Emerging concepts in monocloal antibody therapy

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Monoclonal antibodies have emerged as useful therapeutic vehicles for a variety of malignancies. The first generation employed polyclonal antibodies from various species, nearly all of which were ill-suited as cancer-directed pharmaceuticals, and predated hybridoma technology, which marked the second generation. Hybridoma technology enabled the production of murine monoclonal antibodies, and yielded a handful of promising clinical results, but these were outweighed by disappointing outcomes that nearly destroyed this nascent field. The third and current generation, now winding down, is characterised by the development, testing and use of antibodies with essentially human properties and broad clinical applicability. We will consider the opportunities for future improvement of unconjugated antibody therapy of human cancer and predict the defining elements of the next generation of this field.

Although antibodies were initially envisaged as delivery vehicles for various toxic compounds [1], most clinically useful antibodies are not conjugated. Only a few immunoconjugates have exhibited clinical utility and have been approved for use in human malignancy. For example, radioimmunoconjugates directed against CD20 exhibit significant anti-tumour activity [2,3]. An anti-CD33 antibody conjugated to the drug, calicheamicin (an antibiotic which binds to specific DNA sequences and induces apoptosis) has been approved for use in refractory acute myeloid leukaemia [4]. Immunotoxins have demonstrated anti-tumour activity as well [5].

The breakthrough represented by the development of hybridoma technology [6] led to the design and testing of unconjugated monoclonal antibodies designed to possess anti-tumour effects. Antibody-based therapeutics have emerged as important treatments for an increasing number of human malignancies [7–15]. An unconjugated anti-ERBB2 antibody (trastuzumab, also known as Herceptin) is widely used alone and in combination with chemotherapy agents in breast cancer [7]. Unconjugated antibodies directed against the B-cell idiotype [8] and CD20 exhibit significant utility in the therapy of lymphomas, and rituximab, an anti-CD20 antibody, has become a widely used, FDA-approved agent with applications to non-malignant diseases as well [9]. Alemtuzumab, an anti-CD52 antibody that fixes complement, has been approved for use in chemotherapy-refractory chronic lymphocytic leukaemia [10]. Cetuximab and panitumumab, which are directed against the extracellular domain of the epidermal growth factor receptor, are clinically active in advanced colorectal cancer [11,12]. Antibodies that promote CD28-mediated T-cell activation and proliferation by blocking the function of the CTLA-4 co-receptor on T-cells exhibit pre-clinical and clinical promise [13,14]. Finally, bevacizumab, an antibody directed against the vascular endothelial growth factor, has demonstrated broad utility in common neoplasms such as colorectal, breast and non-small cell lung cancers, particularly when combined with moderately effective chemotherapy regimens [15].

The current generation of clinically effective unconjugated antibodies did not emerge until fundamental advances in antibody engineering permitted the development of antibodies with human properties due to the replacement or avoidance of rodent immunoglobulin sequences. These advances improved the pharmacology and reduced the immunogenicity of antibodies, thus permitting repeated therapy for prolonged periods of time [16]. Interestingly, many of the clinically validated targets of unconjugated antibodies have consistently emerged as being abundantly expressed in human malignancies, and so represent the ‘low hanging fruit’ available to investigators seeking to develop cancer-directed drugs.

Most of the effective therapeutic unconjugated monoclonal antibodies possess human backbones of the IgG1 isotype. IgG1 effectively mediates the Fc domain-based functions of antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent complement lysis [17]. Several new strategies incorporate additional Fc domain modifications to increase the efficiency of each of these mechanisms [18–20]. Antibody size, valence and human composition can be

effectively manipulated to obtain tumour targeting that is customised for the intended therapeutic applications. We have conducted a series of studies that demonstrate the powerful influences of intrinsic binding site affinity on selective tumour targeting, and on selected anti-tumour mechanisms such as antibody-dependent cellular cytotoxicity (ADCC). These observations have important implications for the design of therapeutic antibodies.

It is now evident that antibody structures can be optimised to improve antibody targeting and the capacity to manipulate target cell and effector cell signalling, and this will improve the efficacy of antibody-based cancer therapy. Further improvements in efficacy will require the identification of appropriate tumour targets, and the development of strategies to activate immune effector mechanisms.

Conflict of interest statement

None declared.

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