Short Communication

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The Role of Computation Deciphering the Mechanism of N-Glycan Processing α-Mannosidases

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ABSTRACT

During the last decade, computation has become a powerful tool to decipher the reaction mechanism of enzymes. In this mini-review, we summarize and highlight the achievements of computer science in modelling N-glycan processing enzymes.

SHORT COMMUNICATION

N-glycosylation is one of the most important processes in medicine, biology and industry. Mannose-containing N-glycans are highly present in nature and the role of mannosidases is crucial on its regulation and processing. In medicine, a deficiency or malfunction of lysosomal α-mannosidase causes alpha-mannosidosis, a lysosomal storage disorder described in humans, cattle, cats and guinea pigs [1]. In mice, the mutation of Golgi α-mannosidase II leads to a human lupus-like autoimmune disease [2]. In biology, mannosidases present in the Golgi apparatus and the endoplasmic reticulum play an important role in recognition and protein quality control in eukaryotes [3]. and mannose trimming in viral processes [4]. These enzymes are also well-known in the food and pharmacological industry [5]. and recently, the power of α-mannosidases in the proper development of fruit has been reported [6].

Families 38, 47, 76, 92, 99 and 125 of glycoside hydrolases (GH) are α-mannosidases involved in N-glycan processing. Deciphering its hydrolytic mechanism is key to developing inhibitors and designing drugs for pharmacological purposes. Furthermore, during the last decades, some of the designed inhibitors have played an important role to show experimental evidence of the different reaction intermediaries (Michaelis complex, transition state, enzyme-glycosyl intermediates, final product). In parallel to those empirical works, computation has evolved to complement and expand our knowledge about enzyme reactivity. In 2010, the mechanism of the glycosylation step of GH38 Golgi α-mannosidase II was studied combining quantum and classical molecular dynamics [7]. The same methodology was used, in 2012, to confirm the Michaelis complex conformation of the GH47 α-mannosidase [8]. and, in 2015, to decipher the transition state conformation of the GH76 α-mannanase [9]. all in good agreement with the experiments.

However, the empirics were more elusive at a time to shed light on GH92, GH99 and GH125 hydrolytic mechanisms. In 2017, the disagreement between initial experiments and computer simulations led to a computational design of new experiments for GH125 α-mannosidase [10]. In 2020, simulations confirmed a mechanism for GH99 enzymes different from the mechanism observed in a major part of glycosidases [11]. And, recently, quantum mechanics helped to find and describe the elusive and controversial mechanism for GH92 α-mannosidases. Furthermore, those calculations inspired the use of a new synthetic inhibitor as Michaelis complex mimic for glycoside hydrolases [12-14].

CONCLUSION

The last decade has been key to drawing the catalytic pathway of N-glycan processing α-mannosidases and the development of powerful computational tools has helped in this achievement.

Quick Response Code:

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