BirEx JOURNAL
Budapest International Research in Exact Sciences
Medical, Biological, Argiculture, Engineering
Science and other related areas
e-ISSN : 2655-7827
p-ISSN : 2655-7835
http://www.bircu-journal.com/index.php/birex

Study of Thymus and T- cell Development and Tumor Immunology

Sareh Sangy[1], Fatemeh Alsadat Miryousefi Ata[2], Faegheh Miryousefiata[3]

[1]*Department of Biology, Faculty of Science, Shiraz University, Shiraz, Iran*

[2]*General Practitioner, School of Medical Sciences, Tehran Branch, Islamic Azad University, Tehran, Iran*

[3]*General practitioner,Gunesli Erdem Hospital, Emergency department, Istanbul, Turkey*

sareh.sangy@gmail.com, fatemeh.miryousefiata@gmail.com

Abstract: *Monoclonal antibodies have proven to be effective therapeutic agents for a wide range of human cancers. However, unlike other modes of antibody action, the capacity of antibodies to activate tumor antigen-specific immune responses has received less attention. The rationale and evidence for generating anti-cancer antibodies that can induce host tumor antigen-specific immune responses are described in this paper. This can be performed by stimulating the idiotypic network, generating antibody-dependent cellular cytotoxicity, or boosting antibody-targeted cross-presentation of tumor antigens. To improve the clinical benefits of antibody therapy for human cancer, future therapeutic modifications or combinations should be able to extend, magnify, and shape these immune responses.*

Keywords: *monoclonal antibody; dendritic cells; cross presentation; anti-idiotype*

I. Introduction

In the last 20 years, monoclonal antibody-based cancer treatment has proven to be one of the most effective therapeutic options for both hematologic and solid cancers. The original combination of serological approaches for cancer cell surface antigen detection and hybridoma technology resulted in a series of groundbreaking clinical studies that cleared the way for next-generation antibody development. Monoclonal antibodies have proven to be effective treatments for a growing range of human cancers. They've grown to be one of the most popular classes of novel cancer treatments approved in the previous decade. An unconjugated antibody and two radio immune conjugates directed against CD20 have demonstrated to increase survival in both indolent and aggressive B-cell non-Hodgkins lymphoma [1-4].

In refractory acute myeloid leukemia, an anti-CD33 antibody-calicheamicin combination has been licensed [5-8]. Immunotoxins targeting CD22 have also shown anti-tumor effect in hairy cell leukemia. Antitumor efficacy of unconjugated tumor antigen-specific monoclonal antibodies has been attributed to a variety of methods.

The ability of such antibodies to modify crucial signaling pathways that perpetuate the malignant phenotype and to trigger or amplify self-tumor antigen-specific immune responses has received the greatest attention in recent years [9-12]. Antibodies' ability to induce anti-tumor effects by regulating tumor antigen-specific immune responses has gotten less attention than it deserves. The potential of monoclonal antibodies as immunotherapy vehicles will be examined in this paper. While there are a variety of potential immunomodulatory pathways to explore (e.g., complement activation, interference with inhibitory costimulation), we will focus on three main processes here:

1) Mediating cellular cytotoxicity of tumor cells,
2) Targeting Fc receptors on DCs to promote antigen presentation and induction of adaptive immune responses,
3) Eliciting tumor antigen-specific immune responses by triggering the idiotypic network.

1.1 Antibody-Dependent cellular cytotoxicity (ADCC)

Antibodies bind to antigens on tumor cells, and the antibody Fc domains interact with Fc receptors on the surface of immune effector cells, resulting in ADCC. Several Fc receptor families have been found, and characterized Fc receptors are expressed by distinct cell types [13-16]. Antibodies that bind to activating Fc receptors aid the recruitment of adaptor proteins and the activation of immune effector cells. Despite the fact that several tumor antigen-specific antibodies have been demonstrated to mediate ADCC in vitro, the relevance of this hypothesized mode of action to clinical efficacy has been challenging to establish [17-20].

Clinical efficacy has also benefited from the optimization of anti-tumor immune responses by Fc alterations. Targeting T cell receptors to modulate the immune system's interaction with tumor cells has emerged as a powerful new therapeutic method for tumor therapy and improving cancer vaccine efficacy. The advent of humanization techniques by Winter and colleagues [21] in which human germline amino acids were used to substitute murine Fc and Fv framework portions of murine antibodies, changed the field of antibody therapies. Minimal immune reactions to antibodies were detected with this approach, allowing several infusions of modified antibodies to be administered, resulting in the successful admission of numerous antibodies into the clinic [6, 22].

Ravetch and colleagues looked studied the efficacy of clinically effective tumor antigen-specific monoclonal antibodies to suppress human tumor xenografts growing in either wild-type mice or murine Fc RII/III knockout animals to see how important Fc domain: Fc receptor interactions are. Antibodies were discovered in the late 1800s, and the idea that they may be used as "magic bullets" in cancer diagnosis and treatment has been around since then. Several decades later, a significant effort was made to immunize a number of animal species with human cancer in the hopes of developing antisera with some degree of cancer specificity [1]

The anti-tumor effect of Fcy receptor knockout mice was reduced, but it was preserved when just the inhibitory Fc receptor isoform was removed. These findings back up the idea that Fcy domain: Fcy receptor interactions are involved in anti-tumor efficacy in mice, and that such interactions with antibodies may be relevant for anti-tumor activity in humans [21-24].

This method could explain why rituximab has a much higher efficacy in lymphoma patients with “high responder” Fcy receptor polymorphisms. Furthermore, our findings suggest that antibody Fcy domain: Fcy receptor interactions are responsible for at least some of the clinical benefit of rituximab, and that ADCC, which is dependent on such interactions, is clinically relevant. The potential for altering antibody interactions with activating and inhibitory Fc receptors is discussed below. The effector cell populations required for these effects have not been identified, however mononuclear phagocytes and/or natural killer cells are thought to be involved. Fcy domain structure can be tweaked to modify antibody clearance and Fc domain interaction with cellular Fcy receptors. The pharmaceutical sector has put a lot of work into developing monoclonal antibodies that stimulate ADCC more effectively by interacting with human Fcy receptors more efficiently [25-28].

An anti-tumor monoclonal antibody binds to an antigen on a tumor cell and interacts with a killer cell's Fc receptor. Antibody-promoted phagocytosis or direct cytolysis occurs, culminating in antigen processing and presentation on antigen-presenting cells via MHC Class I or Class II molecules. This leads to the induction of host anti-tumor immunity manifested by either the production of tumor-directed host cytotoxic T-lymphocytes and/or antibodies.

II. Review of Literatures

As medicine progresses into a new era of personalized therapy, the use of monoclonal antibodies to treat a wide range of diseases lies at the heart of this new forefront. Since the licensing of the first monoclonal antibody for clinical use 30 years ago, the monoclonal antibody industry has expanded exponentially and is now valued at billions of dollars. With major advances in genetic sequencing and biomedical research, much research into monoclonal antibodies now focuses on identifying new targets for development and maximizing their efficacy for use in clinical practice. However, a balance has to be struck with regards to reducing numbers of side-effects and overall economic cost, which arguably somewhat blighted their early clinical and commercial successes. Nowadays, there are approximately 30 monoclonal antibodies that have been approved for use in clinical practice with many more currently being tested in clinical trials. Some of the current major limitations include: the use of inefficient models for generation, a lack of efficacy and issues of cost-effectiveness. Some of the current research focuses on ways to improve the efficacy of existing monoclonal antibodies through optimizing their effects and the addition of beneficial modifications. This review will focus on the history of monoclonal antibody development – how it has increasingly moved away from using laborious animal models to a more effective phage display system, some of the major drawbacks from a clinical and economical point of view and future innovations that are currently being researched to maximize their effectiveness for future clinical use. The structure of antibodies also has an interesting history, initiated by the "side chain" theory of Paul Ehrlich in 1901.This totally empirical concept was incredibly accurate, imagining that some cells carried the so-called side chains, specific for given structures, at that time diphtheria or tetanus toxins. He proposed that these side chains could be released in the serum when the structures they recognized entered the animal. Before this, having become head of the Institute of Serum Research and Testing in Berlin, he applied the immunization protocols he had developed with Koch and von Behring. He was the one who proposed the use of horses for the standardized commercial production of immune serum. In the golden age of serotherapy, countless brave, 9BÉNÉhorses and rabbits have to be commended for having produced protective sera, rich in specific immunoglobulins, that, among other feats, saved soldiers of World wars from tetanus, diphtheria or other ailments. The era of serotherapy blossomed and progressed. Many re-searchers, Edwin Cohn among others,12 devised ways to purify human immunoglobulins in order to provide patients that needed it with passive immunization. This led to precious preparations directed toward infectious agents, helpful to alleviate infections in immunocompromised/immunodeficient patients. Broader preparations of IVIG or intravenous immunoglobulins were developed, still widely used not only for immunodeficient patients but also for the treatment of such autoimmune disorders as immune thrombocytopenic purpura. Nowadays, IVIG are processed in order to try and limit the adverse reactions they may yield.

III. Discussion

Monoclonal antibody-based treatment of cancer has been established as one of the most successful therapeutic strategies for both hematologic malignancies and solid tumors in the last 20 years. The initial combining of serological techniques for cancer cell surface antigen discovery with hybridoma technology led to a series of landmark clinical trials that paved the way for new generation antibodies and subsequent clinical success. Optimization of anti-tumor immune responses through Fc modifications has also made a

major contribution to clinical efficacy. Targeting T cell receptors to modulate the immune system's interaction with tumor cells has emerged as a powerful new therapeutic method for tumor therapy and improving cancer vaccine efficacy. This commentary will present an overview of antibody discovery of tumor surface antigens, antigenic targets for antibody-based therapy, and antibody modes of action. Antibodies were discovered in the late 1800s, and the idea that they may be used as "magic bullets" in cancer diagnosis and treatment has been around since then. Several decades later, a significant effort was made to immunize a number of animal species with human cancer in the hopes of developing antisera with some degree of cancer specificity. Unfortunately, with the exception of the discovery of carcinoembryonic antigen (CEA), a marker for colon and other cancers, and -fetoprotein, a diagnostic for hepatocellular cancer, this technique had limited early success. With the advent of the cytotoxic test as a potent instrument to investigate the cell suture, the introduction of inbred mice ushered in a new era of cancer serological inquiry. As a result, the cell surface has been identified as a highly specialized structure. Lloyd Old made a series of discoveries in the 1960s and 1970s that transformed our understanding of the immune system. He pioneered the notion of cell surface differentiation antigens, which may identify lineage and functional subsets of leukocytes in conjunction with Ted Boyse. The discovery of the thymus-leukemia (TL) antigen, the connection of the major histocompatibility complex (MHC) with leukemia, and the subsequent Ly series of antigens were all notable contributions at the time. These discoveries led to the exact and systematic discovery of cell surface antigens that differentiated normal cells from malignant cells, and hence to the CD classification [29-33]. Monoclonal antibodies (mAbs) were used to dissect the surface structure of human cancer cells after Köhler and Milstein developed hybridoma technology, which was combined with serological techniques and analytical tools such as fluorescence-activated cell sorting (FACS) to pave the way for the identification of cancer cell surface antigens suitable for antibody targeting [34-38]. Proteomic, genomic, and bio informatics techniques to finding antigen targets on cancer cells, as well as in cancer stroma and vasculature, have improved the characterization of the cancer cell "surface me" in recent years [39-40].

3.1. Anti-Idiotypic Antibodies as Tumor Antigen Mimics:

The expression of conformational and structural antigenic determinants that are unique or expressed on a few antibody populations reflects the significant variability of the amino acid sequence of an antibody's heavy and light chain variable regions. Because of their limited distribution on antibody populations, these determinants are recognized as foreign by the host immune system and might consequently induce an immunological response. Some idiotopes are found near the antibody's antigen binding region, which binds with the appropriate antigen.

As a result, they are complementary to the antigenic determinant in question. Others, despite being located in the antibody's combining site, are not directly involved in the antigen binding and thus have no complementarity with the corresponding epitope. [38] Based on Jerne's idiotypic network theory

The idiotypic cascade in a host is triggered by the induction of an antibody (Figure 1). As a result, the evoked antibody causes anti-idiotypic antibodies to be produced against its idiotopes. Some of them may detect idiotope(s) that are complementary to the antigenic determinant that has triggered the idiotypic network, and so react with the same area(s) of the antigen binding site as the antigenic determinant that has triggered the idiotypic network. The reactivity of the nominal antigen and some anti-idiotypic antibodies is due to homology between the implicated antigenic determinant and portion(s) of the anti-

idiotypic antibody's variable regions. This similarity, which is mostly conformational but also structural in some situations, explains why some anti-idiotypic antibodies can operate as surrogate antigens. (Figure 2). Anti-idiotypic antibodies that imitate tumor antigens are appealing vaccines because they can overcome patients' resistance to tumor antigens, which, due to their self-nature, have poor or no immunogenicity. Anti-idiotypic antibodies with well-defined properties can also be manufactured in large quantities in a repeatable manner using hybridoma technique.

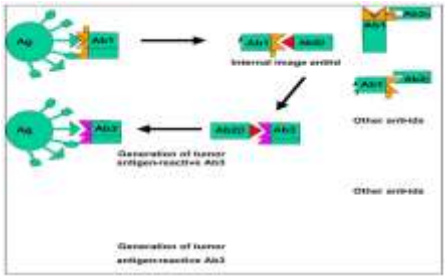

Figure 1. *Triggering of the Idiotypic Network by Immunization with a Tumor Antigen*

Furthermore, using hybridoma technique, anti-idiotypic antibodies with well-defined properties can be made in large quantities in a repeatable manner, easing vaccine standardization for clinical use [40]. Anti-idiotypic antibodies to the idiotopes expressed on its variable region are induced by the antibody Ab1, which is evoked by a tumor antigen. Some anti-idiotypic antibodies, known as Ab2, react with the variable portion of the Ab1 antibody that binds to the nominal antigen. Because these anti-idiotypic antibodies have the internal image of the nominal antigen, they can produce tumor antigen binding antibodies (Ab3). Anti-idiotypic antibodies known as Ab2 bind to portions of the Ab1 variable region that do not bind to the nominal antigen. They can prevent Ab1 from binding to the nominal antigen, resulting in anti-anti-idiotypic antibodies that don't recognize the nominal antigen. Other anti-idiotypic antibodies, known as Ab2, b0pv ind to parts of the Ab1 variable region that are not near the antigen combining site. They have no effect on Ab1's ability to bind to the nominal antigen and produce anti-anti-idiotypic antibodies. They cause anti-anti-idiotypic antibodies that do not attach to the nominal antigen and do not interfere with Ab1 binding to the nominal antigen [39].

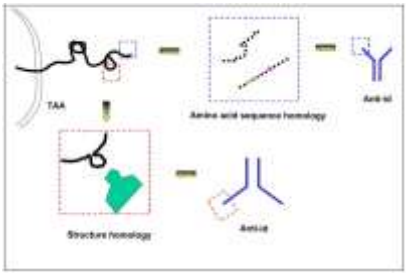

Figure 2. *Molecular Basis of Tumor Antigen Mimicry by an Anti-Idiotypic Antibody*

The homology of a tumor antigen amino acid sequence stretches with a stretch of the anti-idiotypic antibody variable region amino acid sequence or conformational similarity between a tumor antigen determinant and an anti-idiotypic antibody idiotope may explain the mimicry of a tumor antigen by an anti-idiotypic antibody.

3.2. Monoclonal Antibody Therapy

The ability to induce adaptive tumor antigen-specific immune responses holds great promise for cancer prevention and treatment. Monoclonal antibodies offer undervalued prospects for cancer immunization. Antibodies can alter immunological pathways that are important for immune surveillance in addition to targeting antigens involved in cancer cell physiology. Antigen-specific immune responses are the consequence of a dynamic interaction between antigen-presenting cells, T lymphocytes, and target cells. To do this, tumor-directed antibodies, anti-idiotype antibodies, or a combination of these approaches together with additional immune manipulation techniques may be used.

ADCC induced by monoclonal antibody therapy can result in tumor elimination, as well as antigen uptake, processing, and presentation by DCs and other professional antigen presenting cells, resulting in adaptive T-cell-mediated immune responses. Improved ADCC can be mediated by monoclonal antibodies, which should improve antigen presentation and T cell activation. [38] This can be done by boosting antibody affinity for tumor antigen targets or modifying antibody Fcy domains to boost Fc receptor affinity (s). As previously mentioned, it may be able to fine-tune antibody engineering to selectively activate activating rather than inhibiting Fcy receptors. Alternatively, antibodies that selectively disrupt the interactions of tumor antigen-specific antibodies with inhibitory Fcy receptors may be beneficial. Antibody architectures can also be changed to include immunostimulatory motifs that selectively induce, shape, and amplify antigen processing, presentation, and costimulation in order to facilitate the induction of therapeutically effective host anti-bodies. [34] Tumor antigen-specific antibodies could be coupled with other treatments that improve antigen presentation (e.g., toll receptor agonists), costimulation (e.g., anti-CTLA-4 antibody), or T-cell activation or expansion instead of direct modification of antibody structures (e.g., interleukin-2). Other immunological therapies, such as DC vaccinations, may benefit from antibody therapy as well [40]. It's worth noting that several clinically useful antibodies that mediate ADCC are frequently used in combination with chemotherapy agents; more research is needed to see if chemotherapy-based tumor destruction works in tandem with monoclonal antibody therapy to promote adaptive, tumor antigen-specific immunity. The link between tumor antigen-specific immune responses induced by anti-idiotypic antibodies and clinical responses highlights the necessity for randomized clinical trials to prove the efficacy of this vaccination technique. Furthermore, methods should be developed to strengthen anti-idiotype antibodies' ability to generate a significant tumor antigen-specific immune response, with the hope of improving their anti-tumor effects. [35] The characterization of the structural basis of tumor antigen mimicry by the corresponding anti-idiotypic antibodies, as well as the relationship between the extent of antigen mimicry and the immunogenicity of a mimic, will be beneficial to these studies. This knowledge will make it easier to replace anti-idiotypic antibodies with peptide mimics, which are more responsive to changes to improve performance. [36]

IV. Conclusion

One of the most important contributions of tumor immunology to cancer patients is the use of monoclonal antibodies for cancer therapy. His achievements are the result of decades of scientific research focused on serological characterization of cancer cells, techniques for producing optimized antibodies to tumor targets, detailed investigations of cancer-related signaling pathways, and an understanding of the complex interplay between cancer cells and the immune system. The clinical development of antibodies is intrinsically

connected to a thorough investigation of their characteristics in vivo and evaluation of their functional impact on cancer cells. To further research this vital field, the Cancer Vaccine Collaborative, a combined academic clinical trials infrastructure founded by LICR and the Cancer Research Institute (CRI), is ready to start on a series of trials evaluating NY-ESO-1 vaccines in combination with ipilimumab. Tumor immunology's full potential for regulating and treating cancer will hopefully be fulfilled in this way.

References

[1]. McLaughlin P, Grillo-Lopez AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol. 1998;16:2825–33.

[2]. Kaminski MS, Estes J, Zasadny KR, et al. Radio immunotherapy with iodine (131)I tositumomab for relapsed or refractory B-cell non-Hodgkin lymphoma: updated results and long-term follow-up of the University of Michigan experience. Blood. 2000;96: 1259–66.

[3]. Coiffier B. Rituximab in combination with CHOP improves survival in elderly patients with aggressive non-Hodgkin's lymphoma. Semin Oncol. 2002;29(2 Suppl 6):18–22.

[4]. Witzig TE, Gordon LI, Cabanillas F, et al. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. J Clin Oncol. 2003;20:2453–63.

[5]. Sievers EL, Appelbaum FR, Spielberger RT, et al. Selective ablation of acute myeloid leukemia using antibody-targeted chemotherapy: a phase I study of an anti-CD33 calicheamicin immunoconjugate. Blood. 1999;93:3678–84.

[6]. Kreitman RJ, Wilson WH, Bergeron K, et al. Efficacy of the anti-CD22 recombinant immunotoxin BL22 in chemotherapy-resistant hairy-cell leukemia. N Engl J Med. 2001;345:241–47.

[7]. Cobleigh MA, Vogel Cl, Tripathy D, et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol. 1999;17:2639–48.

[8]. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344:783–92.

[9]. Vogel CL, Cobleigh MA, Tripathy D, 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;20:719–26.

[10]. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 2005;353:1673–84.

[11]. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004;350:2335–42.

[12]. Miller RA, Maloney DG, Warnke R, et al. Treatment of B-cell lymphoma with monoclonal anti-idiotype antibody. N Eng J Med. 1982;306:517–22.

[13]. Leonard JP, Link BK. Immunotherapy of non-Hodgkin's lymphoma with hLL2 (epratuzumab, an anti-CD22 monoclonal antibody) and Hu1D10 (apolizumab) Semin Oncol. 2002;29(1 Suppl 2):81–86.

[14].Lundin J, Kimby E, Bjorkholm M, et al. Phase II trial of subcutaneous anti-CD52 monoclonal antibody alemtuzumab (Campath-1H) as first-line treatment for patients with B-cell chronic lymphocytic leukemia (B-CLL) Blood. 2002;100:768–73.
[15].Figlin RA, Belldegrun AS, Crawford J, Lohner M, Roskos L, Yang X-D, Foon K, Schwab G, Weiner L. ABX-EGF, a fully human anti-epidermal growth factor receptor (EGFR) monoclonal antibody (mAb) in patients with advanced cancer: phase 1 clinical results. Proceedings ASC0. 2002;21:35. Abstract.
[16].Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med. 2004; 351:337–45.
[17].0egen JG, Kuhns MS, Allison JP. CTLA-4: new insights into its biological function and use in tumor immunotherapy. Nat Immunol. 2002; 3:611–18.
[18].Phan GQ, Yang JC, Sherry RM, et al. Cancer regression and autoimmunity induced by cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma. Proc Natl Acad Sci U S A. 2003; 100:8372–77.
[19].Steplewski Z, Lubeck MD, Koprowski H. Human macrophages armed with murine immunoglobulin G2a antibodies to tumors destroy human cancer cells. Science. 1983; 221:865–67.
[20].Heijnen IA, van de Winkel JG. Human IgG Fc receptors. Int Rev Immunol. 1997; 16: 29–55.
[21].Sulica A, Morel P, Metes D, et al. Ig-binding receptors on human NK cells as effecter and regulatory surface molecules. Int Rev Immunol. 2001; 20:371–414.
[22].Clynes RA, Towers TL, Presta LG, et al. Inhibitory Fc receptors modulate in vivo cytoxicity against tumor targets. Nat Med. 2000; 6:443–46.
[23].Cartron G, Dacheux L, Salles G, et al. Therapeutic activity of humanized anti-CD20 monoclonal antibody and polymorphism in IgG Fc receptor FcgammaRIIIa gene. Blood. 2002; 99:754–58.
[24].Weng WK, Levy R. Two immunoglobulin G fragment C receptor polymorphisms independently predict response to rituximab in patients with follicular lymphoma. J Clin Oncol. 2003; 21:3940–47.
[25].Umana P, Jean-Mairet J, Moudry R, et al. Engineered glycoforms of an antineuroblastoma IgG1 with optimized antibody-dependent cellular cytotoxic activity. Nat Biotechnol. 1999; 17:176–80.
[26].Ghetie V, Ward ES. Multiple roles for the major histocompatibility complex class I-related receptor FcRn. Annu Rev Immunol. 2000; 18:739–66.
[27].Shields RL, Namenuk AK, Hong K, et al. High-resolution mapping of the binding site on human IgG1 for Fc gamma RI, Fc gamma RII, Fc gamma RIII, and FcRn and design of IgG1 variants with improved binding to the Fc gamma R. J Biol Chem. 2001;276:6591–604.
[28].Clark JI, Alpaugh RK, von Mehren M, et al. Induction of multiple anti-c-erbB-2 specificities accompanies a classical idiotypic cascade following 2B1 bispecific monoclonal antibody treatment. Cancer Immunol Immunother. 1997;44:265–72.
[29].Heath WR, Carbone FR. Cross-presentation, dendritic cells, tolerance and immunity. Annu Rev Immunol. 2001;19:47–64.
[30].Amigorena S. Fc gamma receptors and cross-presentation in dendritic cells. J Exp Med. 2002;195:F1–3.
[31].Dhodapkar KM, Dhodapkar MV. Recruiting dendritic cells to improve antibody therapy of cancer. Proc Natl Acad Sci U S A. 2005;102:6243–64.
[32].Dhodapkar MV, Dhodapkar KM, Palucka AK. Interactions of tumor cells with

dendritic cells: balancing immunity and tolerance. Cell Death Differ. 2008;15:39–50.
[33].Chamuleau ME, Souwer Y, Van Ham SM, et al. Class II-associated invariant chain peptide expression on myeloid leukemic blasts predicts poor clinical outcome. Cancer Res. 2004;64:5546–50.
[34].den Haan JM, Bevan MJ. Constitutive versus activation dependent cross presentation of immune complexes by CD8+ and CD8− dendritic cells in vivo. J Exp Med. 2002;196:817–27.
[35].Dhodapkar KM, Krasovsky J, Williamson B, et al. Antitumor monoclonal antibodies enhance cross-presentation of cellular antigens and the generation of myeloma-specific killer T cells by dendritic cells. J Exp Med. 2002;195:125–33.
[36].Nagata Y, Ono S, Matsuo M, et al. Differential presentation of a soluble exogenous tumor antigen, NY-ESO-1, by distinct human dendritic cell populations. Proc Natl Acad Sci U S A. 2002;99:10629–34.
[37].Rafiq K, Bergtold A, Clynes R. Immune complex-mediated antigen presentation induces tumor immunity. J Clin Invest. 2002;110:71–79.
[38].Schuurhuis DH, Ioan-Facsinay A, Nagelkerken B, et al. Antigen-antibody immune complexes empower dendritic cells to efficiently prime specific CD8+ CTL responses in vivo. J Immunol. 2002;168:2240–46.
[39].Selenko N, Majdic O, Jager U, et al. Cross-priming of cytotoxic T cells promoted by apoptosis-inducing tumor cell reactive antibodies? J Clin Immunol. 2002;22:124–30.
[40].Akiyama K, Ebihara S, Yada A, et al. Targeting apoptotic tumor cells to FcR provides efficient and versatile vaccination against tumors by dendritic cells. J Immunol. 2003;170:1641–48.
[41].Sangy S, Miryousefiata F, Bahaoddini A, Dimiati H. The Effects of Gavage Extract of Papaver Rhoeas L on Blood Pressure of MIA Induced Osteoarthritis and Its Interaction with Nitrergic System in male Rat. Budapest International Research in Exact Sciences (BirEx) Journal. Volume 2, No 4 October 2020, Page:458-466. www.bircu-journal.com/index.php/birex.
DOI:https://doi.org/10.33258/birex.v2i4.1260
[42].Zigta, Binyam. (2019).Thermal Radiation, Chemical Reaction and Viscous DissipationEffects on Unsteady MHD Flow of Viscoelastic Fluid Embeddedin a Porous Medium. Budapest International Research in Exact Sciences (BirEx) Journal Volume 1, No 3, July 2019, Page: 35-57www.bircu-journal.com/index.php/birex