Medical & healthcare, Drug development

Development of CAR-T cell therapy targeting cancer-specific antigen structures formed by post-translational changes

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Abstract

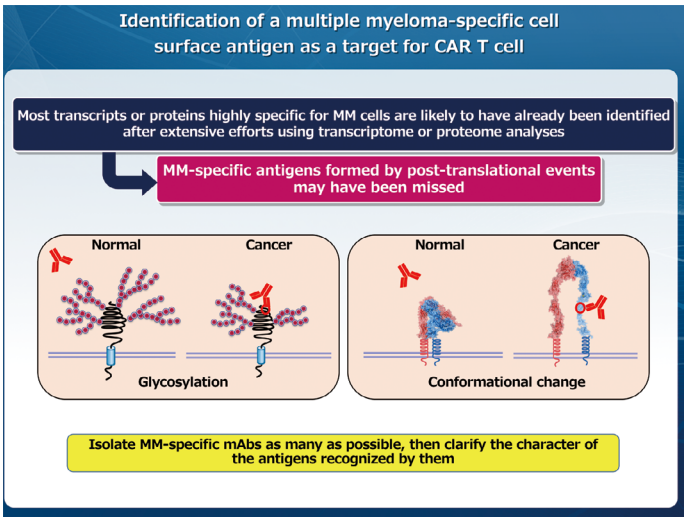
We have isolated a new antibody that recognizes CD98hc, a ubiquitously expressed protein, yet exhibits specific binding to multiple myeloma (hereinafter referred to as "myeloma"). Remarkable advances have been made in its treatment of myeloma. Among them, antibody drugs are highly effective for myeloma, and recently, the development of various treatments with antibody-derivatives such as CAR-T cells is extremely active. However, it is still difficult to cure myeloma, and further identification of target antigens is desired. Among more than 10,000 anti-myeloma monoclonal antibodies, we identified R8H283 as a myeloma-specific mAb and found that R8H283 recognized CD98hc, which is also expressed in normal leukocytes. Normal leukocytes expressed CD98hc glycoforms distinct from those expressed in MM cells, which may explain the lack of R8H283 reactivity in normal leukocytes. R8H283 exerted anti-MM effects without damaging normal hematopoietic cells. These findings suggest that R8H283 is a new source for mAb-based therapies against MM. In addition, our findings show that a cancer-specific conformational epitope in a ubiquitous protein, which cannot be identified by transcriptome or proteome analyses, can be found by extensive screening of primary human tumor samples.

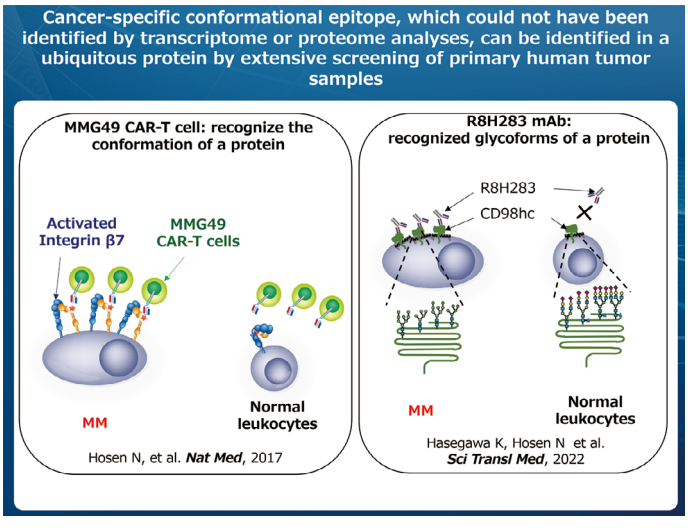
Background & Results

A monoclonal antibody drug that targets multiple myeloma cell surface antigens has significantly improved the prognosis of myeloma patients. Furthermore, in recent years, the development of various treatments with antibody-derivatives such as CAR-T cells is progressing. However, it is still very difficult to cure myeloma. Therefore, it is important to identify more therapeutic target antigens, but the search for genes and proteins specifically expressed in myeloma cells has already been extensively conducted all over the world, making it extremely difficult to identify new therapeutic targets. We generated more than 10,000 clones of monoclonal antibodies that bind to myeloma cells, and among them, we identified an antibody called R8H283 that binds to myeloma cells but not to normal blood cells. Next, we clarified that the protein recognized by R8H283 is CD98hc. Curiously, although CD98hc is also expressed on normal blood cells, R8H283 did not bind to normal blood cells. We found that the attached N-glycans differ greatly between CD98hc expressed on myeloma cells and CD98hc expressed on normal blood cells. Furthermore, R8H283 was found to bind more strongly to cells expressing CD98hc with immature N-glycans attached. These results suggest that the difference in N-glycosylation of CD98hc expressed in myeloma cells and normal blood cells may be responsible for the myeloma specificity of the R8H283 antibody. Furthermore, in experiments using mice, we showed that administration of R8H283 specifically eliminated myeloma cells without damaging normal cells.

Significance of the research and Future perspective

These results suggest that R8H283, which recognizes the multiple myeloma-specific antigen structure present in CD98hc, can be used for new antibody therapy against myeloma or CAR-T cell therapy applying it.





Patent	
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URL	https://www.med.osaka-u.ac.jp/pub/bldon/ http://www.ifrec.osaka-u.ac.jp/en/laboratory/naoki_hosen/
Keyword	cancer, multiple myeloma, CAR-T cell