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Opinion Article

Engineering Bispecific Antibodies to Overcome Immune Escape in Multiple Myeloma

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DESCRIPTION

Multiple myeloma is a type of blood cancer characterized by uncontrolled growth of plasma cells within the bone marrow. Despite substantial advances in treatment, including drugs that block protein degradation, drugs that modulate the immune system, antibodies targeting tumor cells, and transplantation of the patient's own stem cells, multiple myeloma remains largely incurable because of frequent relapses caused by tumor diversity and immune escape mechanisms. The bone marrow microenvironment in multiple myeloma is highly immunosuppressive, with dysfunctional T cells, regulatory T cells, and immature myeloid cells contributing to tumor evasion. In this context, bispecific antibodies have emerged as a promising immunotherapy strategy to redirect cytotoxic immune cells to target myeloma cells and overcome mechanisms of immune escape.

Bispecific antibodies are engineered proteins that can simultaneously bind to two different antigens. In multiple myeloma, one part typically targets a tumor-associated antigen on the surface of malignant plasma cells, while the other part binds to an immune cell such as a T cell or natural killer cell. This dual specificity allows bispecific antibodies to bridge immune effector cells directly to tumor cells, bypassing conventional antigen presentation pathways and overcoming inhibitory signals that often limit immune cell activity in the bone marrow environment.

B-cell maturation antigen is a prominent target for bispecific antibody development because it is highly and selectively expressed on malignant plasma cells and has minimal expression on normal tissues. Bispecific antibodies targeting B-cell maturation antigen and T cells have shown strong effectiveness in laboratory studies and early clinical trials. These antibodies promote the formation of a physical connection between T cells and myeloma cells, triggering T cell activation, proliferation, and release of cytotoxic molecules that induce tumor cell death. This mechanism works independently of additional signals that are often reduced in the immunosuppressive bone marrow environment.

Other emerging targets, such as G protein-coupled receptor class C group 5 member D and Fc receptor-homolog 5, expand treatment options and address tumor diversity and resistance to B-cell maturation antigen-targeted therapies. Bispecific antibodies directed against these targets have shown strong anti-myeloma activity in preclinical models and early-phase clinical trials. Combining two tumor-associated antigens in a single bispecific or trispecific antibody can further reduce the risk of tumor cells escaping treatment through loss of a single antigen.

The design of bispecific antibodies requires careful consideration of molecular structure, binding strength, and pharmacokinetic properties. Various bispecific antibody formats exist, including tandem single-chain variable fragments, antibody-like molecules with two binding domains, and dual-variable domain antibodies. Each format affects tissue penetration, stability, half-life in the blood, and the potential to trigger unwanted immune reactions. Optimizing these characteristics is crucial to maximize tumor-killing activity while minimizing side effects such as excessive immune activation and neurological toxicity. For example, antibody formats with extended half-life allow less frequent dosing and more sustained tumor control compared to smaller molecules that are rapidly cleared from the body.

Laboratory studies have shown that bispecific antibodies not only directly kill tumor cells but also modify the immune environment in the bone marrow. Activated T cells release signaling molecules that recruit additional immune effector cells, enhancing anti-tumor immunity. However, overactivation of the immune system can lead to excessive inflammation, requiring careful adjustment of doses, pre-treatment strategies, and stepwise introduction of therapy in clinical trials. Combining bispecific antibodies with immune checkpoint inhibitors, immune-modulating drugs, or drugs that block protein degradation can further enhance immune cell function and overcome inhibitory signals in the bone marrow.

Mechanisms of resistance to bispecific antibodies include reduction of target antigen expression, exhaustion of T cells, and upregulation of inhibitory molecules on immune cells. Spatial heterogeneity in the bone marrow and expansion of

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immunosuppressive cells also limit therapeutic effectiveness. Advanced laboratory studies have shown that optimizing bispecific antibody design, targeting multiple antigens, or combining with immune checkpoint blockade can reduce these resistance pathways. Engineering bispecific antibodies with optimized constant regions or additional co-stimulatory signals may further improve T cell persistence and killing activity.

Future directions in bispecific antibody therapy for multiple myeloma include the development of trispecific antibodies, incorporation of natural killer cell engagement, and rational combination strategies with existing treatments. Personalized approaches that profile antigen expression and immune cell composition in the bone marrow can guide patient selection and dosing strategies. Advances in antibody engineering, such as conditional activation and tumor-specific activation, aim to reduce systemic toxicity while maintaining strong anti-myeloma activity.

CONCLUSION

Bispecific antibodies represent a transformative immunotherapy approach to overcome immune escape in multiple myeloma. By simultaneously targeting tumor antigens and engaging cytotoxic immune cells, bispecific antibodies bypass conventional immune evasion mechanisms, activate potent anti-tumor responses, and provide accessible treatment options. Ongoing research continues to refine antibody design, optimize safety and effectiveness, and integrate these agents into combination treatment regimens. As engineering approaches advance and mechanistic understanding deepens, bispecific antibodies are poised to play a central role in improving outcomes for patients with multiple myeloma.