Reversible blocking of antibodies using bivalent peptide-DNA locks

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Abstract:

Monoclonal antibodies have become important therapeutics for the treatment of a range of human diseases. However, their inability to distinguish antigens displayed on diseased and healthy cells can result in severe side-effects. Controlling the binding mode of therapeutic antibodies by a dual-specific targeting strategy increases the tissue specificity and can lower off-target side-effects. We developed a generic approach to reversibly block antibodies by taking advantage of their intrinsic ability to engage in multivalent interactions. Bivalent peptide-DNA conjugates were shown to be generic, non-covalent and easily applicable molecular locks that allow the control of antibody activity. The bivalent peptide-DNA locks with dsDNA as a rigid linker were shown to effectively bridge the relatively large distance between the two antigen binding sites within the same antibody, yielding exclusively the cyclic 1:1 antibody-ligand complex. The interaction between the bivalent peptide-DNA lock and the antibody is 500-fold stronger than that of the monovalent peptide, allowing effective blocking of the antigen binding sites in a non-covalent manner. The disruption of the strong bivalent peptide-DNA lock and antibody interaction by proteases or toehold-mediated DNA displacement reactions was shown to effectively restore the binding activity of the antibody in different in vitro binding assays. Furthermore, the use of DNA as a linker allowed signal integration of two different oligonucleotide inputs, yielding logic OR- and AND-gates. The range of molecular inputs could be further extended to protein-based triggers by using protein-binding aptamers.

Monday, April 20th, 2015, 10:00

Room ZNN, Ground Floor Seminarraum

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