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Chicken Immunization Creates Bifunctional Two-in-one Antibodies

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Introduction

Bispecific antibodies come in a variety of forms, including Two-in-One antibodies, which include two Fab arms that may bind to two distinct antigens. Their IgG-like architecture compensates for reduced immunogenicity while also avoiding time-consuming engineering and purification steps that would otherwise be required to ensure proper chain matching. For the first time, we report the discovery of a Two-in-One antibody using yeast surface display (YSD) screening of chicken immunological libraries. The resultant antibody has two non-overlapping paratopes that target the epidermal growth factor receptor (EGFR) and programmed death ligand 1 (PD-L1) on the same Fv fragment. By attaching to dimerization domain II and disrupting the PD-1/PD-L1 connection, the dual action Fab can suppress EGFR signalling. Furthermore, on EGFR/PD-L1 double positive cells, the Two-in-One antibody displays specific cellular binding capabilities [1].

Bispecific antibody (bsAb) techniques have become increasingly popular in recent years. BsAbs, which may target two different antigens at the same time, have enabled new treatment mechanisms that can't be addressed by traditional monoclonal antibodies (mAbs) or their combination. Two-in-One antibodies with dual action Fabs (DAFs) are a subclass of bsAbs in which each Fab arm targets two different antigens, resulting in a bispecific, tetravalent IgG-like molecule. Only 12.5 percent of appropriately formed molecules in the typical IgG-like bispecific antibody setting require perfect heavy chain heterodimerization as well as accurate light chain pairing. Two-in-One antibodies, on the other hand, have two identical heavy and light chains and can be manufactured without the need for further constant chain engineering. As a result, there is no need to include non-natural amino acid sequences like those seen in knob-into-hole antibodies or orthogonal Fab interfaces [2].

Description

Bostrom developed the first Two-in-One antibody by mutating the light chain complementarity-determining domains (CDRs) of the HER2 specific antibody trastuzumab, which resulted in HER2 and VEGF binding. Following that, mutagenesis techniques were employed to create Two-in-one antibodies that targeted HER3 and EGFR, IL-4 and IL-5, or VEGF and angiopoietin. Duligotuzumab, a two-in-one antibody that targets HER3 and EGFR, has been studied in clinical trials for treating epithelial-derived cancer, underscoring the importance of this therapeutic class. However, these antibodies all have partially overlapping CDR residues, resulting in antigen 1 preventing antigen 2 binding and only enabling one antigen to attach at a time.

Within the CDR loops of DutaFabs, however, there are two separate binding sites. CDR H1, H3, and L2 make up the H-side paratope, while CDR L1, L3, and H2 make up the L-side paratope. As a result, these Fabs can target two antigens at the same time using the same Fv region; nevertheless, the design of DutaFabs is more complicated [3]. Furthermore, tetravalent IgG-like bispecific constructs were described, which are made up of designed arms with one VH domain connected to each of the constant CH1 and CL domains rather than ordinary Fab arms. In a standard IgG, one VH is inserted in its regular position, while the second VH substitutes the VL domain. bsAbs are ideal therapeutic entities for cancer treatment because of their capacity to cross-link receptors, mediate closeness between immune effector cells and tumour cells, or disrupt two disease-related signalling pathways. The tumor-specificity of bsAbs can be increased by targeting two cancer-specific antigens on the same malignant cell at the same time. The programmed death ligand 1 (PD-L1) and the human epidermal growth factor receptor are two therapeutic targets that are increased in many solid cancers (EGFR). Overexpression of PD-L1 is seen in a number of cancers and is thought to be a way for cancer to elude immune surveillance.

EGFR is overexpressed in a variety of malignancies, including bladder cancer, lung cancer, colorectal cancer, and breast cancer, where it is involved in tumour growth and metastasis. It is naturally expressed on epithelial cells in the skin and lung. Koopmans and colleagues found that EGFR-directed PD-L1 inhibition can improve tumour selectivity, resulting in a potentially favourable safety profile for the disclosed bsAb [4]. The majority of authorised therapeutic mAbs were developed by immunising mice, rabbits, or other mammalian species. Targeting epitopes that are broadly conserved in mammalian species is difficult due to their strong phylogenetic link to humans. Chicken immunisation, on the other hand, may result in antibodies that target epitopes that are not accessible by mammalian immunisation. Additionally, due of the gene diversification in birds, library synthesis can be done with a single set of primers, considerably lowering hands-on time and expenses when compared to rodents [5]. Our team recently described how they used yeast surface display (YSD) and fluorescence-activated cell sorting to isolate highly affine chicken-derived antibodies (FACS).

The first Two-in-One antibody, which targets PD-L1 and EGFR with two separate paratopes on a single Fab, was isolated and characterised. It's made from immunised chickens by joining the heavy chain of a common light chain antibody with an immune light chain library without changing the CDR portions of the antibodies. On EGFR- and PD-L1-expressing tumour cells, the Two-in-One antibody displayed unique cellular binding capabilities, as well as suppression of EGFR-dependent signal transduction and obstruction of the PD-1/PD-L1 relationship [6].

Conclusion

In antigen binding, most antibodies use the heavy chain CDRs as the dominant moiety and can tolerate some changes in the light chain CDRs. By altering the light chain CDR segments, this feature was used to extract the first Two-in-One antibody from a phage display library. Following that, further engineering techniques such as computational-based design, structural-guided design, or random mutagenesis were utilised to create Two-in-one antibodies.

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