IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Applications of Immunoglobulin Isotypes in Cancer Immunotherapy - A Review

[1]Sruthi Menon, [2]Siddhi Bhutada, [3]Dhruv Bhatia

[1]Assistant Professor, [2]Student, [3]Student

[1]Department of Biotechnology,

[1]Thadomal Shahani Engineering College, Mumbai, India

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 antimetastatic 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

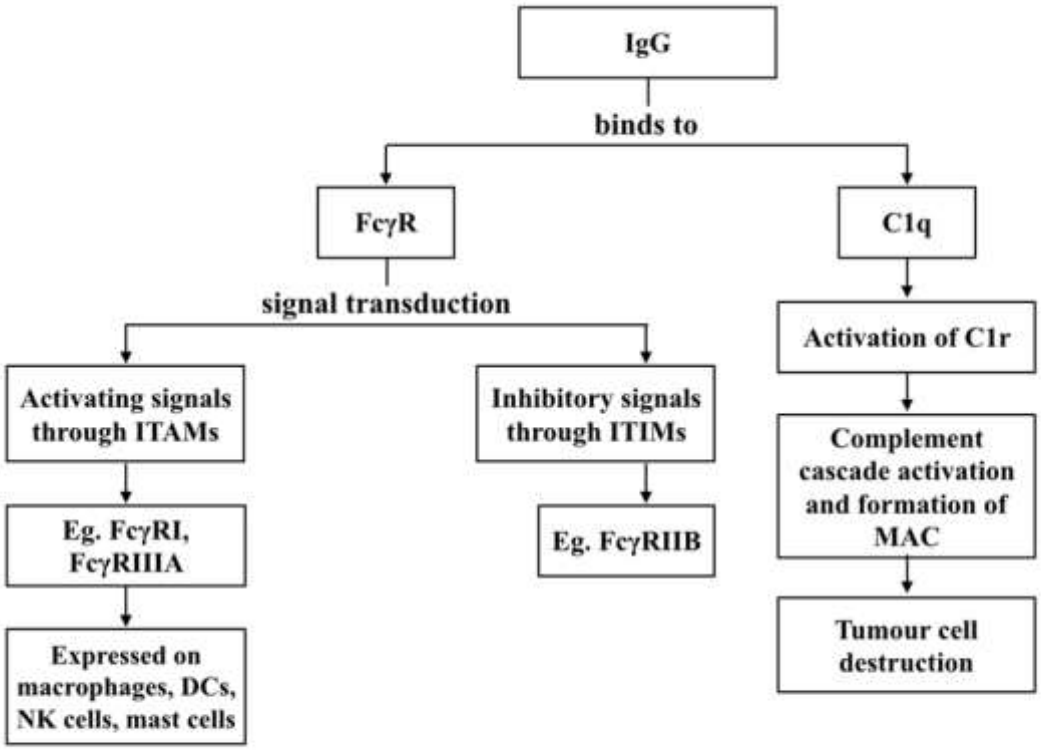
IgG is the most widely present antibody in the blood serum and has four subclasses, IgG1, IgG2, IgG3, and IgG4, which are highly conserved and differ in their constant region. These constant regions are involved in binding to both IgG-Fc receptors (FcγR) and C1q [10]. As explained in Fig.1, the binding 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 FcγIIB. 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].

Most of the monoclonal antibodies that are successfully used against cancer belong to the IgG class, thereby stating the predominant significance of this class of immunoglobulin in cancer therapy.



ITAMs - immunoreceptor tyrosine-based activation motifs; ITIMs - immunoreceptor tyrosine-based inhibitory motifs (ITIMs); DC - Dentritic cells, NK cells - Natural Killer cells; MAC - Membrane Attack Complex

Figure 1: Role of IgG in Tumour cell destruction [11-13]

III. IMMUNOGLOBULIN E

IgE is mostly known for its predominant role in allergic reactions. But in many of the cancer-based studies, it has also shown to have efficiency in tumour cell destruction by developing strategies to specifically target this antibody class towards relevant tumour antigens [20].

IgE is seen to engage both cell surface IgE receptors, FcεRI and CD23 with very high affinity (FcεRI: Ka = 1011 M−1 and CD23: Ka = 108 M−1) and activate several lines of effector cells against tumour cells in vitro and in vivo. Tumours are generally associated with inflammatory responses which causes the infiltration of almost all key players of immune system including B and T lymphocytes, neutrophils, natural killer cells, mast cells, macrophages and eosinophils expressing the IgE receptors [20,21]. Thus, IgE has a superior activity than other immunoglobulins with respect to antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) reactions [22].

Many reports have shown positive results in ovarian cancer treatment using IgE antibody. Ovarian cancer spreads in the peritoneal cavity, which hosts cells such as macrophages, dendritic cells and mast cells. These cells are receptor accepting cells for IgE. The presence of these cells may indicate more anti-tumour immune supervision and stronger retention of antibodies in the tissues [23,24].

Also, allergy and cancer are noted to have inverse relation. Ovarian cancer risk was reduced with allergy and as the number of allergies increased, the risk decreased [25]. A current meta-analysis has established a substantial inverse relation between both hay fever and asthma and colorectal cancer and overall cancer mortality [26]. People with autoimmune diseases or allergies have a decreased possibility of glioma [27,28]. Atopic diseases are also linked with diminished risk of cancer [29,30].

Kershaw et al. demonstrated that the mIgE, targeted against a human colon carcinoma antigen, presented a brief survival advantage to the mice implanted with the human colon tumour cells. [31]. MOv18 IgE, a chimeric antibody, directed against an ovarian tumour antigen, folate binding protein, in amalgamation with human Peripheral Blood Mononuclear Cells (PBMC), was more effective than MOv18 IgG1 in

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 FcεRI 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 Fcε-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 Fcε-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 uttermost importance [42].

IV. IMMUNOGLOGULIN M

Secreted IgM normally exists as a pentamer but it can be also 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 types 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 quantity in serum, but results demonstrated that the combined biomarker ANG–IgM has greater sensitivity and specificity in early diagnosis 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 FcαRI [52]. It is expressed on neutrophils, eosinophils, monocytes, macrophages, interstitial dendritic cells and Kupffer cells [53]. The activation of the FcαRI can lead to multiple cellular functionalities including ADCP, ADCC, respiratory burst, degranulation, cytokine release and antigen-presentation [51].

IgA has a potential of being used effectively for cancer immunotherapy because of its dimer forming ability with improved signaling 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 FcαRI 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 FcαRI, 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 effectivity 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 also 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

[1] M. T. Lotze, L. W. Frana, S. O. Sharrow, R. J. Robb, and S. A. Rosenberg, "In vivo administration of purified human interleukin 2. I. Half-life and immunologic effects of the Jurkat cell line-derived interleukin 2," Journal of Immunology, vol. 134, no. 1, pp. 157–166, 1985.

[2] Jeffrey Koury, Mariana Lucero, Caleb Cato, Lawrence Chang, Joseph Geiger, Denise Henry, Jennifer Hernandez, Fion Hung, Preet Kaur, Garrett Teskey, and Andrew Tran, "Immunotherapies: Exploiting the Immune System for Cancer Treatment", Journal of Immunology Research Volume 2018, Article ID 9585614.

[3] Ehrlich P. Collected studies on immunity. New York: J. Wiley & Sons; 1906.

[4] Adams GP, Weiner LM. Monoclonal antibody therapy of cancer. Nat Biotechnol. 2005;23:1147–1157.

[5] Dunkelberger JR, Song WC. Complement and its role in innate and adaptive immune responses. Cell Res. 2010;20:34–50.

[6] Nimmerjahn F, Ravetch JV. Fcgamma receptors: old friends and new family members. Immunity. 2006;24:19–28. Comprehensive review of FcγR biology and the importance of FcγR interactions in modulating the immune response.

[7] Sapir, T., Shoenfeld, Y. Uncovering the hidden potential of intravenous immunoglobulin as an anticancer therapy. Clinic Rev Allerg Immunol 29, 307–310 (2005).

[8] Kazatchkine MD, Kaveri SV. Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin. N Engl J Med. 2001;345(10):747–755.

[9] Subhadra C, Dudek AZ, Rath PP, Lee MS. Improvement in visual fields in a patient with melanoma-associated retinopathy treated with intravenous immunoglobulin. J Neuroophthalmol. 2008;28(1):23–26.

[10] Vidarsson, G., Dekkers, G., & Rispens, T. (2014). IgG subclasses and allotypes: from structure to effector functions. Frontiers in immunology, 5, 520.

[11] Dunkelberger JR, Song WC. Complement and its role in innate and adaptive immune responses. Cell Res. 2010;20:34–50.

[12] Weiner, L. M., Surana, R., & Wang, S. (2010). Monoclonal antibodies: versatile platforms for cancer immunotherapy. Nature reviews. Immunology, 10(5), 317–327..

[13] Nimmerjahn F, Ravetch JV. Fcgamma receptors: old friends and new family members. Immunity. 2006;24:19–28.

[14] Coiffier B, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med. 2002;346:235–242.

[15] Vogel CL, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol. 2002;20:719–726.

[16] Weiner LM, et al. Dose and schedule study of panitumumab monotherapy in patients with advanced solid malignancies. Clin Cancer Res. 2008;14:502–508.

[17] Brüggemann, M., G. T. Williams, C. I. Bindon, M. R. Clark, M. R. Walker, R. Jefferis, H. Waldmann, M. S. Neuberger. 1987. Comparison of the effector functions of human immunoglobulins using a matched set of chimeric antibodies. J. Exp. Med. 166: 1351-1361.

[18] Dyer, M. J. S., G. Hale, F. G. J. Hayhoe, H. Waldmann. 1989. Effects in vivo in patients with lymphoid malignancies; influence of antibody isotype. Blood 73: 1431-1439.

[19] Ellis LM, Hicklin DJ. VEGF-targeted therapy: mechanisms of anti-tumour activity. Nat Rev Cancer. 2008;8:579–591.

[20] Jensen-Jarolim E, Achatz G, Turner MC, Karagiannis S, Legrand F, et al. AllergoOncology: the role of IgE-mediated allergy in cancer. Allergy. 2008;63:1255–1266.

[21] Brigati C, Noonan DM, Albini A, Benelli R. Tumors and inflammatory infiltrates: friends or foes? Clin Exp Metastasis. 2002;19:247–258.

[22] Gould HJ, Sutton BJ, Beavil AJ, Beavil RL, McCloskey N, Coker HA, et al. The biology of IGE and the basis of allergic disease. Annu Rev Immunol. 2003;21:579–628.

[23] Chan, J. K., A. Magistris, V. Loizzi, F. Lin, J. Rutgers, K. Osann, P. J. DiSaia, M. Samoszuk. 2005. Mast cell density, angiogenesis, blood clotting, and prognosis in women with advanced ovarian cancer. Gynecol. Oncol. 99: 20-25.

[24] Wei, S., I. Kryczek, L. Zou, B. Daniel, P. Cheng, P. Mottram, T. Curiel, A. Lange, W. Zou. 2005. Plasmacytoid dendritic cells induce CD8+ regulatory T cells in human ovarian carcinoma. Cancer Res. 65: 5020-5026.

[25] Mills, P. K., W. L. Beeson, G. E. Fraser, R. L. Phillips. 1992. Allergy and cancer: organ site-specific results from the Adventist Health Study. Am. J. Epidemiol. 136: 287-295.

[26] Turner, M. C., Y. Chen, D. Krewski, P. Ghadirian, M. J. Thun, E. E. Calle. 2005. Cancer mortality among U.S. men and women with asthma and hay fever. Am. J. Epidemiol. 162: 212-221.
[27] Wiemels, J. L., J. K. Wiencke, J. Patoka, M. Moghadassi, T. Chew, A. McMillan, R. Miike, G. Barger, M. Wrensch. 2004. Reduced immunoglobulin E and allergy among adults with glioma compared with controls. Cancer Res. 64: 8468-8473.
[28] Brenner, A. V., M. S. Linet, H. A. Fine, W. R. Shapiro, R. G. Selker, P. M. Black, P. D. Inskip. 2002. History of allergies and autoimmune diseases and risk of brain tumors in adults. Int. J. Cancer 99: 252-259.
[29] Wang, H., T. L. Diepgen. 2005. Is atopy a protective or a risk factor for cancer? A review of epidemiological studies. Allergy 60: 1098-1111.
[30] Wang, H., D. Rothenbacher, M. Low, C. Stegmaier, H. Brenner, T. L. Diepgen. 2006. Atopic diseases, immunoglobulin E and risk of cancer of the prostate, breast, lung and colorectum. Int. J. Cancer 119: 695-701.
[31] Kershaw, M. H., P. K. Darcy, J. A. Trapani, D. MacGregor, M. J. Smyth. 1998. Tumor-specific IgE-mediated inhibition of human colorectal carcinoma xenograft growth. Oncol. Res. 10: 133-142.
[32] Gould, H. J., G. A. Mackay, S. N. Karagiannis, C. M. O'Toole, P. J. Marsh, B. E. Daniel, L. R. Coney, V. R. Zurawski, Jr, M. Joseph, M. Capron, et al 1999. Comparison of IgE and IgG antibody-dependent cytotoxicity in vitro and in a SCID mouse xenograft model of ovarian carcinoma. Eur. J. Immunol. 29: 3527-3537.
[33] Karagiannis, S. N., Q. Wang, N. East, F. Burke, S. Riffard, M. G. Bracher, R. G. Thompson, S. R. Durham, L. B. Schwartz, F. R. Balkwill, H. J. Gould. 2003. Activity of human monocytes in IgE antibody-dependent surveillance and killing of ovarian tumor cells. Eur. J. Immunol. 33: 1030-1040.
[34] Samoszuk M. Eosinophils and human cancer. Histol Histopathol. 1997;12:807–812.
[35] Iwasaki K, Torisu M, Fujimura T. Malignant tumor and eosinophils. I. Prognostic significance in gastric cancer. Cancer. 1986;58:1321–1327.
[36] Munitz A, Levi-Schaffer F. Eosinophils: 'new' roles for 'old' cells. Allergy. 2004;59:268–275.
[37] Ionescu MA, Rivet J, Daneshpouy M, Briere J, Morel P, Janin A. In situ eosinophil activation in 26 primary cutaneous T-cell lymphomas with blood eosinophilia. J Am Acad Dermatol. 2005;52:32–39.
[38] Kayaba, H., D. Dombrowicz, G. Woerly, J. P. Papin, S. Loiseau, M. Capron. 2001. Human eosinophils and human high affinity IgE receptor transgenic mouse eosinophils express low levels of high affinity IgE receptor, but release IL-10 upon receptor activation. J. Immunol. 167: 995-1003.
[39] Fridman WH. Fc receptors and immunoglobulin binding factors. FASEB J. 1991;5:2684–2690.
[40] St John AL, Abraham SN. Innate immunity and its regulation by mast cells. J Immunol. 2013;190:4458–4463.
[41] Riemer, A. B., E. Untersmayr, R. Knittelfelder, A. Duschl, H. Pehamberger, C. C. Zielinski, O. Scheiner, E. Jensen-Jarolim. 2007. Active induction of tumor-specific IgE antibodies by oral mimotope vaccination. Cancer Res. 67: 3406-3411.
[42] Jutel M, Akdis CA. Immunological mechanisms of allergen-specific immunotherapy. Allergy. 2011;66:725–732.
[43] Paolo Casali, IgM, in Encyclopedia of Immunology (Second Edition), 1998.
[44] Brändlein S1, Lorenz J, Ruoff N, Hensel F, Beyer I, Müller J, Neukam K, Illert B, Eck M, Müller-Hermelink HK, Vollmers HP. Human monoclonal IgM antibodies with apoptotic activity isolated from cancer patients., Hum Antibodies. 2002;11(4):107-19.
[45] Stephanie Brändlein, Tina Pohle, Nele Ruoff, Ewa Wozniak, Hans-Konrad Müller-Hermelink and H. Peter Vollmers, Natural IgM Antibodies and Immunosurveillance Mechanisms against Epithelial Cancer Cells in Humans, Cancer Res November 15 2003 (63) (22) 7995-8005.
[46] Yulia A. Savitskaya, Genaro Rico, Luis Linares, Roberto González2 René Téllez, Eréndira Estrada, Norma Marín, Elisa Martínez, Alfonso Alfaro, Clemente Ibarra. Circulating Natural IgM Antibodies Against Angiogenin in the Peripheral Blood Sera of Patients with Osteosarcoma as Candidate Biomarkers and Reporters of Tumorigenesis, Biomarkers in Cancer 2010:2 65–78.
[47] Wiley SR, Schooley K, Smolak PJ, Din WS, Huang CP, Nicholl JK, Sutherland GR, Smith TD, Rauch C, Smith CA et al. Identification and characterization of a new member of the TNF family that induces apoptosis. Immunity 1995; 3:673-82; PMID:8777713;
[48] Kischkel FC, Hellbardt S, Behrmann I, Germer M, Pawlita M, Krammer PH, Peter ME. Cytotoxicity-dependent APO-1 (Fas/CD95)- associated proteins form a death-inducing signaling complex (DISC) with the receptor. EMBO J 1995; 14:5579-88; PMID:8521815.
[49] Xiuhong Piao, Tatsuhiko Ozawa, Hiroshi Hamana, Kiyomi Shitaoka, Aishun Jin, Hiroyuki Kishi & Atsushi Muraguchi (2016) TRAIL-receptor 1 IgM antibodies strongly induce apoptosis in human cancer cells in vitro and in vivo, OncoImmunology, 5:5.
[50] Woof JM, Kerr MA, IgA function--variations on a theme.Immunology. 2004 Oct; 113(2):175-7.
[51] Bakema JE, van Egmond M, The human immunoglobulin A Fc receptor FcαRI: a multifaceted regulator of mucosal immunity. Mucosal Immunol. 2011 Nov; 4(6):612-24.
[52] Murphy K.M. Janeway's Immunobiology. Garland Science; New York, NY, USA: 2011.
[53] Monteiro RC, Van De Winkel JG, IgA Fc receptors. Annu Rev Immunol. 2003; 21():177-204.
[54] M. Dechant, T. Valerius , IgA antibodies for cancer therapy. Crit Rev Oncol Hematol. 2001 Jul-Aug; 39(1-2): 69–77.
[55] Hart, F., Danielczyk, A., & Goletz, S. (2017). Human Cell Line-Derived Monoclonal IgA Antibodies for Cancer Immunotherapy. Bioengineering (Basel, Switzerland), 4(2), 42.
[56] Louise W. Treffers, Toine Ten Broeke, Thies Rösner, J. H. Marco Jansen, Michel van Houdt, Steffen Kahle, Karin Schornagel, Paul J.J.H. Verkuijlen, Jan M. Prins, Katka Franke, Taco W. Kuijpers, Timo K van den Berg, Thomas Valerius, Jeanette H.W. Leusen and Hanke L. Matlung, IgA mediated killing of tumor cells by neutrophils is enhanced by CD47-SIRPα checkpoint inhibition, Cancer Immunol Res November 5 2019
[57] Valerius T, Stockmeyer B, van Spriel AB, Graziano RF, van den Herik-Oudijk IE, Repp R, et al. FcalphaRI (CD89) as a novel trigger molecule for bispecific antibody therapy. Blood 1997; 90:4485 - 4492.
[58] Jantine E. Bakema & Marjolein van Egmond (2011) Immunoglobulin A, mAbs, 3:4, 352-361
[59] Van Egmond M, van Vuuren AJ, Morton HC, van Spriel AB, Shen L, Hofhuis FM, Saito T, Mayadas TN, Verbeek JS, van de Winkel JG, Human immunoglobulin A receptor (FcalphaRI, CD89) function in transgenic mice requires both FcR gamma chain and CR3 (CD11b/CD18). Blood. 1999 Jun 15; 93(12):4387-94.
[60] Xu Q, Zhang Z, Chen Z, Zhang B, Zhao C, Zhang Y, Zhao C, Deng X, Zhou Y, Wu Y, Gu J. Nonspecific immunoglobulin G is effective in preventing and treating cancer in mice. Cancer Manag Res. 2019;11:2073-2085