Can B- cell based immunotherapy be our new perspective to exit cancer?

Stepping on to a new decade, it is a great opportunity for all of us to rethink and reconsider our conventional strategies of patient diagnosis and conventional treatment modalities. Our extended research prospective, if widened over its present horizon, can definitely readdress our current system of therapeutic strategies. It can undoubtedly claim a better prognosis and improved survival rates for our patients with decreased burden of morbidity.

Apparently, the concept of immunotherapy has only gained its acceptance very recently. The concept of "immunosurveillance"[1] is the ability of the body to recognize self and nonself. Both natural and acquired immunity have undoubtedly proven their role in check and balance system against tumor progression. The pivotal role of both B- and T-cells has been widely discussed in hope to rediscover a novel possibility in finding a natural cure. Researchers have optimistically refocused their attention and interest toward this concept. With the exemplified results and evidence, T-cell immunotherapy has hit its target and is now considered as a credible therapeutic entity. The recent introduction of targeted T-cell based therapy, CAR-T (chimeric antigen receptor) and its success has nailed it's best attempt. Definitely, it has already evoked a fresh interest for the researchers to contribute and experiment furthermore in this field of interest.[2,3]

ROLE OF B-LYMPHOCYTE – STILL AT CONTROVERSY!!

However, the role of B-lymphocyte in tumor microenvironment is much less discussed or almost neglected for many reasons. Reconsidering the potentiality of B-lymphocyte, it could redefine the role of B-cell in tumor microenvironment. The role of B-lymphocyte is yet considered as a controversy by various authors and researchers. Surprisingly, both the characteristic role of B-lymphocyte as pro-tumorigenic and antitumorigenic entity can be reconsidered to improvise our existing immunotherapeutic strategy.[3] The antitumorigenic response of B-lymphocyte is mainly based on the production of tumor-specific antibodies.[4,5] As in any other regular pathogenic infection, it evokes the patient's innate immunity to resolve the infection by itself through the recognition of antigen and producing antibodies against it. It is mediated through the pathway of IgG-dependent antibody production.[6] And thereby, the body develops a permanent resistance toward the causative agent. The production of tumor antigen and tumor-associated antigen is also crucial for activating the immune system.

Normally, the IgG binding to bacteria makes it more visible for removing both the pathogenic organism and the toxic products secreted by it.[6] The potent cytotoxic function of Ig can be therapeutically targeted to produce tumor-specific cytotoxic antibodies and enhance the tumor response of tumor. The evidence based data obtained through clinical trial on human lymphoma patients, when treated with Rituximab, proved with a convincing evidence of FcYRs being involved in the therapeutic pathway.[7,8]

Tumor-infiltrating B lymphocytes (TIL-Bs) are considered as better antigen-presenting cells (APCs) of our immune system.[10] Activated B cells can serve as APCs for both $CD4^+$ and $CD8^+$ T-cells; the prime advantage over the dendritic cells (DCs) is that they can selectively present the cognate Antigen (Ag) collected, through the Surface Immunoglobulin (Ig) Molecules, even at a minimal concentration of Ag.[9] However, DCs are considered essential for the initial T cell priming, whereas B cells may promote T cell expansion and memory formation.[11-13] Consistent with the findings of ovarian cancers, it establishes the fact that lack of intratumoral DCs contains TIL-Bs in close reaction with T cells. This establishes the complex and powerful interaction between both.[11]

B cells can also promote differentiation of Th1, Cytotoxic T-cell and can aid in better T cell mediated immune response. The release of Granzyme B can directly kill cancer cells and support the tumor suppressive actions of B-cells in tumor microenvironment.[14] Release of IFNα can stimulate TLR agonist to kill tumor cells through the TRAIL signaling activity.[15] Notably, these were, however, not approved in murine prostate cancer study.[16]

CAN PRO-TUMOROGENIC RESPONSE BE A REAL THREAT??

On the other hand, the pro-tumorigenic responses include the production of various cytokines and interleukins (ILs), especially IL-35, transforming growth factor-beta (TGF-β) and IL-10, which aids in tumor progression. The various B regulatory cells subtypes also promote metastasis

through the activation of various angiogenic and pro-inflammatory factors. The secretion of IL-8 and vascular endothelial growth factor can promote angiogenesis and tumor growth.[17-19] The presence of chemokine CXCL-13 is closely contributed as a factor for tumor progression along with various lymphotoxins such as STAT3 and nuclear factor-kappa B.[20-24] Evidence of bladder metastasis holds determinable in the role played by B-cells in the metastasis of tumor progression to various sites of the body.[25,26]

The tumor-induced proliferation of B-cells can directly have a role in the regulatory activity of myeloid-derived suppressor cells, which suppresses the cytotoxic activity of T-cells by downregulation of the production of $CD4^+$ and $CD8^+$ cells. Tumor Bregs are also closely associated with the activity of TGF-β, which suppresses the antitumor response through the upregulating activity of reactive oxygen species and nitric oxide production.[27] Studies conducted on mice with implanted murine mammary tumor demonstrate the association of B cells with the recruitment and proliferation of Treg cells and reduced recruitment of $CD49^+$ and $CD8^+$ cytotoxic T lymphocytes (CTL) within the tumor microenvironment.[27-30]

B cells play an important role in adaptive immune response which is widely recognized through the pan markers of CD19 and CD20.[27] However, the heterogeneity in B-cell function does not appeal both for its pro-tumorigenic and antitumorigenic responses. Therefore, the clinical information and standardisation of immune based staining methods and procedures are to be standardised first .establishing the role of B-lymphocytic activity in tumor microenvironment from studies conducted prior would be a due necessary to start with. Methodological re-evaluation of the same can also help in deriving certain discrete conclusions to proceed further with the future research aspects of the same entity. The immune escape of a tumor through the PD-1/PD-L1 (programmed cell death-1 / programmed cell death Ligand -1) activity is also to be critically recommended to be discussed in reversing the immune escape mechanism of tumors and improving anticancer immune responses.[31-33] A study conducted to understand the clinicopathologic implication of mi-197 and PD-L1 analyzed the number of recruited TILs and the correlation with various clinicopathologic features and prognosis in oral squamous cell carcinoma patients.[34]

HOW FAR CAN THE RESEARCH ROAD TAKE US ??

The variable dynamic nature of B-lymphocyte can be selectively activated or suppressed through targeted therapy. Illustration of Biagei *et al.* is the first clinical trial cancer vaccine that used CD40 cells as cellular adjuvant in cancer regression therapy.[35] This involved vaccine contained transduced autologous leukemic B cells isolated from patients diagnosed with chronic lymphocytic leukemia (CLL) combined with an adenoviral vector that contained human CD 40L gene were administrated to 9 patients. Out of which, 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 favorable proof in implementing B-cell-based immunotherapy and its role played in generating an antitumor response through the activation of T-cells directly.[36]

Therefore, researches carried out to determine the actual functionality of B-lymphocyte in tumor microenvironment are highly critical and recommended.[37] There is a need in identifying the pro-tumorigenic B cell markers to elucidate a criterion in isolating them and separating them within the tumor microenvironment. Identifying the genes of immune resistance and suppressing them through targeted therapy can also be considered at a genetic-level study. Identifying the genes of tumors assosciated with immune –resistance and suppressing them through targeted therapy can also be considered at a genetic level study.

The selective knocking off pro-tumorogenic responses of tumor can also be an integral part of genetic work up study. It may help in switching of cancer susceptibility from an immune-resistant to an immune susceptible state. In turn can be a possible way out for the most favourable outcome desired in immunotherapy protocols.

Possibilities of B-lymphocyte associated with immune therapy can be fairly considered as a treatment option or as an adjuvant therapeutic aid in the present scenario. The factor of feasibility if isolated within the patient's own body can also play a very determinable role in avoiding the chances of foreign cell-based immunoreactions and better systemic revival of patients through innate immune response. This could also reassure the survival rate and improve the quality of life after regular treatment protocols.

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Anela Thomas, Smitha T

Department of Oral Pathology, VSDC, Bengaluru, Karnataka, India
E-mail: smitha.iaomp@gmail.com

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