Review Article

Is it Time to Reconsider and Re-Strategise B Lymphocyte Based Immunotherapy?

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Introduction

The present scenario of pandemic era has witnessed milestone development in the field of immunotherapeutic and vaccine engineering. It has evoked a breech in the routine therapeutic strategies that was conventionally followed. The new outlook in the immunological aspect of major diseases as helped to re-focus back on to the basic immune responses associated with innate response against disease prevention and progression. The current trend to re-strategize the treatment options for patients suffering from cancer in the light of immunotherapy has gained its importance. Recently, immune-therapeutic has gained a great interest in treatment of Oral Squamous Cell Carcinoma (OSCC). The T-cell based immune targeted approach of T-cell based therapy, CAR-T (chimeric antigen receptor) and its success has nailed its best attempt in immunotherapy of Head and Neck Cancer (HNSCC) [1,2]. However, the role of humoral response against the tumor especially of B lymphocytes has not gained its due importance for many reasons. The present situation on the other hand is more encouraging to attempt and utilize the vast potentiality of the B lymphocyte especially the antigen and antibody associated immune response.

Role of B Lymphocyte - Debatable

The role played by B lymphocyte in the tumor microenvironment is still at debate. This is mainly associated with the bidirectional response of B lymphocytes in the tumor microenvironment. Both the pro-tumorogenic and anti-tumorogenic response of B lymphocytes remains controversial, as the literature evidence to support both is limited. Generally, the pro-tumorogenic response of B lymphocytes include mainly the production of various cytokines and interleukins (ILs), especially IL-35, transforming growth factor-beta (TGF-β) and IL-10, that aid in tumor progression [3,4]. The B cell subtype of regulatory cells (Bregs) tends to promote metastasis. The B lymphocytes stimulate secretion of various angiogenic and pro-inflammatory factor especially, secretion of IL-8 and vascular endothelial growth factor that promote angiogenesis and tumor growth [5-7]. The presence of chemokine CXCL-13 is considered closely as a contributing factor for tumor progression along with various lymphotokins such as STAT3 signalling pathway and nuclear factor-kappa B [8-10]. Mature B cells are divided into three main subsets: B1- B cells, mainly found in peritoneal and pleural cavities; B2 or follicular (FO) B cells, that is the most abundant and are located in the B cell areas of lymph nodes, Peyer’s patches and spleen; Marginal Zone (MZ) B cells, located in the marginal sinus of the spleen [11]. B cells of different subsets vary in terms of their location and in the way they are activated in a T-dependent or a T-independent way. The studies conducted to evaluate the role played by the B lymphocytes in OSCC is gaining wide acceptance. For instance, the most recent study conducted by C. Phanthunane et al (2021) [12], study, using multiplex in situ immunofluorescence and computational image analyses of 138 patients with T1-T2 primary oral-tongue squamous cell carcinoma, observed a high density of CD20 cells that clustered together in the IM-S regions. Notably, it introduced the term of CD20 Cluster Score (a score that combines the number of CD20 cells within 20 μm radii of CD20 as well as CD4 cells, which probably yielded a significant association with OS (overall survival), DFS (disease free survival) and local recurrence rate. It is mostly pronounced in cases of low densities of CD20 cells at IM (invasive margin)-S (surface) regions. The study concluded that the presence of stromal clusters of B-cells together in the IM-S regions. Notably, it introduced the term of CD20 Cluster Score (a score that combines the number of CD20 cells within 20 μm radii of CD20 as well as CD4 cells, which probably yielded a significant association with OS (overall survival), DFS (disease free survival) and local recurrence rate. It is mostly pronounced in cases of low densities of CD4 cells at IM (invasive margin)-S (surface) regions. The study concluded that the presence of stromal clusters of B-cells together with CD4 T-cells at IM, which yields the so-called CD20 Cluster Score, acts as a strong independent prognostic factor in early-stage oral-tongue cancer. The other gathered data obtained from various studies Tsou P et al (2016), [13], Lao X M et al (2016),[14] and...
Wirsing A M et al (2018) [15], study results suggested the anti-tumor response of B lymphocytes in the tumor microenvironment. This includes secretion of antibodies, presentation of tumor antigen to adjacent T-cells, and production of immune-potentiating cytokines, such as IFNγ and IL12. [16-20], B cells can associate with T cells and organize in Tertiary Lymphoid Structures (TLS) within the tumor, where it is believed that naïve T cells is usually activated, [21], which majorly highlights the potential role of B cells in modulating anti-tumor immunity. In the majority of cancer types, the infiltration of B cells is often associated with a good prognosis.

On the other hand, B lymphocytes, considered to mediate a pro-tumorogenic effect through induction of neovascularization, becoming regulatory B-cells (Bregs) is considered to cause progression of tumor to distant sites. This was suggested from the results of the study conducted by Zhou X, et al. (2016) [22]. The other studies conducted by de Viscer KE, et al. (2005) [23] and Ammirante, et al. (2010) [24], suggested the production of immune-suppressive cytokines, such as IL10, IL-35, and TGFβ would promote the pro-tumorogenic response in the tumor microenvironment. This tends to deregulate the tumor process. The study results of Wouters MCA, et al. (2018) [25] and Gentles A J, et al. (2015) [26], contradicting pointing out that tumor infiltrated B-cells and B-cells associated genes expressed in cancers tends to give a negative prognosis or even no effect on patients’ survival. The other factor that often promote pro-tumorigenic response include Granzyme B that when transferred to T cells, tends to degrade the T cell receptor ξ chain without inducing T cell apoptosis. Lymphotoxin usually activates non-canonical and canonical NF-κB signalling and STAT3 usually provides inhibitory effect of B cells and survival signals to tumor cells.

B Cells and Tumor Microenvironment

To determine the role of B lymphocytes in tumor microenvironment, it requires to first evaluate the initiation of the tumor process from its inception. The pre-malignant state general transforms into a fully transformed tumor state through a steady or rapid escalation seen in both cellular and molecular elements. The role of B lymphocytes is critically expressed in pre-tumor environment or pre-malignancy state. However, there is only restricted data on the actual role played by B lymphocyte in the precancerous environment. The study results of Auclair and Ellis, et al. (1996) [27], done on the tongue lesions showed an increase in CD4 and B cells, but not in HLA/DR positive cells. Whereas, Ito, et al. (1999) [28], had no similar results of infiltrative cells. The increase in immune cell infiltration with progression of oral epithelium from hyperkeratosis to dysplasia and carcinoma is noted by G Gannot, et al. (2002) [29]. The results of the study however, revealed that in the tongue lesions, the changes in the epithelium from normal appearance to transformed were accompanied by a corresponding increase in the infiltration of CD4, CD8, CD14, CD19+20, and HLA/DR positive cells. The most significant change was an increase in B lymphocytes in tongue lesions, that was in accordance with the transformation level.

B Cell-Based Cancer Therapeutics

The future perspectives to introduce B lymphocytes into therapeutic protocol could aim for either suppressing or enhancing tumor specific response of B cells. The successful illustration contributed by Biagei, et al. (2005) [30] as the first clinical trial in the approach cancer vaccine, used CD40 cells as cellular adjuvant in cancer regression therapy. The vaccine composition included transduced autologous leukemic B cells isolated from patients diagnosed with Chronic Lymphocytic Leukaemia (CLL) combined with an adenoviral vector that contained human CD 40L gene. It was then administrated to 9 patient subjects. Out of the same, three patients demonstrated with positive results through 50% reduction in the size of the lymph node. Unfortunately, the drawback of the study was that the study induced T-cell response, which could not extend over the long-term tumor induced suppression. This study was the first-ever favourable proof in implementing B-cell-based immunotherapy and its role played in generating an antitumor response through the activation of T-cells directly.

The critical challenge that is usually faced would include in isolating and segregating each component of the tumor microenvironment and studying them separately. It has been described that B cells could help to predict response to some therapies, or Immune-Related Adverse Effect (irAE). Additionally, B cells can directly impact the efficiency of some cancer treatments. Efforts have been made in order to target these cells, either through their activation or, on the contrary, through their depletion/inhibition. Current therapies can influence B cells functions, leading to resistance to immunotherapy by the activation of Breg, or release of ATP which is converted into adenosine by B cells through extracellular vesicles, leading to the inhibition of T cells. Activation of antibody production contribute towards the adverse side effects of immunotherapy. On the other hand, other therapies activate anti-tumoral activities of B cells either by activating B cells with anti-tumorigenic functions or by inhibitions of Bregs.

However, the B Cells has an implicatory role in immune-suppression and resistance during cancer treatment. The experimental studies conducted in mice is of immunosuppressive B cells expressing IgA, IL-10 and PD-L1 in the Transgenic Adenocarcinoma Of The Mouse Prostate (TRAMP) model of metastatic Prostate Cancer (PC) in humans. In study subjects of patients, these cells are found to be enriched in therapy resistant patients. Affara N.I, et al. (2014) [31], study conducted on chemotherapy patients implied that the Squamous cell carcinomas (SCC) were highly enriched in CD20+ B cells, which are at least in part responsible for the resistance to platinum- (cisplatin and
carboplatin) and taxol-based (paclitaxel) chemotherapy as their removal using an anti-CD20 antibody prevents this resistance [32]. As opposed to chemotherapy, targeted therapy involves the modulation of specific pathways involved in oncogenic processes, such as signalling kinases like homolog B (BRAF) and MAPK (mitogen-activated protein kinase)/ERK kinase (MEK) inhibitors are widely used. Despite the high level of initial response rate, a very high percentage of patients tend to develop resistance [33]. Somasundaram R, et al. (2017) [34], demonstrated that tumor-associated B cells induce resistance through these inhibitors in vitro through the secretion of IgF-1 and confirmed an increase of CD20 and IgF-1 gene expression in tumor of resistant patients. Immunotherapy constitutes the reactivation of the immune system which is mainly immunosuppressive in the tumor microenvironment. Despite the fact that immunotherapy has revolutionized the field of oncology, a high proportion of patients still don’t benefit from this advanced modality of treatment.

B Cell-Based Cancer Vaccine A Possibility

The activation of B cells appears to be a promising approach, and several strategies have been developed in order to fully unleash the anti-tumor potential of B cells. B cell-based cancer vaccines consist in the stimulation of B cells in order to activate cytotoxic T cells against tumors. The use of CD40 stimulation has been widely studied the ligation of CD40 with its ligand CD40L induces the expression of co-stimulatory molecules and cytokines. CD40-activated B cells gain the potential to promote the activation of naïve and memory T cells [35]. The other great advantage associated with CD40-activated B cells, that they are not sensitive to the immunosuppressive microenvironment [36]. They can still, efficiently reach secondary lymphoid organs when injected in vivo, where they can efficiently activate T cells [37]. The potential of these CD40-activated B cells has been validated and reported by Rossetti, R.A.M (2018) in vivo in models of Human papillomavirus 16 (HPV16) E6 and E7 expressing TC-1 tumor [38], which is most commonly linked with viral etiology of OSCC (Oral Squamous Cell Carcinoma). Other tumors include B16-F10 melanoma, E.G7 lymphoma [39], 4T1 breast tumor metastasis [40], sarcoma [41] and in spontaneous non-Hodgkin's lymphoma in dogs. [42]. In conclusion, CD40-activated B cells represent an interesting tool in cancer immunotherapy, and further studies, including clinical trials, should be performed to confirm this potential. The other important class of molecules that can also be stratized include Cytosine guanine dinucleotide-oligodeoxynucleotides (CpG-ODN), is a Toll-like receptor 9 (TLR9) ligand that can also be used to activate B cells. The other signalling pathway through “fusiokine” GIFT4, is a fusion between GM-CSF and IL-4 cytokines which cluster the respective receptors on B cells and leads to the activation of Janus kinase (JAK)/STAT pathway in the experimental study was reported by Deng, J, et al. (2014) [43]. This clustering triggers the proliferation of B cells and their differentiation from naïve B cells to activated helper B cells up-regulating CD19, CD25, CD27, CD40, CD69, MHC class I and II, CD80, CD83 and CD86 expression. These activated B cells act as APCs, secrete cytokines and express co-stimulatory markers, leading to the activation of T cells into cytotoxic T cells.

The other significant approach is through tumor-derived autophagosomes enriched in defective ribosomal products (DRibbles) that is usually captured and internalized by B cells. These DRibbles contain tumor specific antigens, and lead to the activation of B cells associated with increased expression of MHC class I and II molecules, CD86 and CD40. These cells can the stimulate tumor specific T cell response. The experimental evidences conducted in mice bearing lymphoma and hepatocellular carcinoma induce the control of tumor growth. Antibodies produced by B cells are also considered for therapeutic efficiency. Several examples of antibody-based therapies can include various clinical outcome, some of them targeting directly on tumor antigens. Anti-CD20 in B-cell related lymphoma/leukemia, anti-HER2 in breast cancer and other antibodies have immunomodulatory effects such as the one used for immune checkpoint blockade (anti-CTLA4, anti-PD-1/PDL-1, anti-LAG) [44,45].

Conclusion

B cells are usually, overlooked for their role in the anti-tumor immunity. However, they tend to play a fundamental role in the TME, where they can either enhance an efficient immune response by activating cytotoxic T cell response, producing anti-tumor antibodies and cytokines, or inhibit immunity and participating in cancer immune evasion [46-48]. These contradictory activities are achieved by different B cell populations, which can be induced or on the contrary inhibit in the TME. In this context, efforts should be done in order to either activate B cells with anti-tumor activities or inhibit the regulatory B cells. In fact, a better understanding of the B cell sub-populations appears to be essential in order to be able to develop new strategies to target them specifically for the targeted therapy. The identification of specific signalling pathways, expression of cell surface markers and immune checkpoint molecules, or dependency to cytokines could be useful in this approach. In this context, it is clear that more B cell markers should be included in order to distinguish it from other B cells populations. The recent arrival of novelities like mass cytometry or single-cell RNA-sequencing, has made the fine analysis of immune sub-populations possible. Unfortunately, the majority of the analyses have investigated T or myeloid cells; with very little focus on the B cell populations, though they represent an important fraction of the immune cells [47-55]. The use of these powerful tools should be applied to B lymphocytes, as they remain mysteries that need to be solved in order to fully develop their potential in the fight against cancer. The present circumstances, the recent bioengineering have revoked back to the potential of
natural immune response that is extensively used in vaccine engineering and other therapeutic methods to determine a better clinical outcome.

References


