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α-Dysroglycan Paradox between Electron-microscopy Findings and Three-Dimensional Structure

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ABSTRACT

We reported negative staining findings and three-dimensional structure of α-dystroglycan, however, there was a structural discrepancy between electron microscopy (negative staining) findings and three-dimensional structure. The mucin-like region using negative staining was longer than three-dimensional structure. On the other hand, three-dimensional structure of α-dystroglycan, based on negative staining results, showed the mucin-like region shorter than negative staining findings. Was the mucin-like region of negative staining unfolded? Was some structure of the mucin-like region omitted? Or both? Solution of this paradox seems to require more high-resolution structure of α-dystroglycan with atomic modeling.

Keywords

α-dystroglycan
Three-dimensional structure
Negative staining
Single-particle analysis

We reported negative staining findings and three-dimensional structure of α-dystroglycan, however, there was a discrepancy between electron microscopy (negative staining) findings and three-dimensional structure [1].

Previously, rotary shadowing showed dumbbell-like molecules with two globular units connected by a 20-30nm long rod-shaped and frequently curved segment [2]. Rotary shadowing involves evaporating a heavy metal onto a specimen at a low angle while sample is rotated. This creates a shadow effect that enhances contrast and reveals surface topography of molecules. However, resolution is lower than negative staining and there are artifacts. X-ray crystallography showed not whole structure but N-terminal partial structure of α-dystroglycan [3]. Resolution is very good. However, using E. coli, glycosylation is not sufficient.

Negative staining findings of α-dystroglycan of our study were similar to the previous report using rotary shadowing [2]. There were the N-terminal domain, the mucin-like region, and the C-terminal domain. However, the N-terminal domain and the C-terminal domain were relatively smaller than previous report. Moreover, the mucin-like region was longer than three-dimensional structure.

On the other hand, three-dimensional structure of α-dystroglycan, which was based on negative staining results, showed the mucin-like region shorter than negative staining findings. The N-terminal domain of this map was well matched X-ray structure [3]. Therefore, the N-terminal domain (or the C-terminal domain) structure seemed to be good.

There was a discrepancy of shape or structure of the mucin-like region between electron-microscopy (negative staining) findings and three-dimensional structure. Was the mucin-like region of negative staining unfolded? Was some structure of the mucin-like region omitted? Or both?

A limitation of negative staining is limited resolution. It is 10 Å at most. Therefore, atomic modeling is unable to build by negative staining. A limitation of single particle analysis is difficult to reconstruct soft flexible part of protein. Usually, soft and flexible part is unable to reconstruct by single particle analysis. The mucin-like region of α-dystroglycan is soft and flexible. Fortunately, we were able to reconstruct certain structure of α-dystroglycan, however, it seemed to be only one structure of many possible structures. Therefore, there may be better structure. Furthermore, glycosylation variability or sample preparation artifacts could also contribute to the observed differences.

Solution of this paradox seems to require more high-resolution structure of α-dystroglycan with atomic modeling or other methodology such as individual particle electron tomography.

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