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Bacterial Immunoglobulin (Ig)-Receptors: Past and Present Perspectives

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Abstract The new contributions of this paper include the identification of bacterial Ig receptors as valuable reagents for the detection of Ig molecules in species of wild, domestic and laboratory animals. It is important to detect antibodies as markers of infection and zoonotic diseases. The techniques used to investigate the binding of the bacterial Ig receptors with immunoglobulins present in different specimens were established techniques such as ELISA and immunoblot analyses. In addition, the affinity chromatography allowed for the purification of immunoglobulins and their fragments. The use of commercially available conjugates of enzyme labelled proteins L, A, G and SpLA is discussed.

Keywords: *staphylococcal protein A, streptococcal protein G, peptostreptococcal protein L, bacterial Ig-receptor, immunoglobulin, protein LG, protein AG, protein LA, chimeric protein LAG (SpLAG)*

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1. Introduction

Several bacterial immunoglobulin (Ig)-receptors have been identified in recent years. They have proved to be powerful tools for binding, detection and purification of immunoglobulins. The better studied bacterial Ig receptors include the protein A (SpA) of *Staphylococcus aureus* [1]; protein G (SpG) of *Streptococci* [2,3]; and protein L (SpL) originally isolated from the cell wall of the anaerobic bacterium *Peptostreptococcus magnus* [4].

These bacterial proteins displayed on the cell wall of microorganisms play an important role in bacterial escape mechanisms from the immune system. They cause activation of the complement system by the classical pathway, polyclonal activation of B-lymphocytes, inhibition of phagocytosis and other effects [5,6,7,8]. In addition, they have the biological property of binding to a wide range of mammalian and non-mammalian immunoglobulins. This binding does not interfere with the antigen binding sites on the immunoglobulin receptors. These receptors have been called immunoglobulin-binding protein, IBP [9-14].

Protein A and G have been used as immunological tools in serological tests used in the immunodiagnosis of infectious diseases, such as Borrelia burgdorferi in zoo animals [14]. Ongoing studies suggest that the bacterial Ig receptors are also potential tools in biomedical research, therapy of human diseases, biotechnology and industry [5,15,16].

2. Bacterial-immunoglobulin Receptors

Protein A was the first of the bacterial immunoglobulin receptors described. It is displayed on the cell wall of *Staphylococcus aureus* and it has been shown to react in a non-specific manner with human IgG in immunodiffusion tests [1]. Kronvall and Williams (1969) described differences between IgG subclasses in their Staphylococcal protein A binding capacities [17]. Based on their Ig-binding properties, bacterial Ig receptors were classified as Fc receptors and Fab receptors. The types I and II Fc receptors are found on *S. aureus* and on group A *Streptococci*, respectively. The type III Fc receptors are found on groups C and G *Streptococci* [19]. It was named Streptococcal protein G and binds to IgG from a wider range of mammalian species than does SpA [3,17]. Protein L from *Peptostreptococcus magnus* is a bacterial Fab receptor, which binds to the kappa light chains of Igs from various mammalian species [4,10,18]. Other bacterial Ig receptors have been described in another bacterial species [19-31]. Table 1 displays the SpA domains and their functions as an example of bacterial Ig receptor [32].

3. Biological Significance of bacterial-Ig receptors.

Through diverse interactions with IgG molecules, the cell wall bound Ig receptors may play a critical role in

the virulence of bacteria. Such interactions include interference with the antibody-dependent host immune response and coating of the bacterial cell surface with Igs [6]. Muñoz et al (1998) described the ability of a small recombinant protein G domain, B2, of molecular weight (MW) 6.5 kDa to inhibit the covalent binding of C3b to the Fc portion of the rabbit IgG without affecting binding to the Fab portion of the molecule. A similar inhibition of C3b binding was observed when protein A was used. The authors concluded that this could be a general mechanism of escape of these bacterial proteins [33].

4. Staphylococcal Protein A (SpA) Biology and Immunological Applications

SpA has MW approximately of 42 kDa [5]. It binds to the Fc fragment of IgG produced by many animal species including human, dog, rabbit, hamster, monkey and others [5,9,13,34,35,36,37]. The native SpA consists of five domains. Of these, four show high structural homology, containing approximately 58 amino acids and have the capacity of binding to Fc regions of IgG [38,39]. Structural changes following SpA binding to the Fc region of IgG have been studied by nuclear magnetic resonance (NMR) and spectroscopy, which showed that the interaction involves the Z domain of SpA and does not involve helix unwinding [39,40,41]. The SpA-binding site is in the interface CH_2-CH_3 of human and guinea pig IgG. It may be similarly located in another species [42].

In addition to Fc gamma domains of IgG, SpA can interact with the Fab domains. It mediates conventional antigen binding by Ig heavy-chains belonging to the VH3+ family [9,34,43-49]. Sasso et al (1989) studied the binding of Ig Fab regions to SpA and reported the SpA binding of 24 isolated human monoclonal IgM antibodies, measured in a solid phase radioimmunoassay (RIA) [50]. The same authors in 1991 reported the purification of human IgA by SpA-affinity chromatography. They suggested that the binding of SpA to the Fab domains of Ig molecules is restricted to those possessing the VH3+ gene product regardless of Ig isotype [51].

Hillson et al (1993) reported the structural basis for the interaction of SpA and VH3+ Ig molecules. The results demonstrated that among human IgM molecules, specificity for SpA was encoded by at least 11 different VH3 germline genes. The binding of the SpA to human IgM has similarities with the bacterial superantigen binding to T cells [52,53,54]. In 1994 Kristiansen and colleagues studied the capacity of SpA to induce Ig production by VH3-expressing human B cells preferentially. The results of these experiments suggested that SpA is an Ig-superantigen [55].

Kozlowski et al (1996) have shown that the interactions of the Fab binding site on SpA with VH3+ Ig molecules can lead to activation of the complement system proteins by the classical pathway [7]. Feijo et al (1997) characterized a mouse IgM monoclonal antibody that bound to Fab binding region of SpA [56]. Cary et al (1999) reported similar interactions, between SpA and mouse IgM, which induced important effect on the clonal selection of B-cell in mice [57].

SpA was found to augment the natural killer (NK) cell activity of peripheral blood lymphocytes against Burkitt's lymphoma-derived Raji and Daudi cells, most likely mediated by the SpA-induced interferon [58]. Macrophages/monocytes and T helper cells play a role in the regulation of B-cell antibody secretion induced by SpA [59].

When used in enzyme-linked immunosorbent assays (ELISA) conjugates of SpA labelled with enzyme have higher binding affinity and produce less background than antiglobulins labelled with enzyme [35,38,60]. For example, SpA labelled with horseradish peroxidase has been used to study lymphocyte surface markers; the expression of viral antigens on the membranes of cells infected with and herpes simplex virus [5]; and for the determination of specific antibodies in different mammalian species [35,36,61].

The prevalence of antibodies to *Toxoplasma gondii* in the sera of rare wildlife zoo animals of various species has been determined by SpA ELISA [16]. Similarly, iodine $[I]^{125}$ labelled SpA has been used in immunocytochemical techniques for the study of the connectivity of neural cells in the central nervous system [62]. Fluorescein-labelled SpA has been used in flow cytometry to study specific antigen expression in cell membranes [63]. Colloidal gold labelled with SpA has been used for the electronmicroscopic localization of IgG, C3, diverse antigens including alloantigens in B cells, study of the major histocompatibility complex (MHC) in guinea pigs, and enumeration of T- and B-cells in humans [5].

SpA has been labelled with other molecules including biotin [64], photoproteins [65] and europium [61] in the determination of low concentrations of specific antibodies in serum. In addition, SpA has been used in antibody capture ELISA [66], and in the discrimination of IgG and IgM for immunodiagnosis purposes in other settings [67].

SpA may be considered a nature's universal anti-antibody as suggested by Surolia et al (1982) [5], and it may be used as immunological markers for immunodetection in several mammalian species. Taylor et al (2002) purified see otter plasma IgG using protein-A-agarose. This reagent was further used for the development of a test to determine serum Ig concentration in this sea mammal [68].

Table 1. Regions and functions of SpA molecular domains as an example of bacterial Ig receptor

No	Staphylococcal protein A		
	Domains	Regions	Functions
1	YSIRK Signaling peptide	1-40	Substrate recognition
2	IgG binding	41-330	Capable of binding to Fc and Fab regions of many mammalian IgG
3	Octapeptide	331-420,	Unknown
4	LysM (lysine motif) domain	421-460	Peptidoglycan binding
5	LPXTG domain	461-517	Cell wall anchoring

Protein A mimetic affinity ligand, obtained from the screening of a multimeric combinatorial peptide library was used to purify, in a single isolation step, immunoglobulins from sera of rabbits, mice, humans, horses and other mammals [69].

5. Streptococcal Protein G (SpG) Biology and Immunological Applications

Streptococcal protein G, type III bacterial Fc receptor, is a small globular protein produced by several Streptococcal species and is composed of two or three nearly identical domains, each of 55 amino acids. SpG binds the Fc regions of IgG from many mammalian species [3,70,71,72,73,74]. The primary amino acid sequence of the IgG-binding regions (C1, C2 and C3) of SpG are not homologous to those of the corresponding regions (E, D, A, B and C) of SpA [70,75]. A prerequisite for adequate binding affinity for IgG by bacterial IgG receptors is the possession of at least two domains [76].

Streptococcal protein G has been shown to have high binding affinity to sera from various mammalian species including rabbit, human, pig, goat, sheep, cow by using competitive RIA [77] and to cervids, giraffes and peccaries by direct ELISA [14]. More recently using direct ELISA, some new interactions of SpG with free-ranging nondomestic hoofstock (order Artiodactyla) such as addax, antelope, bison, bontebok, elk, impala, kudu/nyala, muntjac, oryx, sheep, and white-tailed deer have been reported [78]. SpG does not bind to the Fc region of the immunoglobulin Y (IgY) of avian species [79,80].

Deruaz et al (1996) reported that a peroxidase labelled-protein G conjugate was efficient in the detection of antibodies to *Borrelia burgdorferi*, the causative agent of Lyme disease in wild animal. The ELISA used correlated well with the passive hemagglutination test [81]. In fact, Sugiyama et al (1998) carried out serological surveillance for Lyme borreliosis in Japanese rupicaprine bovid, *Capricornis crispus* using a protein G-ELISA [82]. Marin et al (1998) compared polyclonal, monoclonal and SpG-peroxidase conjugates in an ELISA for the diagnosis of *Brucella ovis* in sheep [83].

The immunoblot analysis for the detection of monoclonal antibodies using protein G conjugates was reported by Akerstrom et al (1985) [84]. Hu et al (1997) later reported a procedure for the optimization of immunoblot analysis using protein G-horseradish peroxidase (SpG-HRP), which avoided the false positive reactions often caused by secondary antibodies and increased the detection of autoantibodies [85].

Akerstrom et al (1985) used immobilized protein G for the purification of IgG from different mammalian species [84]. Perosa et al (1997) reported that SpG binding to F(ab')2 is restricted, as indicated by the lack of reactivity of F(ab')2 fragments from human IgG with SpG-sepharose columns [86]. Graham et al (1999) used SpG affinity chromatography for the selective removal of IgG, which often hinders the determination of serum IgE concentrations and IgM rheumatoid factors [87]. Aybay and Imir (2000) reported the use of SpG affinity chromatography to separate the IgG fraction from fetal calf serum in a rapid procedure [88]. Saha et al (2003) measured the binding constant of IgG using an acoustic wave sensor. This study showed that antigen binding induces conformational changes in SpG binding sites [89].

6. Peptostreptococcal Protein L (SpL) Biology and Immunological Applications

The Ig-binding capacity of P. magnus strains was studied in a sensitive binding assay using purified human Ig preparations. Myhre and Erntell (1985) showed that the binding of immunoglobulin to P. magnus was due to non-immune reactivity mediated by a heat-stable surface protein. Mutanolysin-extracted protein with a MW of 95 kDa was obtained highly purified by a single isolation step on IgG-Sepharose. Further experiments utilizing immunoblot assays showed that the isolated bacterial protein binds immunoglobulins through L chain interaction [4]. Subsequently the gene for protein L was cloned and sequenced. The molecule contains 5 homologous "B" repeats of 72-76 amino acids each. These B repeats were found to be responsible for the interaction with immunoglobulin L chains [90].

Protein L is comprised of an alpha-helix packed against a 4-stranded beta-sheet [91]. The SpL binds strongly to human kappa light chain subclasses I, III and IV from the 5 classes of human immunoglobulins. Also, SpL binds to other mammalian Ig molecules without interfering with the antigen-binding site, strong protein L-binding activity was shown in the serum of 12 out of 23 tested mammalian species, including primates and rodents [10]. SpL shares a similar binding mode to SpG [92].

Nilson et al (1993) purified various genetically engineered antibodies using protein L affinity chromatography. IgG, IgM, and IgA were purified from human and mouse serum in a single step using an affinity chromatography protocol [93]. Likewise, Bottomley et al (1995) immobilized a single purified Ig-binding domain of SpL (SpL-1) on to an agarose gel for testing against an array of Ig molecules and Ig fragments. The purification of immunoglobulins by SpL-1 binding was then confirmed by ELISA [94].

7. Recombinant Protein LA (SpLA), Biology and Immunological Applications

Protein LA, a novel hybrid protein, structurally contains 4 of the Ig Fc-binding and 4 of the Ig Fab binding regions on SpA with 4 of kappa light chain-binding sites of protein L. It has a MW of 65 kDa. Protein LA combines the binding properties of the both SpL and SpA and in some cases, give higher binding affinity than either protein alone [12]. The binding of an Ig to SpL does not interfere with binding of another Ig molecule to the SpA domains and vice versa. Protein LA has been shown to bind effectively to immunoglobulins and their fragments from many species of animals. ELISA, dot blot and immunoblot analyses were used to show these interactions [12,13].

8. Recombinant Protein LG (SpLG) Biology and Immunological Applications

Kihlberg et al (1992) synthesized protein LG by genetic engineering. SpLG comprises of 4 Ig-binding domains of SpL and 2 IgG Fc-binding SpG domains. This hybrid molecule was found to bind many intact human Ig molecules and Ig fragments. It proved a powerful tool for the binding, detection and purification of antibodies [95]. Axcrona et al (1995) reported that chimeric SpLG was a potent mitogen for mouse splenic B cells, and induced cell differentiation and the production of immunoglobulins. Inhibition experiments demonstrated that the Ig-binding capacity of both SpG and SpL in the chimeric molecule are independent of each other [96]. It was also shown that SpLG selectively absorbed Igs present in the sera of humans, rabbits, mice and rats [97].

9. Recombinant Protein AG (SpAG) Applications

A recombinant protein that combines the IgG-binding domains of SpA and SpG was developed [36,98], and labelled to horseradish peroxidase. It was used as universal conjugate in ELISA for the assessment of antibodies against *Brucella spp* in cattle, sheep, dogs, goats and pigs [98]. The authors, Nielsen et al (2004) reported that similar results as the one shown using the chimeric protein AG were obtained when murine monoclonal antibody-enzyme conjugates were used [98].

10. Bacterial Ig-receptors and Recent Developments.

Vaz and collaborators (2015) reported that for examining exposure to pathogens in wildlife populations serological studies are often carried out. Species-specific antibodies are not available for many wild animals and bacterial Ig receptors have shown to be very useful in epidemiological studies of infectious diseases in zoo and wild animal populations. SpA, SpG and SpL binding capacities to immunoglobulins from 17 species of mammalian animal including those of Marsupialia and Monotremata were assessed and evidenced that the bacterial reagents binding to Igs was not predictable of the evolutionary distance between animal species [99].

Albano et al, 2014 reported the use of SpA-ELISA and SpG-ELISA to study the prevalence of antibodies against *Paracoccidioides brasiliensis* in wildlife population in a geographical area of Brazil. SpA-ELISA showed the highest sensitivity in immunodetection [100].

Pelli et al, 2014 reported that sera collected from 23 different Brazilian wild mammals where shown to bind SpA and/or SpG indistinctly. A high SpA binding rate was observed in all species, except for the orders Artiodactyla, Didelphimorphia and Rodentia. Affinity for SpG was higher in animals of the order Artiodactyla, and low affinity was observed in the order Carnivora, specifically felines [101].

SpA-affinity chromatography was also used for the preparation of an anti-camel immunoglobulin G, that was then conjugated with horseradish peroxidase using glutaraldehyde based assay. This reagent was then used in ELISA to quantify specific antibodies [102].

A chimeric protein SpLAG-HRP was chemically engineered to be used as universal conjugate in ELISA for the detection of mammalian and avian Igs. SpLAG showed high affinity to ostrich IgY and IgGs from the following species: pig, rabbit, goat, sheep, human, mouse, cat, dog, skunk, coyote, mule, donkey and raccoon [13]. It did not react with the panel of avian immunoglobulin Y including the following species: pheasant, duck, guinea hen, goose, quail, bantam hen and chicken. SpLAG had higher binding affinity as compared with its individual components, which bind to Fc or Fab regions of IgG as shown in Figure 1 [13].

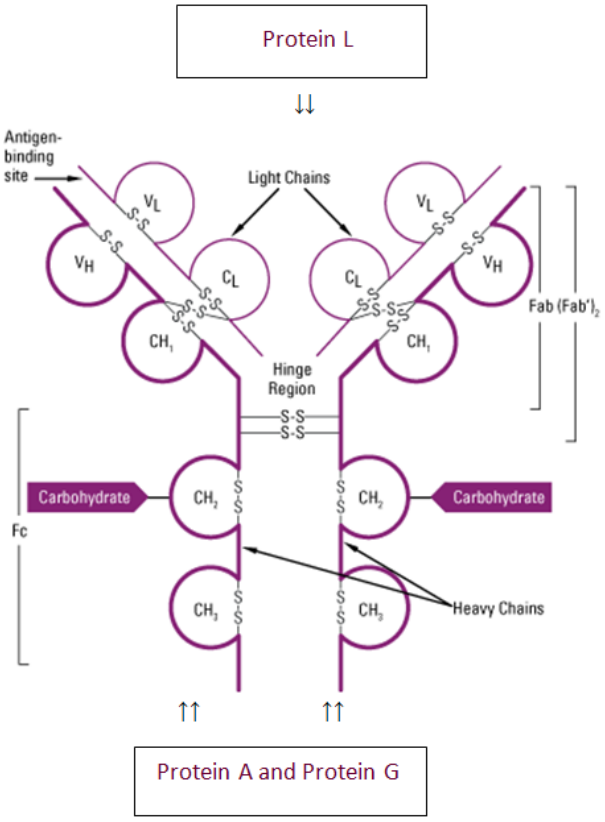

Figure 1. Interactions between IgG molecules and bacterial Ig receptors. SpA and SpG interact with IgG heavy chains but protein L interacts with light chains

In summary, bacterial Ig receptors have shown to be an important tool in various techniques used in molecular biology, laboratory medicine, immunology and biochemistry. The authors of this paper look forward to report in future new developments in this field.

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