論文の内容の要旨

Prediction of protein folding mechanisms by structure-based statistical mechanical models

(構造ベースの統計力学モデルによる タンパク質のフォールディング機構の予測)

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Elucidation of protein folding mechanisms is one of the most important problems in biophysics. Free energy landscapes of protein folding based on statistical mechanics provide comprehensive understanding of protein folding pathways and folding intermediates. Wako-Saitô-Muñoz-Eaton (WSME) model, a coarse-grained statistical mechanical model of proteins, is a promising strategy for predicting the free energy landscapes based on protein structures. The WSME model has successfully predicted experimentally observed folding mechanisms of small proteins. However, the WSME model is unsuitable for prediction of folding reactions of large multi-domain proteins that are stabilized by non-local interactions. To overcome this limitation, the WSME-L model having the linker term, representing the non-local interaction was developed and the exact analytical solution was established.

The WSME-L model was applied to hen egg-white lysozyme by introducing the linkers at the non-local disulfide bonds. The model predicted parallel folding pathways with several intermediates, which was consistent with the experimentally observed folding mechanisms of the disulfide-intact lysozyme. Furthermore, the kinetic behaviors of the folding pathways were consistent with the experimental observations.

Next, the free energy landscapes of four proteins homologous to hen egg-white lysozyme (canine milk lysozyme, human α-lactalbumin, goat α-lactalbumin, and bovine α-lactalbumin) were calculated. Although these proteins have similar backbone structure, folding experiments showed that they have different folding pathways depending on the derived species. The WSME-L model successfully predicted the dominant folding pathways and residue-specific folding processes of these proteins consistent with the experimental observations. Moreover, virtual mutational analysis suggested that the folding pathways of lysozyme and α-lactalbumin are sensitive to the distribution of the native contacts. Therefore, the WSME-L model can extract subtle differences of folding mechanisms encoded in native structures.

Finally, the WSME-L model was modified to be applicable to transient formation of non-local interactions by introducing a virtual linker and was applied to apomyoglobin that does not have disulfide bonds but forms non-local interactions by hydrophobic collapse early in the folding process. The model successfully predicted the folding pathway of apomyoglobin consistent with the experimental observation. Thus, the WSME-L model may pave the way for predicting the folding mechanisms of large multi-domain proteins.