A myeloma-targeting monoclonal antibody offers new hope for treating multiple myeloma

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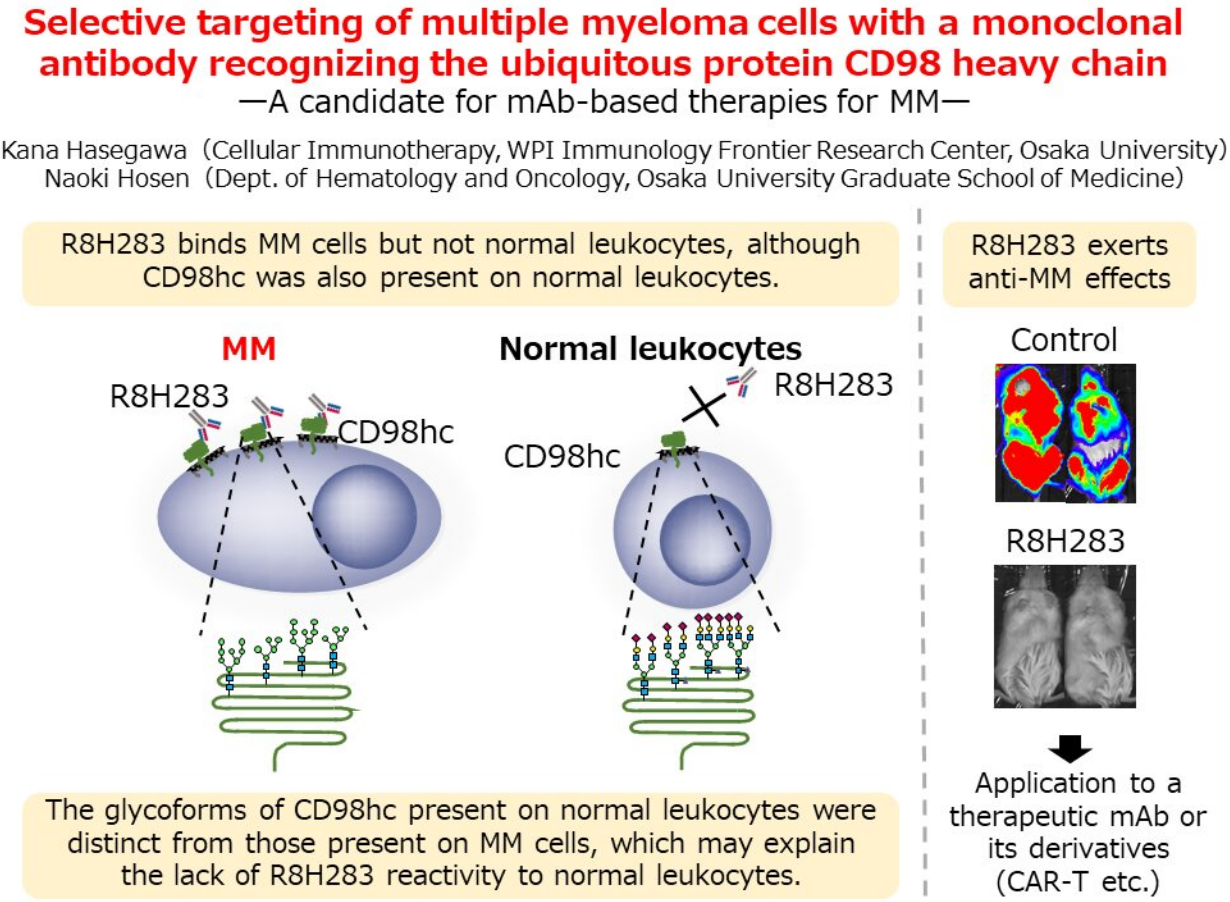

Summary of the research. Credit: Naoki Hosen

Multiple myeloma (MM) is a largely incurable cancer of plasma cells with an extremely poor prognosis. However, investigators from Japan have recently found that a common component of amino acid transporters, CD98 heavy chain, represents an effective monoclonal antibody target in treating MM.

In a study published this month in *Science Translational Medicine*, researchers from Osaka University have revealed a new approach that involves extensive screening of monoclonal antibody clones against primary human tumor samples. The aim was to identify cancer-specific conformational epitopes on ubiquitous proteins that cannot be identified by transcriptome or proteome analyses.

Some patients with MM show relapse in disease often due to immune-evading mutations that arise, making the cancer cells resistant to treatment. New target antigens are therefore urgently needed to develop a multi-targeted approach that can circumvent immune evasion and thereby avoid relapse of disease.

Extensive previous efforts have focused on targeting cancer-specific cell surface antigens identified by transcriptome or proteome analyses. But these efforts may have missed cancer-specific antigen epitopes formed by covalent, enzymatic modification of proteins (i.e., posttranslational modifications), such as glycosylation, or conformational changes. To widen the search for novel target antigens, Hasegawa and colleagues screened for cancer-specific monoclonal antibodies and then characterized their target-presenting antigens.

"By screening over 10,000 monoclonal antibody clones raised against MM cells, we identified R8H283, a monoclonal antibody that recognizes the CD98 heavy chain protein, which is part of an amino acid transporter," says lead author of the study Kana Hasegawa. "Despite the CD98 heavy chain being present on all cells, the antibody only bound to

MM cells. This selectivity may reflect the differing glycosylation patterns between normal cells and MM cells."

In-depth analysis of the R8H283 antibody revealed specific binding to CD98 heterodimers, not CD98 heavy chain monomers. Heterodimer complexes, comprising the CD98 heavy chain and light chain, modulate the uptake of amino acids for the production of immunoglobulin. "Interestingly, the glycoforms of CD98 heavy chain in the heterodimers present on normal leukocytes were distinct from those present on MM cells, which we think explains the lack of R8H283 reactivity to normal leukocytes," explains Naoki Hosen, senior author. "This is significant because it means that R8H283 antibody can exert anti-MM effects without damaging normal host cells."

To assess the effectiveness of the R8H283 antibody in an animal model, the researchers employed a mouse MM xenograft model. They found that R8H283 injections prolonged the survival of mice. This confirmed that R8H283 is a candidate for monoclonal antibody-based therapy for MM.

Taken together, these findings highlight an effective approach by which cancer-specific conformational epitopes on widely expressed proteins, which are unable to be detected by transcriptome or proteome analyses, may be identified via the screening of primary tumor samples. This methodology may be useful in broadening the array of cancer-specific surface antigens available for future drug development.

More information: Kana Hasegawa et al, Selective targeting of multiple myeloma cells with a monoclonal antibody recognizing the ubiquitous protein CD98 heavy chain, *Science Translational Medicine* (2022). DOI: 10.1126/scitranslmed.aax7706

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