Applications of Immunoglobulin Isotypes in Cancer Immunotherapy - A Review

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Abstract: Immunoglobulins form a very crucial part of cancer immunotherapy. Stimulating host tumour-antigen-specific immune responses such as induction of antibody-dependent cellular cytotoxicity, promotion of antibody-targeted cross-presentation of tumour antigens, activation and degranulation of immune effector cells and complement based cell destruction is the most essential role of immunoglobulins in cancer treatment. This review discusses the potentials of the different isotypes of antibodies - IgG, IgE, IgA and IgM in cancer therapy. It also gives insights of current treatment modifications and combinations which can further be studied in order to prolong and amplify immune responses to increase the clinical benefits of antibody therapy for human cancer.

Index Terms - Cancer Immunotherapy, antibodies, IgG, IgE, IgA, IgM.

I. INTRODUCTION

Immunotherapy has great potential in treating different types of cancer. Different immune components have proven to show varying effect in cancer treatment. Use of blocking antibodies to cytotoxic T lymphocyte antigen-4 (CTLA-4), use of High-dose IL 2 reported as immunotherapy capable of mediating a long-term and complete response in patients with advanced melanoma and renal cancer, targeting programmed cell death protein 1 (PD-1), use for different types of antibodies to name a few [1,2].

Paul Ehrlich had proposed the use of antibodies for selective targeting of tumour cells [3] and this theory was enhanced by the advent of humanized and fully human monoclonal antibodies which increased the specificity to the target [4].

Out of the five classes of antibodies i.e. IgA, IgG, IgD, IgE and IgM; IgG is most widely studied for immunotherapeutic applications. The Fc region of the immunoglobulin is linked to immune effector functions because of its binding to the FcR (Fc Receptors), and thereby initiating immune responses like complement cascade activation, mediating antibody dependent cell cytotoxicity (ADCC), activation of macrophages, neutrophils, mast cells, etc. [5,6].

Intravenous immunoglobulin (IVIg) is prepared from human plasma and has proven to cause regression in cancer. It is seen to have antitumour effects, suppression of tumour cell growth, induction of IL12 and thereby NK cell activation, and cell cycle arrest at G1 phase [7-9]. This review focuses on the different types of immunoglobulins and their application in cancer therapies.

II. IMMUNOGLOBULIN G

IgG is the most widely present antibody in the blood serum and has four subclasses, IgG1, IgG2, IgG3, and IgG4, which are highly conserved and differ in their constant region. These constant regions are involved in binding to both IgG-Fc receptors (FcγR) and C1q [10]. As explained in Fig.1, the binding of two or more IgG, generally IgG1 and IgG3, molecules to the cell surface leads to high-affinity binding of C1q to the Fc domain, which causes activation of C1r enzymatic activity and subsequent activation of downstream complement proteins, thereby forming the active membrane attack complex MAC formation. Also, the production of chemotactic molecules e.g. C3a, C5a etc. triggers the recruitment and activation of immune effector cells, such as macrophages, neutrophils, basophils, mast cells and eosinophils [11,12]. FcγRs can transduce activating signals through ITAMs (immunoreceptor tyrosine-based activation motifs) for example FcγIIIA and FcγI; and inhibitory signals through ITIMs (immunoreceptor tyrosine-based inhibitory motifs) for example FcγIIIB. FcγI and FcγIIIA are generally as high-affinity receptor expressed by macrophages, DCs, neutrophils, eosinophils, mast cells etc. The binding of IgG antibodies to tumour cells enables the recognition of these targets by immune effector populations that express Fcγ receptors, thereby promoting ADCC and tumour cell destruction [12,13].

Many chimeric IgG monoclonal antibodies are successfully used to target the specialized cancer proteins for example members of the epidermal growth factor receptor (EGFR) family, including EGFR (also known as ERBB1), HER2 (also known as ERBB2), HER3 (also known as ERBB3), and HER4 (also known as ERBB4). Chimeric IgG1 mAb called Rituximab has been developed against Non-Hodgkin lymphoma [14], humanized IgG1 mAb targeting HER2 has been developed against breast cancer [15], human IgG2 mAb Panitumumab has been developed against colorectal cancer [16] to be stated as few examples.
Ovarian cancer is obdurate to chemotherapies currently in use, but immunotherapies that use IgG antibodies, right now in clinical trials, are presenting favorable results. Waldmann’s work [17,18] on the efficiency of Campaths-1H (alemtuzumab) IgG antibody subclasses in complement-dependent immunotherapy of non-Hodgkin’s lymphoma is the basis of the recent use of IgG1 antibody isotope in antibody immunotherapy. The chimeric IgG1 had much more efficacy than other IgG subtypes in complement-dependent hemolysis. It was also the most effective in facilitating ADCC using both human target and human effector cells [18]. All these results propose that IgG1 could be the preferred subclass of IgG for therapeutic applications.

In a few studies, researchers have proved that mIgG injections led to increased expression of TNF-α, INF-γ, and IL-1β in the mice, which in turn led to proinflammatory reaction in the microenvironment of the tumour. IgG also increased the expression of GM-CSF, which stimulates differentiation and maturation of monocytes and granulocytes [19].

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shielding of mice against ovarian cancer growth in two xenograft models of ovarian carcinoma in SCID and nude mice. It was also seen that mice with PBMC and MOv18 survived longer than mice with just PBMC [32,33]. This mechanism of increased efficiency in killing was again linked to the ability of IgE to bind to both FceRI and CD23 as discussed earlier, thus leading to cytotoxic and phagocytic elevation [20,32].

IgE along with eosinophils has shown to have a crucial role in several types of cancers including oesophageal squamous cell carcinoma, gastric cancer, head and neck cancer and colorectal carcinoma [34,35]. Triggering eosinophils by engagement of receptors for cytokines, immunoglobulins or complement lead to the secretion of numerous cytokines [IL-2, -4, -5, -10, -12, -13, -16, -18, transforming growth factor (TGF)-α/β, chemokines etc]. Also, eosinophilic granules contain cytokines, cationic proteins, and other molecules capable of generating reactive oxygen species (ROS) which has many deleterious effects. This eosinophilia is named TATE for 'tumor-associated tissue eosinophilia' [36,37]. FcεRI mediated activation of eosinophils leads to secretion of IL-10, which in turn activates M1 type macrophage to destroy tumour cells [38].

One advantage of using IgE is that, due to its rapid binding to Fce-receptors on cells, it is quickly removed from the circulation, because of which, side-effects due to the short duration of the compound in the bloodstream is seen. Moreover, potential IgE-immunotherapies would be effectively distributed to tumour tissues, as IgE antibodies bound to Fce-receptors on e.g. mast cells can use those cells as shuttle systems to penetrate malignancies and as mast cells are tissue-resident immune cells [39,40]. IgE can also be taken in the form of directed oral vaccine (for mice) [41] under alkaline conditions, which is not possible for IgG. At the same time, one drawback for IgE mediated immunotherapies for cancer is that, recombinant IgE, applied intravenously, always bears the risk of anaphylactic reactions. Thus, the selection of target epitope is of utmost importance [42].

IV. IMMUNOGLOBULIN M

Secreted IgM normally exists as a pentamer but it can also be detected as a monomer. Because of the presence of 10 antigen binding sites, IgM is a powerful agglutinating and precipitating antibody, a strong complement fixing immunoglobulin [43]. Because of its polyvalent (cross-linking) and low-mutation nature, IgM antibodies (less immunogenic) are believed to be the most effective weapons against cancer. The best sources for these types of antibodies are the cancer patients themselves [44]. In the studies by Brändlein et al., antibodies were isolated from patients suffering from lung cancer, pancreatic cancer and colon cancer and labelled as LM-1, PM-1, PM-2, CM-1 and CM-2. When tested in the in vitro system, these antibodies were seen to have inhibitory effect on tumour cell proliferation by inducing apoptosis [44,45].

Another target for IgM based tumour therapy is the TRAIL protein (TNF-related apoptosis-inducing ligand). TRAIL is a trimeric protein that is capable of activating both the intrinsic and the extrinsic pathways for cellular apoptosis [47]. Binding to TRAIL induces the formation of DISC (death-inducing signaling complex) which leads to triggering of the apoptotic pathway via activation of caspase-8 [48]. The IgM antibodies raised against TRAIL receptor 1 (TR1) activated the caspase signal and thus induced strong apoptosis in human tumour cells. This effect was 100 times more efficient when compared to IgG raised against TR1. The higher efficiency was probably because of high valency of IgM that facilitated the crosslinking of the cell surface receptors. Thus, TR1-IgMs may become potential immunotherapeutic agents for cancer therapy [49].

IgM is also an efficient tool for detection of certain cancer targets for example osteosarcoma. During cancer, IgM is prevalent and elevated way before the actual clinical detection of cancer. Natural IgM antibodies to tumour-associated proteins may expand the number of available tumour biomarkers. For example, in osteosarcoma the presence of angiogenin (ANG) is a crucial biomarker but present in less immune immune cells. ANG is normally present in serum, but results demonstrated that the combined biomarker ANG plus IgM in sera of osteosarcoma patients than ANG alone [46].

V. IMMUNOGLOBULIN A

IgA is the predominant immunoglobulin in mucosal secretions, and it serves as first line of defense against pathogens that are ingested or inhaled. Also, it has an important role as second line of defence as it is the second most abundant antibody in serum [50]. The secretory IgA is dimeric in nature and the major receptor binding IgA is FcεRI [52]. It is expressed on neutrophils, eosinophils, monocytes, macrophages, intestinal dendritic cells and Kupffer cells [53]. The activation of the FcεRI can lead to multiple cellular functionalities including ADCC, ADCC, respiratory burst, degranulation, cytokine release and antigen-presentation [51].

IgA has a potential of being used effectively for cancer immunotherapy because of its dimeric binding capacity on tumour cells, and being actively transported into mucosal secretions with the potential for improved targeting of certain carcinomas from the luminal surface [54]. IgA antibodies possess up to five N-glycosylation sites within their constant region of the heavy chain as compared to one site for IgG antibodies. Studies have also proved IgA antibodies exhibiting potent Fab- and Fc-mediated functionalities against cancer cell lines, whereby especially granulocytes are recruited [55]. IgA antibodies can be utilized to complement current therapeutic IgG antibodies due to this ability. IgA is more effective (than IgG) in inducing ADCC of various tumour targets when neutrophils are used as effector cells in many carcinoma and lymphoma cases studies [56]. IgA antibodies can also be used for sites where IgG antibodies can’t be administered or when bivalent bindings, characteristics of IgG antibodies, aren’t adequate for positive immune exclusions of pathogens.

The superior ability of FcεRI of IgA to induce neutrophil-mediated tumour cell killing has now been demonstrated for a multitude of tumor-associated antigens, including HER2/neu (on breast carcinoma), EpCAM (colon carcinoma), EGFR (epithelial carcinoma and renal cell carcinoma), HLA class II (B-cell lymphoma), CD30 (T- and B-cell lymphoma) and carcinoembryonic antigen (CEA) in vitro [57,58].

But, the evaluation of therapeutic IgA antibodies in vivo is difficult because mice do not express FcεRI, which is responsible for cellular cytotoxicity mediated by IgA antibodies. Also, it has a relatively short serum half-life and efficient production systems for IgA is not well established. Because of these reasons, the therapeutic IgA is yet to be instituted [59].
VI. CONCLUSION

As discussed above, the different isotopes of immunoglobulins have varying activity and specificities in targeting tumour cells in vivo and each of them can be exploited for different types of cancers in immunotherapy. Based on the target binding efficiency of the antibodies, IgG has shown effectiveness at low doses against melanoma, colon cancer and breast cancer [60]. Because of the extensive application and higher availability, IgG is targeted as the most commonly studied immunoglobulin in cancer and most of the mAbs developed are of this isotope. IgE’s superior activity of inducing ADCC more efficiently also needs to be explored with different types of carcinomas.

Thus, immunoglobulins are extremely significant in the immunotherapy for cancer. Therapeutic antibodies have characteristics such as low toxicity, target specificity and the ability to activate the immune response of our body. These properties advocate that therapeutic use of antibodies will reach new heights in cancer prevention and treatment. They have already been recognized as the ‘standard of care’ for multiple cancer types such as gastric and colorectal cancer. The validation and identification of new targets, optimization of antibody structure to encourage the augmentation of anti-tumour immune response and exploitation of tumour-host microenvironment will give rise to advances in this field. Also, its effectiveness in being used as a site-specific drug carrier system needs to be explored. Over the next decades, several effective treatments using conjugated and unconjugated antibodies will become available for clinical use.

REFERENCES


