and function. In high doses it can suppress Treg cells, and the systemic inflammation associated with auto-immune diseases [168]. Vitamin E is also helpful with cataracts, heart disease, lung problems, and liver damage. Some of its helpful effects can also be traced to its ability to suppress IGF-1 which can slow down many cancers. IGF-1 is one of the most potent natural activators of the AKT signaling pathway, a stimulator of cell growth and proliferation, and a potent inhibitor of programmed cell death [169].

There are many other nutraceuticals that can effectively reduce the kind of systemic inflammation that suppresses lymphocyte activation [170]. This list includes; Curcumin, the principle phenol found in the south Asian spice turmeric which reduces TNF-a and IL-6 [171-175]. EGCG, extracted from green tea, which can neutralize a long list of reactive oxygen species (ROS) [176] and the granddaddy of them all, Vitamin C [177-179]. Vitamin C, again like many other nutraceuticals, has a biphasic effect [180]. In low doses it has potent anti-inflammatory effects that can neutralize ROS and lipid peroxides, suppress IGF-1 and COX-2, activate lymphocytes, and down regulate VEGF production. In high doses, above 10-15 grams IV, Vitamin C can preferentially kill cancer through a number of mechanisms including apoptosis, pyknosis, necrosis and, with a little K3, autoschizis [181, 182].

12. Conclusion

Cancer, as a disease of our time, has a multitude of biochemical dysfunctions at its core. However, in order for these genetically and phenotypically abnormal cells to survive and thrive, the watchdog of the body, the immune system, must itself be suffering from a number of serious areas of structural and functional damage. Integrating strategies of nutritional support, detoxification, cytokine pathway repair, immune stimulation and dis-inhibition offers the best option for reconstituting an effective, long-term, immune counter-attack, thus converting the cancer into a "chronic disease" or a durable remission.

The by-line for the Society for Immunotherapy of Cancer (SITC) is, "Yes, we said cure". While it is very true that many patients have achieved a durable remission using immunotherapy, it is my experience that many more patients can realize this goal if we pay specific attention to the pattern of damage to the infrastructure of the immune system. By identifying and addressing the issues of immune suppression that lead to anergy, patients can have a more robust immune response with less side effects, thus leading to a higher quality and quantity of life. Anecdotal evidence-based science is but a place to start but, to make this a consistent reality, systematic and methodical clinical research is required. We have many tools available to aid in the process of immune reconstitution and tumor targeting; now, a comprehensive clinically based algorithm is what is needed to make the promise of onco-immunology an everyday reality.

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CONFLICT OF INTEREST STATEMENT

I have no conflicts of interest to report.

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