

Biological Implications of Surface Immunoglobulins Expressed by Cancer Cells

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Abstract

RP215 was one of monoclonal antibodies generated against the extract of OC-3VGH ovarian cancer cells. It was shown to react with a carbohydrate-associated cancer antigen designated as CA215, consisting mainly of immunoglobulin (Ig) heavy chains (expressed by cancer cells) as well as several other immunoglobulins superfamily proteins (IgSF). RP-215-specific epitope in CA215 was elucidated by comprehensive glycoanalysis and was shown to be associated with O-linked Sialyl-T glycans located in the variable regions of heavy chain immunoglobulins. RP215 and its humanized forms were shown to induce apoptosis upon incubation with culturing cancer cells of many tissue origins. Relevant functional roles of CA215 were evaluated through the use of affinity-purified CA215 and cancerous Ig's to capture those specific interacting human serum proteins in circulation. Through analysis by LC-MS/MS methods, greater than 80% of the identified serum proteins were commonly recognized by both CA215 or cancerous IgG as the capturing ligands. These interacting serum proteins can generally be classified into known properties of pro-cancer or anti-cancer in nature. By using semi-quantitative RT-PCR analysis, gene regulation studies were performed with selected genes involved in the expressions of cancerous Ig's and their interactions. Both RP215 and anti-human Ig's were shown to affect gene expressions almost identically to incubated cancer cells. Therefore, it can be assumed that Ig's or CA215 expressed on cancer cell surface may play essential roles to interact with specific serum proteins for protection or growth/proliferation of cancer cells under our human environments. The additional carbohydrate-associated epitope recognized by RP215 makes cancerous Ig's distinguishable to those of B cell origins. Therefore, RP215 may serve to target uniquely surface Ig's on the cancer cells. Further explorations regarding functional roles of cancerous Ig's may contribute more to the therapeutic applications of RP215 in cancer immunology.

Keywords

Cancerous Immunoglobulins, CA215/RP215, O-Linked Glycan-Associated Epitope, T and T_s Antigen

1. Introduction

RP215 was selected from one of three thousand monoclonal antibodies generated from immunizations of ovarian cancer cell extract [1]-[3]. Biological and immunological analysis revealed that RP215 reacts with a carbohydrate-associated epitope (sialyl-T) located in the variable regions of immunoglobulin (Ig's) heavy chains expressed on the surface of almost all cancer cells in humans, but rarely found among those from normal B cells [4]. Tissue specificity of RP215 revealed that most cancer cells of many tissue origins were stained positively, but rarely found in normal tissues, except those of hyperplastic epithelial cells [3]-[5]. RP215 was shown to induce apoptosis to almost all cancer cells in culture. It was also shown to reduce the volume of implanted tumor cells, dose-dependently in nude mouse experiments [6].

Surface expressions of cancerous Ig's were first observed more than two decades ago. By using RP215 as the probe, it has become possible to investigate the roles of cancerous Ig's in the immunology of cancer cells. Upon insertions of humanized ScFv fragments of RP215 into a CAR-T cell constructs (chimeric antigen receptor-T cell constructs), it was revealed that RP215-ScFvCAR-T cells were shown to be effective to eliminate cancer cells when C33A cervical cancer cells served as the *in vitro* model [7]. This was demonstrated by releasing relevant cytokines (IL-2, IL-7 and IFN- γ) for cytotoxic killing of cancer cells [8]. Therefore, RP215 can be used to target cancer cells in therapeutic applications.

In this review, the functional roles of cancerous Ig's and RP215 are summarized and explored in terms of induced apoptosis, mutual interactions with human serum proteins and gene regulation changes upon interactions with the surface-expressed cancerous Ig's.

2. Induction of Apoptosis to Cancer Cells by RP215 and Related Anti-Antigen Receptors

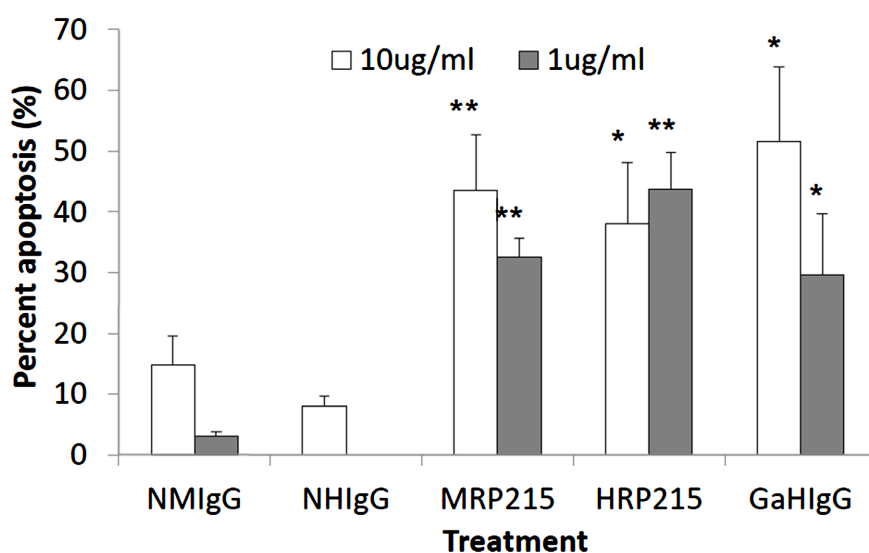
Through analysis by MALDI-TOF-MS, it was disclosed that affinity-purified CA215 consists mainly of Ig heavy chains and numerous other glycoproteins generally classified as immunoglobulin superfamily proteins (IgSF). Among these are antigen receptors (Ig's, T cell receptors, 46.8%), antigen-presenting molecules (MHC1, MHCII, 5.3%) cell adhesion molecules (9.0%) and several other IgSF proteins which are attached with RP215-specific carbohydrate-associated epitope [5]. They are summarized and presented in **Table 1**.

The TUNEL [terminal deoxynucleotidyl transferase dUDP nick end labeling]

assay was employed to study induced apoptosis. It was clearly demonstrated that RP215 at concentrations of 1 - 10 µg/ml was found to induce apoptosis to human cancer cells of many tissue origins [7] [9]. Anti-human Ig's were shown to induce apoptosis of cancer cells, similar to that of RP215. These observations seem to suggest that RP215 and antihuman Ig's affect similar binding targets on the cancer cell surface [9]. The results of this apoptosis study are summarized in **Figure 1** [7] [9].

Table 1. Molecular analysis of CA215 based on MALDI-TOF MS analysis of tryptic peptides.

Molecule function/category	Number of peptides matched Total = 111 (percentage)
I. Antigen receptors	
1. Antibodies and immunoglobulins	52 (46.8%)
2. T-cell receptor chains	7 (6.3%)
II. Antigen-presenting molecules (MHC I and MHC II)	
	6 (5.3%)
III. Adhesion molecules	
	10 (9.0%)
IV. Cytokine and growth factors	
	8 (7.2%)
V. Receptor tyrosine kinase/phosphatase	
	7 (6.3%)
VI. Others	
1. IgSF related (e.g., titin)	12 (10%)
2. IgSF unrelated (e.g., mucin)	9 (8.1%)



24-hour incubation; NMIgG: normal mouse IgG; NHlgG: normal human IgG; MRP215: murine RP215; HRP215: humanized RP215; GaHIgG: goat anti human IgG; Statistics: *p < 0.05, **p < 0.01.

Figure 1. TUNEL Apoptosis assays to reveal induced apoptosis of OC3-VGH ovarian cancer cells in cell culture by antibodies of various origins and concentration.

Based on results of this study, it can be assumed that RP215 or its humanized form can target specifically cancer cells for applications in immunotherapy.

3. Interactions between Cancerous Ig's and Human Serum Proteins

Since the discovery of surface Ig's expressed by almost all cancer cells in humans [2] [3], their functional roles have drawn significant attentions [4].

With generations of RP215 monoclonal antibody, it has become possible to identify and isolate cancerous Ig's from the cancer cell extract. The affinity purified cancerous Ig's can be used to capture those human serum proteins or fragments for further molecular analysis [10]. Based on this strategy, it is possible to use RP215 and goat antihuman Ig's as the affinity ligand to isolate cancerous Ig's. Human serum components or fragments were captured by using cancerous Ig's isolated either from CA215 or cancerous Ig's-based affinity columns [10]. These affinity-purified human serum proteins were subject to molecular analysis by LC-MC/MC procedures.

Among the serum proteins or fragments recognized by cancerous Ig's or CA215, more than 80% were found to be identical. Practically, CA215 and anti-cancerous Ig's are functionally equivalent in recognizing cancerous Ig's as well as the subsequent human serum components. The molecular nature of these isolated serum proteins was analyzed with respect to their intrinsic associations with cancer cells under our normal human environment. In contrast, when normal human IgG was used as ligand for serum protein isolation nothing was identified (data not presented).

4. Biological and Functional Analysis of Human Serum Proteins Identified by Using CA215 and/or Cancerous Ig's as General Affinity Ligands

The affinity-purified serum proteins or fragments were analyzed by liquid chromatography-tandem mass spectrometry (LC-S-MS). Among the commonly detected serum proteins, they are generally considered to interact with cancerous Ig's or CA215, on the cancer cell surface. Further analysis revealed that quite a few were known to have pro-cancer or anti-cancer properties based on many previous studies [10]. Among these, C4b binding protein α chain, complement C3, complement factor H, serotransferrin and fibronectin were shown to exhibit pro-cancer properties. On the other hand, 35 KDa inter- α -trypsin inhibition heavy chain 4, anastellin, apolipoprotein A-1, fibrinogen β -chain and keratin type 1 cytoskeletal 9 were formed to exhibit anti-cancer in nature [10]. Therefore, it can be assumed that cancerous Ig's may play dual roles in cancer immunology. Serum proteins with pro-cancer properties may react with cancerous Ig's for growth/proliferation of cancer cells in normal human circulations.

On the other hand, those with anti-cancer properties in nature may also react with surface bound cancerous Ig's to inhibit the growth/regulation of cancer cells *in vivo* [10]. A list of detected serum proteins associated with pro- or anti-cancer

properties were briefly highlighted in the following sections.

4.1. Serum Proteins with Pro-Cancer Properties

1) **“C4h.-binding protein”** α chain is a soluble protein complex which can inhibit activation of complement through classical pathway by factor I-mediated inactivation of C4b [11] [12]. Therefore, interaction of C4b-binding proteins with cancerous Ig's may help cancer cells by inhibiting complement activation [12].

2) **“C3a and C3b”**

By serving as a central protein in the complement cascade, and as cleavage products, C3a and C3b, have been found to be critical in engrafted in mouse models [12]. Mice deficient in C3 also exhibited significantly decreased tumor proliferation. C3a was shown to exhibit proliferative activities in the neoplasia stage [13] [14]. C3 protein also demonstrates tumorigenic effects by secreting vascular endothelial growth factor [VEGF] to promote tumor angiogenesis and invasion/migration [13]. C3 can also be synthesized by gastric cancer-derived cell lines to promote cancer cell development and promotion.

3) **“Complement factor H”** is a key regulator of the alternative pathway of the complement system by acting as a cofactor of serine protease to induce cleavage and inactivation of C3b and C4b as well as C3 convertase [15]. Complement factor H is widely expressed by primary tumors and cancer cell lines [11] [16] including glioblastomas, myoblastomas, as well as carcinomas of the bladder, ovary and lung [17] to resist complement-mediated cytolysis [16] [17]. Therefore, it has been hypothesized that complement factor H acts to protect cancer cells from complement activation [18].

4) **“Serotransferrin”** is an iron binding and transport protein in human body for iron absorption and heme degradation as well as stimulating cell proliferation of cancer cells [19].

By blocking transferrin binding to the cancer cell surface, inhibition of tumor cell growth can be demonstrated *in vitro* [20]. Therefore, we believe serotransferrin is an important growth factor for the proliferation of cancer cells [20].

5) **“Vitronectin”** is produced in liver and can be found in serum and extracellular matrix. It is an inducer of stem cell differentiation, adhesion and survival in breast and prostatic carcinoma [21] [22].

4.2. Serum Proteins with Anti-Cancer Properties

1) **“Inter- α -trypsin inhibitor”**

Among these proteins with anti-cancer in nature, inter- α -trypsin inhibition heavy chain 4 is a type II acute phase protein from liver [10]. It can be frequently downregulated in multiple solid tumors and was found to increase cell proliferation and migration of cancer cells [10].

2) **“Anastellin”** is a fragment of first type III module of fibronectin and can interact with a variety of proteins, including integrins, proteoglycans, fibronectin

fibrinogen [23]. Anastellin is capable of promoting changes in fibronectin matrix. Through inhibition of angiogenesis, the tumor cells growth and metastasis can be reduced in human serum environment [10].

3) “**Apolipoprotein A-1**” is a major human plasma protein component of high-density lipoprotein (HDL). It exhibits certain properties of anti-inflammation and antioxidant capabilities [24] as well as cardioprotections [25]. Apolipoprotein A-1 was shown to be a biomarker of ovarian cancer and can suppress tumor growth and metastasis in animal model studies [5]. Mice deficient in apolipoprotein A-1 can develop tumors faster than the wild-type mice [25].

4) “**Fibrinogen β** ” is one of the three peptide chains (α , β and γ) of fibrinogen involved in the formation of blood clots. Fibrinogen is known to promote tumor angiogenesis by supporting cell adhesion migration, proliferation and differentiation of activated endothelial cells. Furthermore, the peptide fragments were found to inhibit tumor vascularization and increase tumor necrosis [26].

5) “**Keratin type 1 cytoskeletal 9**” is a structural protein in epidermal cells and was found to be downregulated in the drug resistant human breast cancer tissue and may be correlated with drug sensitivity of cancer tissues [27].

5. Functional Implications of Cancerous Ig's and Interacting Human Serum Proteins

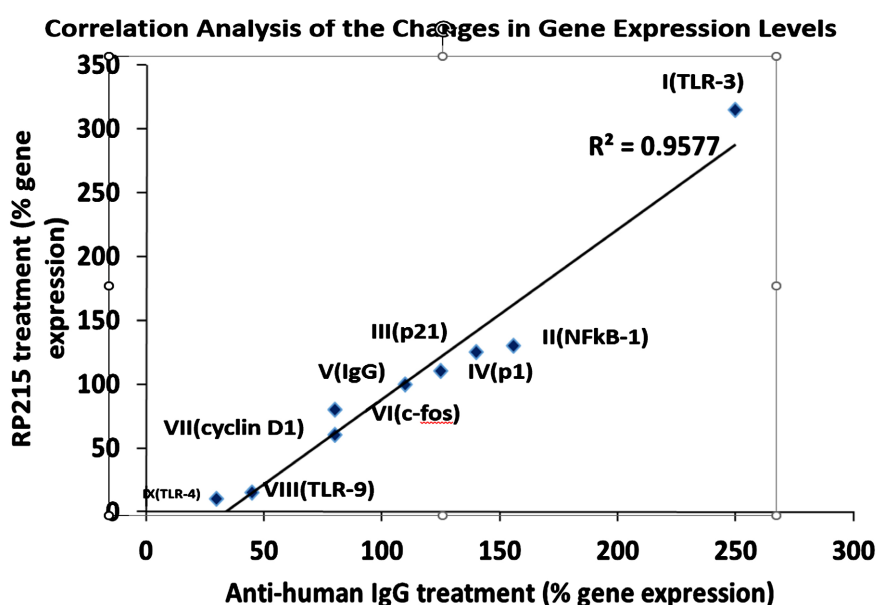
The nature of interactions between cancerous Ig's or CA215 and specific human serum proteins are currently unknown. However, we can not rule out any other possible interactions. Further in-depth investigations between specific serum proteins as described and cancerous Ig's or CA215 may be required to resolve the issues [10].

Based on the results of these observations, it can be hypothesized that dual roles of surface cancerous Ig's are played simultaneously in the immunology of cancer cells under normal human environments. Human serum proteins with either anti-cancer or pro-cancer properties may interact with cancer cells simultaneously. These cancerous immunoglobulins may play roles for growth/protection as well as inhibition of these cancer cells, respectively. Humanized RP215 monoclonal antibody with a carbohydrate-associated epitope and effector functions may be ideal to target uniquely the cancer cells for cancer immunotherapy in humans.

6. Effects of RP215 and Anti-Antigen Receptors on Changes in Gene Regulation Patterns of Cance Cells

Antigen receptors including cancerous Ig's and T cell receptors are widely expressed on the surface of cancer cells. RP215 with specific carbohydrate-associated epitope reacts mainly with cancerous Ig's, T-cell receptors and several other immunoglobulin superfamily proteins [4] [5]. Both anti-antigen receptors including RP215 were shown to induce apoptosis to cancer cells culturing at 1 - 10 $\mu\text{g/ml}$ concentration ranges [7]. Two cancer cell lines, OC-3-VGH (ovary) and C33A

(cervix) were used as the model for gene regulation and correlation studies [28]. By using semi-quantitative PCR as the method, we are able to determine changes in gene expression levels before and after ligand-receptor interactions during the *in vitro* culture [28]. A dozen genes involved in the immune system and growth of cancer cells were selected including those of NFK-B1, IgG, P21, EGF, CyclinD1 ribosomal P, c-fos and Toll-like receptors (TLK-2, -3, -4, -6, -7 and -9) [28] [29]. Basically, three different general receptor ligands, including RP215, anti-human IgG and anti-T cell receptor were used in the comparative studies of gene regulation changes upon incubation with different antigen receptors. Correlation analysis was performed for gene regulation changes in response to binding interactions of three types of antigen receptors on the surface of cancer cells. The results of such comprehensive correlation analysis are demonstrated and presented in **Figure 2** for those between RP215 and Antihuman IgG. Based on results of the analysis, the correlations coefficient between RP215 and antihuman IgG regarding gene regulation changes is 0.9135, whereas that between RP215 and anti-T cell receptors is 0.9071. Our correlation studies clearly indicate functionally equivalence among the three receptor ligands [28] [29]. The results seem to suggest that RP215 is a suitable ligand to study interactions with surface-expressed antigen receptors (anti TCR and anti Ig's) on cancer cells, similar to those of anti-Ig's and anti-T-cell receptors [29] [30].



Gene symbols: I. TLR3; (toll-like receptor3); II. NFKB-1; III. p21; IV. p1; V. IgG; VI. c-fos; VII. cyclin D1; VIII. TLR-9; IX. TLR-4.

Figure 2. Correlation analysis off changes in gene expression levels. Levels with different sets of antibody treatments. Some genes selected for correlational analysis correlations were made between those of RP215 and anti human IgG.

Toll-like receptors (TLRS) are known to be a family of receptors to pathogen-

associated molecular patterns (PAMP) which might play important roles in host-defense from infections [30]. Regulation of TLR's has been implicated in the proliferation and survival of cancer cells, similar to those of surface antigen receptors. Therefore, in terms of changes in gene regulations, it was also found that anti-antigen receptors and toll-like receptors are also well correlated [29].

7. General Conclusions

In this review, RP215 with a specific carbohydrate-associated epitope was recognized as the only monoclonal antibody leading to the discovery of cancerous antigen receptors and immunoglobulin superfamily proteins [1]-[4], widely expressed on cancer cell surface.

The interactions of antigen receptors with detected human serum proteins may play critical roles in growth inhibition or proliferation of cancer cells under normal human environment [10] [28]. It was clearly demonstrated that known anti-cancer and pro-cancer nature of these serum proteins may strongly support this hypothesis [10]. It is also logical to assume that RP215's specific targeting of cancerous antigen receptors may lead to induced apoptosis of cancer cells *in vitro* and *in vivo* [9]. Furthermore, RP215 and related antigen receptors were shown to affect gene regulation changes of targeted cancer cells with greater than 90% of correlations (Figure 2) [9] [10].

Therefore, we believe that RP215 in different molecular forms (humanized, naked, CAR-T or CAR-NK) is an ideal probe to target a variety of cancer cells in humans in cancer immunotherapy.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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Abbreviations

IgSF	immunoglobulin superfamily protein
KC-MS/MS	Liquid chromatography-tandem mass spectrometry
CA215	cancer antigen (biomarker) recognized by RP215 monoclonal antibody
ScFv	single chain variable fragments of immunoglobulins
T	GalNAc-Gal
Tn	GalNAc
Ts	Sialyl-T antigen
CAR-T	chimeric antigen receptor-T cell construct
IL-2	interleukin-2
IL-7	interleukin-7
Γif-7	Γ-interferon-7
MALDI-TOF-MS	matrix adsorption laser desorption, ionization-time of flight mass spectrometry
MHC	multiple histocompatibility complex
C33A	a cervical cancer cell line
OC-3-VGH	an ovarian cancer cell line
NF-KB-1	Nuclear Factor Kappa B, subunit 1
P21	cell cycle regulator
EGF	epidermal growth factor
Cyclin D1	cell cycle regulator
Ribosomal p1	ribosomal subunit 1
c-foss	oncogene
TLK	toll-like receptor
TUNEL	terminal deoxynucleotidyl transferase dUTP nick end labeling