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Mini Review

Variety of Immunoglobulin G Functions

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Abstract

In recent years, several new functional activities of IgG molecules have been described. IgG forms stable, non-immune complexes with anaphylatoxins, toxic cellular proteins of the complement family. In this manner anaphylatoxins are removed from the circulation (the "cleansing" IgG function). Non-immune IgG complexes can activate cells more efficiently than each component acting separately. IgG forms complexes with the abundant cell protein Grp94 that is overproduced in pathological conditions. The detection of IgG-Grp94 complexes in the circulation bears high clinical significance.

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INTRODUCTION

Immunoglobulins are multifunctional protein molecules. Their most important function - antibody activity - has been studied in details. The specific roles of IgA in mucosal immunity and of IgE in allergic reactions are well known. More recently new immunoglobulin G functions were described, after finding non-immune IgG complexes with various proteins.

The diversity of immunoglobulin (Ig) functions may be explained by the peculiar structure of these flexible molecules. Heavy and light Ig chains are composed from compact stable immunoglobulin folds (IgF), or domains belonging to a large protein super family. Proteins composed from IgF have been found in various representatives of animal kingdom even those appeared during the very early stages of evolution [1,2]. Such evolutionary conservation supports the well-known fact that useful structural elements appeared early in evolution later preserved and long-lived. The most important feature of IgF lies in its specific ability to bind molecules of various chemical structures and dimensions from large proteins to small molecules such as peptides and simple carbohydrates. First of Ig interactions are related to the formation of immune complexes (IC) of antibody molecules with antigens at antigen-combining sites. Igs are able to form non-IC with various proteins on sites located on only one domain, or on sites composed from residues on different domains [3,4]. Therefore, IgF acts as a scaffold on which arrays of binding sites are displayed on β strands or on those parts on Ig peptide chains that are connected the strands. One aspect of the Ig interactions outside the antigen binding sites with the formation of non-IC is most important for adaptive immune processes while others aspects are involved in some other functions.

"Cleansing" IgG function

Serum contains thousands proteins of various origin and properties, synthesized by cells of the liver, spleen and other organs, as well as traces of non-self proteins of bacterial and viral origin. IgG molecules could serve as scavengers, removing proteins that are potentially harmful to the body. One example of such a function involves the formation of stable, non-covalent IgG complexes with anaphylatoxin C3a, a small protein that released from C3 complement component following complement activation [5]. Anaphylatoxins are responsible for inflammatory and anaphylactoid reactions that give rise to various pathologies. The IgG sites participating in the interactions with anaphylatoxins are located on Fab subunits and composed of non-variable amino-acid residues. Complexes of IgG with C3a have been found in human normal serum as well as in commercial γ-globulins produced by different companies. One gram of γ-globulins contains appreciable amounts of C3a, about 2-4 mg [6]. Such activity can be considered as a "cleansing" IgG function. Later it was found that C5a anaphylatoxins also interact with IgG [7].

Notably, many microorganisms have on their surface proteins that are able to interact in non immune fashion with IgG molecules [3]. Among the best studied are Staphylococcal Protein A and Streptococcal Protein G that are effectively used for isolation and quantitation of IgG. Virion particles also contain IgG binding proteins. Two proteins of Herpes Simplex Virus form together a receptor on virion envelope that interacts with Fc part of IgG. The gp120 protein of HIV-1 virus is able to bind to the variable portion of IgG molecules coded by the V_H3 gene family.

Interactions of IgG complexes with cells

The properties of non-immune IgG complexes differ from those of their individual components. The IgG complexes with polypeptide hormone prolactin stimulate malignant B lymphocyte proliferation in patients with chronic lymphocyte leukemia, whereas the hormone or IgG separately were inactive [8]. Such costimulatory effect of IgG-prolactin is due to the necessity of

stimulating both prolactin and Fc cell receptors, to activate the leukemia cells. Various receptors are located on the surface of cells together with Fc-receptors and IgG complexes with active ligands, can interact simultaneously with two different types of cell receptors.

In recent years non-immune complexes in which IgG molecules combine with the heat-shock protein Grp94 have been thoroughly studied. This glucose-regulated protein, the abundant cellular glycoprotein, is located in the endoplasmic reticulum but can appear on the cell surface and from there, be released into the circulation. Grp94 concentrations in the plasma of healthy individuals are very low; however its levels increase in diabetic patients. Nearly all Grp94 molecules in diabetic plasma exist in very stable complexes with IgG, in which Grp94 is bound to the C_H2 and C_H3 domains of IgG heavy chains. The Grp94-IgG complexes also form when both components are mixed *in vitro*. Grp94 molecules degrade easily at 37°C but the formation of the complexes with IgG stabilizes their structure and prolongs their activity ("stabilizing" IgG function) [9,10]. The free Grp94 and in complex with IgG stimulate the proliferation of endothelial cells from umbilical vain and promote angiogenic transformation. However, the activity of the Grp94-IgG complexes is more intensive and they induce significant alterations in the cytoskeleton as compare to the free Grp94 [11]. Thus, the IgG in the complexes not only acts as a carrier for Grp94, but also serves as a functional partner. Under the influence of the Grp94-IgG complexes activated peripheral blood mononuclear cells (PBMC) from cancer patients underwent morphological and functional modifications that characterized by the appearance of macrophages of various sizes and the cytokine secretion [12].

IgG complexes with the tumor marker Grp94

During the past decade, it was found that glucose-regulated cell proteins including Grp94 are over expressed in malignant cells of both solid and hematological tumors [13]. Increased production of Grp94 is correlated with the progression of carcinogenesis and metastasis among patients with gastric carcinomas, hepatocellular carcinoma, multiple myeloma, lung and breast cancer and predictive of brain cancer metastasis [14-16]. Accordingly, Grp94 could be considered as a diagnostic and prognostic tumor biomarker and its detection has important clinical significance. Grp94 in the circulation of oncological patients as those with other pathologies is present only in stable complex with IgG. Using the ELIZA assay, it was shown that the concentration of the Grp94-IgG complexes in the blood of patients with primary tumors of the gastrointestinal tract is significantly higher than those in the blood of healthy persons [12]. The highest concentrations of the Grp94-IgG complexes were found in patients with the progressed forms of tumor development when tumor cells are detected also in lymph nodes.

Precise quantitative data of Grp94 in the complex with IgG may be obtained by means of immunochemical methods, for example by the dot-blot assay previously have been applied for the detection of antigens in specific AG-AT complexes [17]. In the assay bacterial Protein G immobilized on Sepharose beads was used for the isolation of the IgG complexes from serum. The beads with the adsorbed complexes are transferred on nitrocellulose membranes and the elution of the adsorbed proteins with acid buffers is performed directly on the membranes. For the evaluation of the marker immobilized on the membranes, corresponding labeled antibodies are used. After the incubation with biotin-labeled antibodies the membranes are covered with enhanced chemiluminescence reagent and just after, X-ray film is placed on the membranes. The film is analyzed using a computing densitometer [17].

CONCLUSION

Immunoglobulins are polyfunctional group of proteins which play most important role in immunity. During the past two decades several IgG functions related to the ability of IgG to form non-IC have been examined. In the 1990s, it was found that IgG molecules are able to form complexes with potentially harmful proteins such as anaphylatoxins and in this manner, remove them from the circulation (the "cleansing" IgG function). Unstable proteins after binding to IgG retain their structure ("stabilizing" IgG function).

IgG molecules bind to cell surfaces using Fc-cell receptors. Non-immune Ig complexes link to cells by the same mechanism and Ig partners of non-IC complexes can also be concentrated on cell surfaces in this way. The important function of IgG molecules lies in their ability to form complexes with the Grp94 tumor biomarker. Such complexes facilitate the detection of the biomarker as well as its isolation.

The adsorption of IgG complexes by the immobilized bacterial Protein G makes it possible to evaluate the exact amount of a IgG partner in a complex by means of quantitative immunochemical methods. There is no doubt that further of studies of non-immune IgG complexes in the circulation provide important new data on the IgG functions with potential clinical ramifications.

REFERENCES

1. Du Pasquier L. The immune system of invertebrates and vertebrates. Comp Biochem Physiol B Biochem Mol Biol. 2001; 129: 1-15.
2. Pasquier LD. Germline and somatic diversification of immune recognition elements in Metazoa. Immunol Lett. 2006; 104: 2-17.
3. Nezlin R, Ghetie V. Interactions of immunoglobulins outside the antigen-combining site. Adv Immunol. 2004; 82: 155-215.
4. Nezlin R. Circulating non-immune IgG complexes in health and disease. Immunol Lett. 2009; 122: 141-144.
5. Nezlin R, Freywald A. Complexes of immunoglobulin G molecules and C3a and C4a complement components in human serum. Eur J Immunol. 1992; 22: 1955-1957.
6. Nezlin R. Detection of the C3a complement component in commercial gamma globulins by dot blotting. J Immunol Methods. 1993; 163: 269-272.
7. Basta M, Van Goor F, Luccioli S, Billings EM, Vortmeye AO, Baranyi L, et al. $F(ab)_2$-mediated neutralization of C3a and C5a anaphylatoxins: A novel effector function of immunoglobulins. Nat Med. 2003; 9: 431-438.
8. Walker AM, Montgomery DW, Saraiya S, Ho TWC, Garewale HS, Wilson J, et al. Prolactin-immunoglobulin G complexes from human serum act as costimulatory ligands causing proliferation of malignant B lymphocytes. Proc Natl Acad Sci US. 1995; 92: 3278-3282.
9. Pagetta A, Tramentozzi E, Tibaldi E, Cendron G, Zanotti G, Brunati AM, et al. Structural insights into complexes of glucose-regulated

Protein94 (Grp94) with human immunoglobulin G. Relevance for Grp94-IgG complexes that form in vivo in pathological conditions. PloS ONE. 2014; 9: e86198.

10. Roveri A, Zaccarin M, Pagetta A, Tramentozzi E, Finotti P. Proteomic Investigation on Grp94-IgG Complexes Circulating in Plasma of Type 1 Diabetic Subjects. J Diabetes Res. 2015; 2015: 815839.

11. Tramentozzi E, Montopoli M, Orso G, Pagetta A, Caparrotta L, Frasson M, et al. Stable complexes formed by Grp94 with human IgG promoting angiogenic differentiation of HUVECs by a cytokine-like mechanism. Mol Immunol. 2008; 45: 3639-3648.

12. Tramentozzi E, Ruli E, Angriman I, Bardini R, Campora M, Guzzardo V, et al. Grp94 in complexes with IgG is a soluble diagnostic marker of gastrointestinal tumors and displays immune-stimulating activity on peripheral blood immune cells. Oncotarget. 2016; 7: 72923-72940.

13. Wu BX, Hong F, Zhang Y, Ansa-Addo E, Li Z. GRP94/gp96 in cancer: biology, structure, immunology, and drug development. Adv Cancer Res. 2016; 129: 165-190.

14. Zheng HC, Takahashi H, Li XH, Hara T, Masuda S, Guan YF, et al. Overexpression of GRP78 and GRP94 are markers for aggressive behavior and poor prognosis in gastric carcinomas. Hum Pathol. 2008; 39: 1042-1049.

15. Martinez-Aranda A, Hernandez V, Guney E, Muixi V, Foj R, Baixeras N, et al. FN14 and GRP94 expression are prognostic/predictive biomarkers of brain metastasis outcome that open up new therapeutic strategies. Oncotarget. 2015; 6: 44254-44273.

16. Wei PL, Huang CY, Tai CJ, Batzorig U, Cheng WL, Hunag MT, et al. Glucose-regulated protein 94 mediates metastasis by CCT8 and the JNK pathway in hepatocellular carcinoma. Tumor Biol. 2016; 37: 8219-8227.

17. Nezlin R. A quantitative approach to the determination of antigens in immune complexes. J Immunol Meth. 2000; 237: 1-17.

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