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Review Article

Therapeutic Vaccination against Cancers - A Conceptual Overview with Updates on the Immunological Approach

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Article Information

Received date: Aug 21, 2015
Accepted date: Oct 30, 2015
Published date: Nov 16, 2015

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Cancer immunotherapy has now finally made its way and entered a new era, after decades of intensive searching of a cure for the incurable. Current attentions are particularly drawn by the very promising outcomes from a series of experimental and clinical studies recently concluded [1], having tested and verified the "Immune Checkpoint Blockade" working hypothesis initially proposed by Dr. James Allison nearly 20 years ago [2]. The next central question is about how to extend or maximize the therapeutic and survival benefits for greater numbers of patients, and of different cancer types. This may be achieved by further identifications of new target checkpoint inhibitors, emphasizing more on the tumor-specific antigenic signals, and through combination with the therapeutic vaccination approach in particular. Here, by joining in the discussion, I intend to start with direct reference to various basic yet constantly evolving concepts based on which vaccination against neoplasm has been developed along, and now progressing towards.

The Concept of Vaccination

Vaccination against illness is conceptually not just an old but ancient medical practice in human history [3]. The significance and great potential attached with were however not widely or formally appreciated until much later, starting late 18th Century after Dr. Edward Jenner in particular had proven its protective effects against Smallpox infection. He demonstrated successfully then (1796), and in a more scientific way we now understand, the prevention of this highly contagious Smallpox (Variola) human disease by inoculation of individuals alternatively, and more safely, with its bovine analog which caused Cowpox (Vaccinia). In particular, this was done even long before virus as a disease causing infectious agent was first identified a century later (Dmitri Iwanowski, 1892). Such a conceptual advance is undoubtedly one of the greatest medical discoveries in human history. It has led to the eradication of this fatal disease, officially announced by the World Health Organization (WHO) in May 1980. The very concept has since been adopted and widely applied thereafter against different types of infections too, preventing illness and death of millions each year on the planet.

Importantly, the Jenner's discovery has laid down the very basis of Immunology subject-wise. His idea of vaccination has later also been further extended immunologically for the prevention and treatment of other types of diseases too, including cancers.

Evidence of Natural Immunity against Cancer

There has been strong evidence indicating that the host immune system is involved in fighting against cancers. Simply based on clinical or pre-mortem data versus postmortem findings, cancer occurrence rates are often found to be greater than those clinically diagnosed [4]. This might of course depend on the ways and sensitivity of the tests used but, on the other hand, it could alternatively also suggest that tumors might simply 'come' and 'go' without being noticed, hinting the existence of certain mechanisms responsible for their elimination. Indeed, spontaneous regression of cancers has been observed clinically and experimentally too, often with evidence of immune cells infiltrating and/or surrounding the tumors [5,6]. In support of these notions, mice lacking an intact immune system have been found to be more susceptible to carcinogen-induced cancers [7,8]. These together with the facts that cancer occurrence rates are also evidently higher in patients with immunodeficient conditions such as the acquired immunodeficiency syndrome (AIDS) [9], and in individuals at certain stages when their immune capacity can be physiologically low (e.g. neonatal or old age), point to a crucial role of the immune system in controlling cancer development.

Moreover, on an oncological basis, tumors by definition are caused by mutations due to genetic defects and/or environmental triggering of various types including chemical carcinogens, irradiation, and many that can be virus-induced (oncoviruses, e.g. HBV, HCV, EBV, HPV…) too. Whichever of these causes, from an immunological point of view, the mutations may potentially give rise to

the so-called 'neo-epitopes' as part of the Tumor-Specific Antigen (TSA). To which, the host immune system may respond specifically against, or directly to the viral-related gene products (e.g. due to virus insertions), i.e. for their 'foreignness' nature [10,11]. Some of the mutations may also cause downstream aberrant expression of certain normal genes leading to over-expression of their encoded cellular proteins (Tumor Associated Antigens, TAA), i.e. at levels above a threshold, but otherwise below which such immune responses would not be triggered. A phenomenon known as the Graft-versus-Leukemia (GVL) anti-tumor effect, observed in leukemia patients following allogenic bone marrow transplantation, has been used by immunologists as good evidence to argue for the existence of host immune capacity against cancer. It is believed that the recognition of TSA/TAA expressed on the leukemic mutants (blasts) by the immunocompetent allogenic donor T cells can be directly responsible for their subsequent elimination [12].

In brief, there is clear evidence that the immune system can protect the host from cancer development. It does so by constantly monitoring and trying to eliminate any potential cancerous cells or neoplastic components in the body, a mechanism explained by the Cancer Immunosurveillance hypothesis [13]. The establishment of such a theory has however also taken a long time to evolve from its initial concept/idea to the present form [14,15].

Cancer Immunosurveillance, Immunoediting & Vice Versa

The concept of cancer immunosurveillance, based on the initial ideas of Drs. William Coley (1891) and Paul Ehrlich (1909) more than a century ago, was proposed, tested and later theorized by Drs. Macfarlane Burnet and Lewis Thomas in the late 1950s [13,14,16-18]. Its original concept predicted that the immune system could have a protective (positive) role against cancers, by ways to block their initiation and development [17]. Cancer formation was therefore considered as a failure of the immune system in this regard. This has however been wondered and queried in many ways since. An immediate question was then how tumors could still manage to 'sneak through' escaping from the host immunosurveillance in the patients. There had been a series of early attempts though with many conflicting findings, trying to prove for the existence of TSA/TAAs, and to figure out the identity of immune cell types or molecules potentially responsible for cancer rejection. Many were then intrigued by the fact that tumors formed in the absence of an intact immune system were in general more immunogenic than those generated in the immunocompetent hosts [7,8]. These findings suggested that the neoplastic cells could have been differentially imprinted, depending on the immunological microenvironment they were in. As a refinement of the cancer immunosurveillance theory, another layer or layers of interpretations were added to embrace the so-called cancer immunoediting hypothesis. In the revised theory, a cancer immunoediting process proceeding sequentially through different stages, namely "Elimination", "Equilibrium" and "Escape" (3-Es), was postulated [18,19]. According to which, as a result of immunoediting, certain selected cancer cells (variants) could acquire an ability of resistance to their elimination being a real cord of tumor formation. It thus has started acknowledging both of the host-protecting (positive) and tumor-sculpting (negative) actions of the immune system on tumor development [19].

Subsequent findings suggest that there may be even more complex interactions between the host immune system and the tumors, mutually shaping each other, through which the cancer cells could actively suppress the host immune system too. There is now strong evidence indicating that tumors can interact directly with host immune cells in return to block their functions, e.g. through the expression of various immunosuppressive molecules or cytokines [20-27]. It is also highly likely that, as a result of immunoediting, the cancer cells may acquire an enhanced such capacities to do so thus facilitating better their immune escape. Indeed, many TSA/TAA-specific T and B cell clones have been identified in cancer patients, but most of them were found in an unresponsive or anergized state [28,29]. These have prompted further questions since, as to how these TSA/TAA-specific lymphocytes are tolerized or suppressed, what are the intrinsic cellular and molecular mechanisms involved and, most importantly, whether and how these anergized lymphocyte clones can be alternatively switched on or redirected to enhance their anti-tumor potential [3,21,30].

Vaccination against Cancer - The Active Immunological Approach

Prompted by his early idea linking the host immune responses to bacterial infections with those against cancers, the bone surgeon William Coley was again the first (1891) to have proposed and shown that post-surgical bacterial infections, or injection of killed bacteria (Coley's toxin or Coley's 'vaccine'), might help in some way to boost the host immunity against tumors [14]. Such a boosting, though seemingly in a rather non-specific way, can be well explained and experimentally verified by the widely observed additional potentiating effects of the so-called Complete Freund's Adjuvant (CFA). CFA contains inactivated mycobacterial components, unlike its incomplete counterpart (IFA, without the mycobacterial components), used in a conventional vaccination procedure against infections. Indeed, the phenomenon of spontaneous cancer regression has also been observed often concomitant with some kind of infection too [5]. Although there had been concerns about potential adverse effects of Coley's approach, his idea at the time did make conceptually an early start of cancer immunotherapy subject-wise. Ever since, a variety of other ideas and approaches have been proposed and tested in different experimental models as well as clinical trials, all with a sole aim to enhance host immunity against the nascent mutant targets.

The main experimental or treatment modalities of cancer immunotherapy include the use of non-specific immune enhancers, e.g. immunogenic cytokines (e.g. IL-2, IFN-α) or molecules (e.g. antibodies) [31,32]; adoptive transfer of ex vivo expanded/activated autologous or allogenic T or Natural Killer (NK) cells [33-35].; and the development of specific cancer vaccines [30,36-38]. By harnessing the two key features of the adaptive immunity, i.e. antigen specificity and immunological memory, vaccination against cancer is by nature a more active or positive immunological approach. It aims to establish a long lasting and self-propagating immunity in the host and, importantly, with specificity hence better strength against those cancerous mutant cells. Different cancer vaccines of therapeutic and prophylactic types have been developed and tested (for details, please see a recent review by LH Butterfield [38]). These include the conventional vaccination regiments by injecting tumor antigens together with certain immune enhancers or adjuvants, DNA vaccines encoding tumor-specific epitopes pre-identified, and even the use of

live cells such as Dendritic Cells (DC) as an immunogenic cell vector for tumor antigen delivery.

The original idea of DC-based tumor vaccine in particular was prompted by the understanding that DC could be a potent Antigen Presenting Cell (APC) essential for T-cell activation [30]. For their uniquely combined immunobiological properties, DC are believed to be the only cell type capable of activating naïve T cells in vivo, crucial therefore in the initiation of the adaptive anti-tumor immunity [39]. These, together with the fact that DC could be generated in vitro in large numbers [40-42] and readily loaded with either defined or even un-defined tumor antigens (e.g. tumor lysates) [43], have led to the attractive concept of using DC as an immunogenic cell vector for cancer vaccine delivery [30,44-48]. Despite some favorable findings mainly from studies in experimental models, however, clinical applications have thus far been limited by a lack of achievable general efficacy and consistency. Outcomes from many clinical trials had not been met with initial expectations [49,50]. The main obstacle identified among others appears to be the highly immunosuppressive tumor microenvironment, under which DC can be switched phenotypically and functionally to induce tolerance instead of immunity [21].

Nevertheless, some promising results from several recently concluded clinical trials of Sipuleucel-T (Provenge), the first and only human DC-based cancer vaccine approved (2010) by the American Food and Drug Administration (FDA) for the treatment of asymptomatic/minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC) [51], have been demonstrated [52,53]. In these studies, clinical improvement in terms of the overall and/or prostate cancer-specific survival rates appeared to be associated with measurable antibody responses against certain non-targeted (secondary) tumor antigens [52], and a transient increase of circulating eosinophils [53], in the patients. Prophylactic vaccines (Gardasil, Cervarix) against the oncogenic human papillomavirus have also recently been shown to be effective in preventing cervical [37,54]. With recent rapid advances in our understanding of the cellular and molecular mechanisms underlying tumor immune escape and beyond, the field of cancer vaccination is now expected to get a real boost soon.

Insights from Studies of Autoimmune Mechanisms - Immunity against 'Self' & the 'Altered-Self'

Recent findings from studies of the mechanisms underlying autoimmunity, and more importantly, the mechanisms protecting against it, have offered some new insights for our understanding of cancer immune escape.

Chronic or persistent autoimmune-like inflammatory conditions are evidently associated with tumor development. These may trigger neoplastic transformation and through the production of inflammatory mediators to promote cancer cell survival, proliferation and invasion [55,56]. The important question is however about their true intrinsic causal relationship. To prevent autoimmune attack, it is believed that the immune system needs to be 'educated' early in life (thymic selection) [57,58], and continuously through adulthood (peripheral tolerance mechanisms) [59]. During which, cells of the adaptive immune system especially T cells with potential self-reactivity are largely removed or immunologically "silenced". As mentioned above, tumors are by nature clones of mutated cells arisen from the body's own tissues, to which the host immune system is largely tolerized otherwise. Although those mutations occurred in cancers may give rise to TSAs and TAAs, most of these newly derived or "altered-self" neo-antigens are likely to remain low immunogenic when presented to the host immune system [20]. The ongoing inflammatory condition may therefore reflect the desperate attempts of the host immune system to mount anti-tumor responses, being a consequence of the continuous yet largely futile triggering by those poorly immunogenic TSA/TAAs. These may then in return trigger further self-protective mechanisms, i.e. anti-inflammatory responses to limit tissue damage. As the result of such a negative feedback loop, an excessive production/expression of anti-inflammatory or immunosuppressive cytokines (e.g. IL-10, TGF-β) or molecules (e.g. PD-1/PD-1L), followed by the exhaustion of the immune effector cells, may instead lower the ability of the host immune system to mount specific anti-tumor responses. It has also been shown that chronic T cell attack on a tumor could silence the expression of certain TSA through epigenetic alterations [60], a process which influences similarly the development and regulation of autoimmunity too [61]. Understandably, cancer immune escape could thus be related to, and well explained by, the immunological mechanisms underlying self-tolerance. In other words, as an original member of 'Self', tumors (the 'altered-Self') can still benefit from, and be largely protected by, these self-tolerance mechanisms.

Through a better understanding of the detailed cellular and molecular mechanisms underlying self-tolerance versus autoimmunity [62,63], we have gained some critical insights into the mechanisms of cancer immune escape [64]. Most importantly, it has also helped to identify better ways to break more effectively the vicious circle involved in the processes of Cancer Initiation, Chronic Inflammation and Cancer Immuno-escape (Ci-Ci-Ci). Among them, IL-10 in particular has been identified as one of the crucial factors limiting the efficacy of vaccination against tumors [21,64]. By blocking selectively the IL-10-IL-10R signaling pathway, greatly enhanced vaccine efficacy has now been clearly demonstrated in various animal models of liver, skin and lung cancers [21,64,65]. Moreover, findings from these conceptually related studies have also helped to explain why the most effective way to enhance the efficacy of cancer vaccines is by targeting the negative arm of immune regulation, i.e. by tipping the immunological 'balance' but in a positive way.

Recent Breakthroughs in Cancer Immunotherapy - The Concept of Immune Checkpoint Blockade & Further Beyond

Immunology is a subject best coinciding conceptually with the ancient Chinese philosophy of 'Yin' and 'Yang'. The so-called 'Yin-Yang' balancing act is indeed well reflected in every part of the immune system, of both the innate and the adaptive arms [66,67].

T cells, which are crucial for anti-tumor responses, require two essential types of signals for their activation. One is delivered through antigen-specific stimulation (Signal 1), and the other refers to a group of antigen-independent but essential co-stimulatory signals (Signal 2), both of which can be provided by the APC they interact with. Ligation of CD28 on T cells by its ligand (B7) on the APC such as DC has been shown to provide such essential co-stimulatory signals required for the activation of T cells, of naïve T cells in particular. It has subsequently also revealed that the so-called Signal 2 could be of two types too, which determined the outcome of T cells either in

a positive or negative way depending on their mutual balance. The Cytotoxic T Lymphocyte Antigen-4 (CTLA-4) molecule (CD152) is one of the key negative regulators identified, and found to be expressed on T cells following activation [68]. CD28 and CTLA-4 are both members of the immunoglobulin super family, and share high (75%) nucleotide sequence homology. CTLA-4 can also bind with the same ligands (B7-1, CD80; B7-2, CD86) as CD28, but with a much higher affinity (10-40 folds). Upon CTLA-4 ligation, in contrast to that of CD28 however, the T cell will receive an inhibitory signal instead, for its inactivation [68]. Such a balancing act, as a necessary 'brake' to prevent overt immune responses, has been shown to be crucial in protecting the host from self-destructive autoimmune, inflammatory as well as lymphoproliferative diseases [69,70].

Prompted by the cellular and molecular understanding of the 'Yin-Yang' balance involved in T cell co-stimulation and inhibition [66], Dr. Allison came up with his original hypothesis of Immune Checkpoint Blockade, and started testing its implications in cancer immunotherapy. This has subsequently led to the identification of CTLA-4 being 'hijacked' by cancer cells and involved in the immunological mechanisms underlying tumor evasion. In 1996, the group led by Dr. Allison demonstrated for the first time that the use of antibodies to block CTLA-4 could boost anti-tumor immunity in animal models [2]. They showed that injection of the CTLA-4 blocking antibodies alone could significantly enhance the host immunity against murine colon carcinoma and fibrosacoma, including the pre-established tumors of either B7-positive or B7-negative genotype [2]. By combining the use of a tumor cell vaccine expressing a pro-inflammatory cytokine, Granulocyte/Macrophage Colony-Stimulating Factor (GM-CSF), they demonstrated subsequently how a further enhancement of such immunity, mediated largely by cytotoxic T cell killing, could be achieved in an otherwise highly tumorigenic but poorly immunogenic melanoma mouse model [71]. Most importantly, these findings from animal studies have later led to the development of the monoclonal antibody (ipilimumab) against human CTLA-4 and tested in a series of clinical trials. Among them, the first randomized Phase III clinical trial using ipilimumab was published in 2010 [72], which showed promising overall survival benefits and durable responses though in a subgroup (20%) of patients with metastatic melanoma. This together with further verification from other related studies has led to its approval by FDA in 2011. Under the very concept, and again based on preclinical findings in animal models, several other key molecular switches including the programmed cell death protein 1 (PD-1) on activated T cells, and the PD-1 ligands (PD-L1, CD274/PD-H1; PD-L2, CD273/PD-DC) on many cell types including tumor cells, have also been identified. The ligation of PD-1 can limit the functions of T cells involved in the mechanisms underlying self-tolerance/autoimmunity versus host immunity against cancers [73-76]. Thereafter, various human or humanized antibodies against PD-1 (nivolumab/BMS936558, pembroluzimab/lambrolizumab) and PD-L1 (BMS935559, MPDL3280A) have been designed, and developed for targeting the PD-1/PD-L1 axis/pathway. The immune enhancing effects of these antibodies have recently been evaluated in a series clinical trials (see review in [77]), which showed promising clinical responses (tumor regression) though again of different degrees, in multiple human tumor types including advanced melanoma, prostate, colorectal, renal and non-small-cell lung cancers [78-81].

These clinical verifications of the Immune Checkpoint Blockade working hypothesis have now clearly opened up a new horizon in the field of cancer immunotherapy, offering hope for many with a disease otherwise classified as irremediable by conventional therapies [23]. In celebrating these achievements, by the end of 2013, the Science magazine selected this very topic and branded it as the "Top Breakthrough of the Year 2013" [1]. Since then, more and more reports have been filed with positive results supporting the concept, and the enthusiasm has been running higher each day. On the other hand, however, this therapeutic approach so far in general appears to have benefited only a subgroup or fraction of patients, and of those with long term remission in particular. Current attention is now focused on how to broaden the clinical benefit for greater number of patients, and of different cancer types. In order to achieve this further, a number of strategies have been proposed and are now being developed. These include the identification of predictive or prognostic biomarkers for patient selection, and rational design of combination therapies of various types.

For the understanding that the CTLA-4/B7 and PD-1/PD-1L mediated T cell inhibitory pathways are through separate and non-overlapping mechanisms, a concept of combining the CTLA-4 and PD-1 blocking agents (ipilimumab, nivolumab) has been tested first in patients with advanced melanoma in a clinical trial (Phase I), which demonstrated very impressive objective responses in more than 50% of patients, most of them with a tumor reduction of 80% or above [82]. There are now many ongoing studies testing the combinational approaches in other cancer types with preliminary but promising results too [23,77]. In this very direction, perhaps we also ought to consider the combinational approach in a wider spectrum to embrace certain key soluble mediators, such as IL-10 and IDO (indoleamine 2,3-dioxygenase), potentially involved in the processes [21,83]. PD-L signaling has previously been shown to induce the expression of IL-10, indicating that this immunosuppressive cytokine may serve as a down-stream molecule involved in the PD-1-mediated immune regulation [84]. In another study, it has also been demonstrated that IL-10 and PD-L1 could operate through distinct pathways to suppress T-cell activity during persistent viral infection [85]. By targeting these molecular switches of multiple types, and through combinations with conventional cancer therapies such as chemotherapy, radiotherapy and also post-surgical operational therapy, better clinical outcomes are now widely anticipated. Another area with great potential is to apply the very concept in combination with the vaccination approach, to focus more on the antigen-specificity and immunological memory too. This together with the possibility to identify Tumor-Specific Mutants (TSA) with high immunogenicity through immuno-epitope mapping [86], higher impact is now also expected timely upon further clinical translation. The ultimate aim is to maximize the clinical benefit and, possibly, to find a real cure for cancer in the future.

Concluding Remarks: Vaccination against Cancers & Its Near Future Prospective

In summary and in brief, through a better understanding of the cellular and molecular mechanisms underlying autoimmunity versus tumor immunity and its regulation, it has greatly advanced our knowledge about the complex tumor immune escaping strategies. It has also helped to explain why the most effective way to enhance host immunity against cancer is by targeting the negative arm of immune functions. By applying clinically the Allison's concept of Immune

Checkpoint Blockade and beyond, it is now anticipated with high optimism that the field of cancer vaccination is to be revolutionized and getting a real boost soon.

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