Estimating cleavage mechanisms of γ-secretase using machine learning

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内 容 梗 概（１ページ目に収めること）

γ-Secretase is an intramembranous protease that generates Aβ, a pathogenic molecule in Alzheimer's disease. Although previous studies revealed that γ-secretase cleavage occurs successively and more than one hundred about 150 γ-secretase substrates were identified, the underlying mechanisms of the cleavage by γ-secretase are only poorly understood. Understanding the cleavage mechanism and specificity of γ-secretase is essential, as it may contribute to developing new drugs and therapies targeting Alzheimer's disease. In this study, we estimated the number of pockets in the active site of γ-secretase, amino acid properties which the active site recognizes and the preferred amino acids for each pocket. Using six pocket models, ten types of peptide properties, and 88 machine learning methods, we exhaustively examined 5,280 regression models trained by the quantitation data of γ-byproduct of Amyloid beta precursor protein cleavage. Using these models, we conducted cleavage site predictions for 35 identified cleavage sites, and obtained a model with the highest prediction accuracy of 85.7%. Notably, cleavage simulations by the best regression model reproduced characteristic cleavages of γ-secretase for APP and Notch1 substrates. Furthermore, in silico cleavage of random peptides revealed amino acid preferences in the cleavage site region of γ-secretase, which we further validated experimentally. We interpreted the model and estimated that the active site of γ-secretase consisted of seven contiguous pockets and the active site recognized amino acid properties associated with protein secondary structure. Further investigation of the model obtained in this study is expected to advance our fundamental understanding of the cleavage mechanism of γ-secretase and provide helpful information for developing γ-secretase inhibitors.