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IgA as therapeutic antibody

Jeanette H.W. Leusen*

Immunotherapy Laboratory, Laboratory for Translational Immunology, UMC Utrecht, The Netherlands

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ABSTRACT

This review is focused on the promises of IgA as a new therapeutic antibody. For more than 30 years IgG molecules have been used in the clinic in the fields of oncology, hematology, auto immune diseases and infections. However, IgA might be a good alternative, since it recruits different effector cells, i.e. polymorphonuclear cells or neutrophils, but can also activate monocytes and macrophages. The present knowledge, but also future direction for IgA- based drugs are discussed.

1. Background

From their inauspicious beginnings in the 1980s, monoclonal antibodies have now become the most successful class of biotech drugs in history to fight cancer, allergy and autoimmunity. An important advantage of antibody therapy is the ability to target disease markers with great selectivity. The first antibody that was FDA approved for cancer patients was rituximab. This antibody is directed against CD20, which is expressed on almost all B-cells, and is very effective in patients with non-Hodgkin's lymphoma and several auto-immune diseases. The success of rituximab has facilitated the entry of many more therapeutic antibodies to the clinic, e.g. trastuzumab to treat Her/2+ breast cancer, and cetuximab (anti-EGFR) for colon cancer. All clinical cytotoxic antibodies are of the IgG isotype and despite their wide use, the major in vivo mechanism of action of these therapeutic antibodies is poorly understood. Based predominantly on in vitro findings, three hypotheses reign within the scientific community: (1) antibodies can induce apoptosis in target cells either directly or by ligand blockade; (2) antibodies can lyse target cells by complement-dependent cytotoxicity (CDC); or (3) antibodies recruit Fc-receptor (FcR) bearing 'killer' immune cells that can interact with the Fc-region of antibodies, leading to antibody-dependent cellular cytotoxicity (ADCC). Tumor antibody therapy is not effective in mice lacking Fc receptors. Furthermore, in humans, allelic variations of Fc receptors that increase the binding of antibodies often associate with better therapeutic outcome. Collectively, these lines of evidence strongly support the notion that Fc receptors are essential for the efficacy of IgG therapeutics. IgA is an antibody that is mostly been associated with mucosal tissues and neutralization of pathogens. However, it is the most produced antibody in our body and the second class in serum. In serum it mainly consists of a monomeric form, and as such it can be very effective against tumor cells. This was shown for the first time about 15 years ago by the group of prof. Valerius (Kiel) in vitro, and recently we could show the activity of IgA antibodies targeting EGFR in vivo.

2. Biology of IgA

IgA represents the most abundant antibody class at mucosal surfaces (Macpherson et al., 2000) and the second prevalent antibody class in human serum. In fact, IgA is produced at a rate of 66 mg kg^{-1} daily, which is more than all other isotypes combined. Two subclasses of IgA (IgA1 and IgA2) exist that differ by a 13-amino-acid longer hinge region for IgA2 (Fig. 1). In human serum, IgA is predominantly monomeric and constitutes 15–20% of the total amount of immunoglobulins. At mucosal surfaces, IgA exists in a dimeric and secretory form. Monomeric and dimeric IgA can bind the IgA receptor, FcαRI, but secretory IgA is a poor binder (Van Spriel et al., 2002). Molecular characteristics FcαRI FcαRI (CD89) is a type I transmembrane receptor belonging to the Ig receptor gene family. A single gene encodes the prototypic leukocyte FcαRI, and uniquely maps to chromosome 19q13.4. Although multiple transcripts have been described, only a single FcαRI transcript specifying two extracellular Ig-like domains, a transmembrane domain, and a short cytoplasmic tail, has been identified on myeloid cells. FcαRI is expressed as a 55–75 kDa glycoprotein on monocytes, neutrophils and subsets of dendritic cells (Geissmann et al., 2001). With an affin-

* Correspondence to: Laboratory for Immunotherapy, Laboratory for Translational Immunology (LTI), Section applied, HP F03.821, Room G03.555, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands. Fax: +31 88 7554305.
E-mail address: jleusen@umcutrecht.nl

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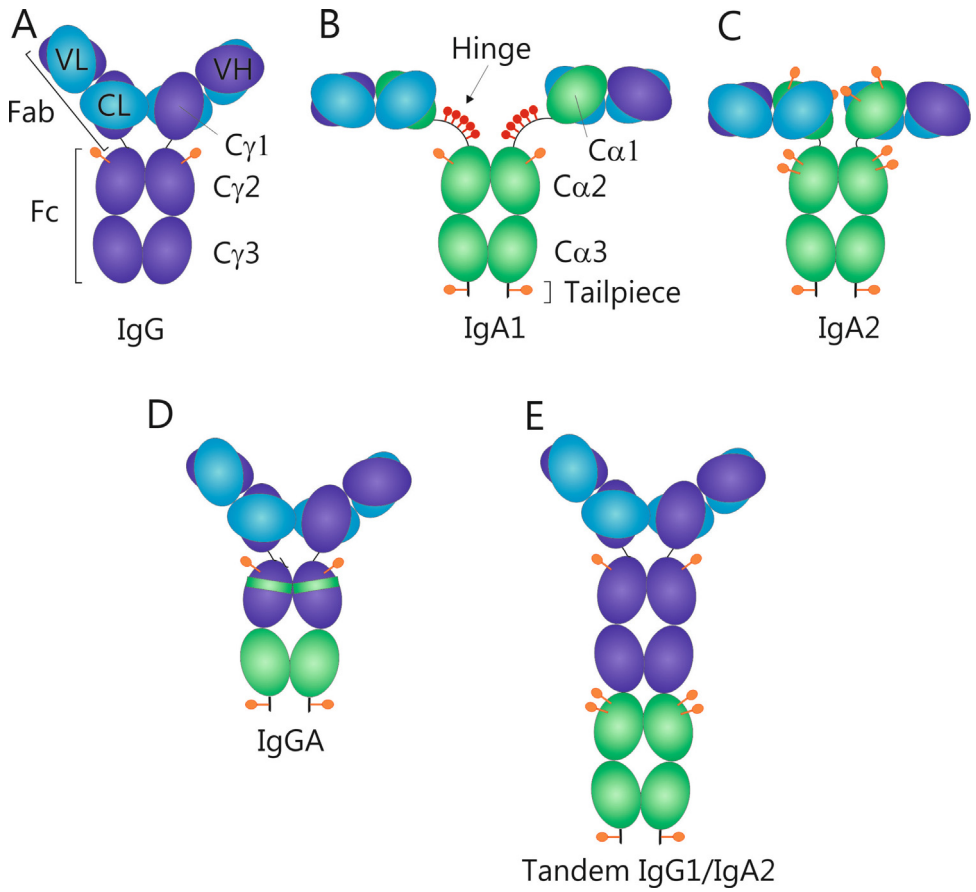

Fig. 1. IgG and IgA formats. Schematic representation of immunoglobulin molecules. In A IgG1 is depicted, with heavy chain in dark blue and light chain in light blue. B: hybrid molecule of IgG and IgA1, C: hybrid molecule of IgG and IgA2m2, D: hybrid molecule of IgG1 and IgA1 as described by de group of Georgiou, E: tandem molecule of IgG1 and IgA2, as described by Barrak et al. In red *o*-glycosylation, and in orange *n*-glycosylation is indicated. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

ity for IgA of ~10e6 M-1, FcαRI is a low affinity receptor (Wines et al., 1999; Monteiro and Van De Winkel, 2003). Accordingly, FcαRI can stably interact with complexed IgA, whereas monomeric IgA presumably binds only transiently. Whereas all other leukocyte Fc receptors (FcR) bind their ligand by the second extracellular Ig-like domain, the ligand-binding site for IgA is located in the first extracellular domain of FcαRI (Morton et al., 1996; Wines et al., 1999; Wenig and Sondermann, 2003; Garman et al., 2000; Herr et al., 2003). Engagement of IgA immune complexes or IgA opsonized targets with FcαRI induces phosphorylation of cellular proteins through its associated FcR γ-chain (FcRγ), including Src and Syk family protein tyrosine kinases, and increases intracellular free Ca2+, resulting in diverse cellular effector functions, such as phagocytosis, antibody dependent cellular cytotoxicity (ADCC), superoxide generation, cytokine production, antigen presentation and inflammatory mediator release (van Egmond et al., 2001). On the other hand, FcαRI can also perform inhibitory functions by the so-called Janus-like function, This means that through an inhibitory ITAM configuration after monomeric IgA binding the recruitment of the tyrosine phosphatase SHP-1 is induced, with a powerful anti-inflammatory role (Pasquier et al., 2005; Rossato et al., 2015). Importantly however, therapeutic IgA antibodies can counterbalance these divalent interactions by inducing strong crosslinking with the antigens leading to aggregation of FcαRI and a potent activation that is often stronger than FcγR, as shown by efficient ADCC of various tumor targets (Valerius et al., 1997; Keler et al., 2000; Deo et al., 1998). Therefore, FcαRI is now considered a promising receptor for immunotherapy of malignant and infectious diseases (Bakema and van Egmond, 2011). Human FcαRI transgenic mice FcαRI transgenic mice were previously generated in our Immunotherapy group (van Egmond et al., 2000). In these mice the expression pattern and regulation of human FcαRI is similar to humans. The receptor is expressed exclusively on monocytes, neutrophils and eosinophils. It can be induced on macrophages, like liver Kupffer cells (van Egmond et al., 2000), upon treatment with G-CSF, an inflammatory mediator known to upregulate FcR. We have crossed FcαRI transgenic mice to C57BL/6, Balb/c and SCID background, enabling testing of various tumor models (Boross et al., 2013).

3. Polymorphonuclear cells (PMN) as anti-tumor effector cells

PMNs are the most abundant cytotoxic cells in humans. Due to their potent cytotoxic capability they represent an attractive effector cell population for immunotherapy. PMN numbers can be easily increased in vivo by growth factors, like granulocyte-colony-stimulating factor (G-CSF). In addition, PMNs are primed by these growth factors. Research suggests an essential role for PMNs in anti-tumor immunosurveillance. In many tumors a PMN infiltrate is observed upon histological examination. PMNs were, furthermore, reported to be the predominant effector cell population for killing of breast cancer cells in the presence of HER-2 mAb in vitro, especially after priming of neutrophils by G-CSF. Elimination of PMNs in mouse tumor models abrogated IgG mAb induced resistance to tumor challenge (Albanesi et al., 2013). Interestingly, an increasing