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Bi-functional Two-in-One Antibodies are synthesized by Chicken Immunization

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Introduction

There are several different types of bispecific antibodies, such as Two-in-One antibodies, which have two Fab arms that may bind to two different antigens. They bypass the time-consuming engineering and purification stages that would otherwise be necessary to achieve optimal chain matching while making up for lower immunogenicity thanks to their IgG-like architecture. We present the first instance of yeast surface display (YSD) screening of chicken immunological libraries leading to the identification of a two-in-one antibody. The resulting antibody targets both the EGFR (epidermal growth factor receptor) and PD-L1 (programmed death ligand 1) on a single Fv fragment. The dual action Fab can block EGFR signalling by adhering to dimerization domain II and severing the link between PD-1/PD-L1. The Two-in-One antibody also exhibits particular cellular binding capacities on EGFR/PD-L1 double positive cells [1].

The use of bispecific antibodies (bsAb) has grown in popularity recently. Traditional monoclonal antibodies (mAbs) or their combination are unable to address new therapy methods made possible by BsAbs, which can simultaneously target two separate antigens. A subclass of bsAbs known as two-in-one antibodies with dual action Fabs (DAFs) binds two separate antigens with each Fab arm, resulting in a tetravalent, bispecific IgG-like molecule. In the normal IgG-like bispecific antibody environment, just 12.5% of appropriately produced molecules require flawless heavy chain heterodimerization and precise light chain pairing. On the other hand, two-in-one antibodies can be produced without the requirement for further constant chain engineering because they have identical heavy and light chains. Thus, non-natural amino acid sequences, such as those seen in knob-into-hole antibodies or orthogonal Fab interfaces, are not required [2].

Description

By altering the light chain complementarity-determining domains (CDRs) of the HER2-specific antibody trastuzumab, Bostrom et al. created the first Two-in-One antibody that bound both HER2 and VEGF. Then, Two-in-One antibodies directed against HER3 and EGFR, IL-4 and IL-5, or VEGF and angiopoietin 2 were made using mutagenesis procedures. Clinical trials have looked at duligotuzumab, a dual antibody that targets HER3 and EGFR, for the treatment of epithelial-derived cancer, highlighting the significance of this therapeutic class. All of these antibodies, however, have CDR residues that partially overlap, which prevents antigen 1 from attaching to antigen 2, allowing only one antigen to attach at a time.

Nevertheless, DutaFabs have two distinct binding sites within the CDR loops. The H-side paratope is made up of CDR H1, H3, and L2, and the L-side paratope is made up of CDR L1, L3, and H2. As a result, these Fabs can simultaneously target two antigens using the same Fv region; nevertheless, DutaFabs have a more complex architecture [3]. Additionally, tetravalent IgG-like bispecific constructions were described, which are composed of designed arms rather than regular Fab arms, with one VH domain coupled to each of the constant CH1 and CL domains. One VH is placed in its normal position in a conventional IgG, while the second VH takes the place of the VL domain. Because of their ability to cross-link receptors, promote proximity between immune effector cells and tumour cells, or disrupt two disease-related signalling pathways, bsAbs are excellent therapeutic agents for the treatment of cancer. By simultaneously focusing on two cancer-specific antigens on the same malignant cell, bsAbs can become more tumor-specific. Many solid tumours have elevated levels of the therapeutic targets human epidermal growth factor receptor and programmed death ligand 1 (PD-L1) (EGFR). Numerous malignancies exhibit overexpression of PD-L1, which is thought to be a strategy used by cancer to evade immune surveillance.

When EGFR is overexpressed, it promotes tumour growth and metastasis in a number of cancers, including bladder, lung, colorectal, and breast cancer. In the skin and lung, epithelial cells spontaneously express it. The reported bsAb may have a favourable safety profile as a result of Koopmans and colleagues' discovery that EGFR-directed PD-L1 inhibition can enhance tumour selectivity [4]. Most of the therapeutic mAbs that are approved for use were created by immunising mice, rabbits, or other mammalian species. It is challenging to target mammalian species' broadly conserved epitopes because of their close phylogenetic relationship to humans. On the other hand, immunisation of chickens may produce antibodies that target epitopes that are inaccessible to immunisation of mammals. Additionally, compared to rodents, library synthesis in birds can be accomplished with just one set of primers due to the gene variety in these animals [5]. Recently, our group demonstrated how they isolated highly affine chicken-derived antibodies using yeast surface display (YSD) and fluorescence-activated cell sorting (FACS).

The first Two-in-One antibody was identified and characterised; it targets PD-L1 and EGFR with two distinct paratopes on a single Fab. It is created using immunised chickens by combining an immune light chain library's heavy chain with a common light chain antibody without altering the CDR parts of the antibodies. The Two-in-One antibody demonstrated distinct cellular binding properties on EGFR- and PD-L1-expressing tumour cells, as well as reduction of EGFR-dependent signal transduction and obstruction of the PD-1/PD-L1 interaction [6].

Conclusion

Most antibodies use the heavy chain CDRs as the predominant component when binding to an antigen, while they can tolerate minor modifications to the light chain CDRs. This property was used to select the first Two-in-One antibody from a phage display library by changing the light chain CDR regions. The development of Two-in-One antibodies then utilised additional engineering methods such computational-based design, structural-guided design, or random mutagenesis.

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