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Cell Research

RESEARCH HIGHLIGHT

Secret(ory) revealed: the long-awaited structures of secretory IgA

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Cell Research (2020) 30:558–559; https://doi.org/10.1038/s41422-020-0351-4

Secretory IgA (SIgA) is a specialized form of antibody present at high concentrations in mucosal secretions, where it acts as the first line of defense of the immune system. In a recent paper published in *Cell Research,* Wang et al. present cryo-EM structures revealing the architecture of SIgA and its interactions with SpsA, a pneumococcal adhesin that piggybacks on SIgA to facilitate gut colonization and host cell invasion by *Streptococcus pneumoniae*.

More IgA is produced per day in humans than any other isotype. A large percentage of serum IgA is packaged with additional polypeptide chains and transported across the mucosal epithelial layer. This creates secretory IgA (SIgA), which is present at high levels in the secretions that coat mucosal surfaces. These mucosal regions, including the oral and nasal cavities, eyes, gut, and urogenital tract, represent the initial site of invasion for nearly all pathogens. SIgA acts at these vulnerable surfaces to protect against pathogen invasion by latching onto the microbes and sterically preventing them from adhering to host cells (i.e., immune exclusion); furthermore, SIgA can escort gut pathogens and antigens into the gut-associated lymphoid tissue (GALT) for immune cell priming.[1] In addition, SIgA is found at high levels in breast milk and maternal SIgA plays a protective role in infants.

SIgA consists of two or more (up to five) IgA antibodies that are covalently attached to additional proteins called the J (joining) chain and secretory component (SC) to form a large, highly stable complex. First, two IgA antibodies are covalently linked to a small protein called the J chain to form polymeric IgA (pIgA). PIgA can then interact with the polymeric Ig receptor (pIgR) on the basolateral surface of mucosal epithelial cells, which then transcytoses the pIgA through the cell and releases it from the apical (mucosal) surface. However, during the process of transcytosis, the ectodomain of pIgR (also called SC) is cleaved and covalently attached to pIgA; this entire complex is what is known as SIgA.[1]

Crystal structures of IgA1-Fc/receptor complexes were reported over 15 years ago;[2,3] however, the molecular details underlying the SIgA complex have remained hazy, despite some important low-resolution structural studies.[4] It was known that IgA (and IgM) antibodies have extended C-terminal tailpieces that interact with J chain to form pIgA (and pIgM), but J chain has no known structural homologs to provide clues as to how this interaction occurred. The recent work by Wang et al.[5] along with results from Kumar et al.[6] reveals that the J chain adopts a strikingly non-globular fold that resembles the Greek letter λ, interacting simultaneously with the tailpieces and the Fc regions from both IgA monomers (Fig. 1). All four IgA tailpieces and the J chain cooperate to form a single intermolecular β-sandwich domain at the core of polymeric IgA; long J chain hairpins extend outward from that domain to interact with the Fc regions of both IgA monomers, holding the entire complex together. In addition to several intramolecular disulfide bonds, J chain forms intermolecular disulfides with one tailpiece from each IgA monomer.

The ectodomain of pIgR (called SC) contains 5 Ig-like domains; the N-terminal domain (D1) engages one IgA-Fc and the J chain simultaneously via surface loops (reminiscent of the antigen-binding CDR loops on antibody Fab fragments). Meanwhile, the linear rod-like configuration of domains D2 through D5 places the D5 domain near the Fc region of the opposite IgA monomer, in position to form a disulfide bond with IgA Cys311.[5] Thus, SC essentially acts as a structural brace, with D1 anchored on one side of pIgA via extensive interactions with its CDR-like loops while D5 is covalently attached to the opposite IgA monomer.

The structure of SIgA illuminates important functional characteristics, including its stability and its poor ability to activate the IgA receptor FcαRI. The remarkable stability of SIgA[7] is explained by the extensive non-covalent interactions formed by both SC and J chain with multiple regions of pIgA, combined with the intermolecular disulfide bonds that they form with IgA subunits. Secretory IgM, which is also unusually stable,[7] shares the same architectural arrangements of J chain and SC, as reported by the Xiao group.[8] In contrast to serum IgA, SIgA does not trigger strong inflammatory responses via the IgA-specific receptor FcαRI alone, but requires an integrin co-receptor that engages SC. Serum IgA engages two FcαRI molecules, one at each IgA-Fc Cα2–Cα3 junction.[2,9] Two of the four FcαRI-binding sites in SIgA are occluded by the J chain and SC, precluding the typical receptor clustering that occurs when FcαRI is activated by a serum IgA-opsonized pathogen.

SpsA is an adhesin from *Streptococcus pneumoniae* that aids in host invasion as well as evasion of host immune responses. It binds to SIgA via the SC, which facilitates *S. pneumoniae* gut colonization by establishing a foothold on mucin-bound SIgA complexes. Wang et al. present the structure of the N-terminal domain of SpsA bound to SIgA, revealing a helical structure that interacts with D3 and D4 of SC, on the opposite side of SC from pIgA.[5] In addition to enhancing gut colonization via interaction with mucin-associated SIgA, SpsA mediates host invasion by targeting uncleaved pIgR on host cells. *S. pneumoniae* binds to pIgR and is transported through the nasal epithelial layer by reverse transcytosis.[10] Furthermore, SpsA could allow *S.*

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Published online: 10 June 2020

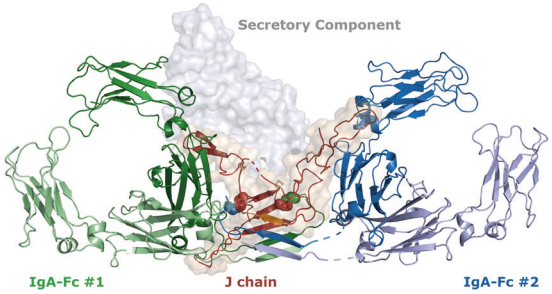

Fig. 1 Overview of the SIgA structure. The IgA subunits are shown in green and blue, J chain is shown as a red cartoon with a tan surface, and SC is shown as a transparent gray surface on the back side of SIgA. Note the unusual, non-globular fold of the J chain, which resembles the Greek letter λ. J chain forms a β-sandwich domain along with the tailpieces from both IgA subunits at the core of the complex; intermolecular disulfide bonds between J chain and IgA tailpieces are illustrated with colored spheres. Extensions from the central core region of J chain interact with the Fc regions of both IgA monomers in the complex. SC forms a structural brace that engages one IgA monomer and J chain via its N-terminal D1 domain; domains D2–D5 form an extended rod that places the D5 domain in position to form a disulfide bond with the Fc region of the opposite IgA monomer. SpsA is not shown in this figure, but it would bind to the back side of SC in the orientation shown.

pneumoniae to modulate SIgA-dependent immune surveillance in the gut. Sampling of gut antigens and microbes occurs at Peyer's patches, where intestinal microfold (M) cells bind to SIgA (along with SIgA-bound antigens or microbes) via the lectin receptors dectin-1 and siglec-5.[11] The SIgA-antigen complex is transcytosed across the M cell and delivered to dendritic cells in the underlying GALT, which generates a tolerogenic immune response to commensal gut microbes.[1]

The cryo-EM structures presented by Wang et al. greatly enrich our understanding of how IgA antibodies, J chain, and SC come together to form the remarkable SIgA complex. They provide insights into normal functions of this key player in mucosal immunity as well as mechanisms by which the mucosal immune response can be subverted by a bacterial pathogen.

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