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Understanding the preferential cleavage mechanism of natural substrate by HIV-1 protease subtypes

Abstract

Introduction

The Human Immunodeficiency Virus type 1 (HIV-1) protease is a crucial target for HIV/AIDS treatment and our understanding of its catalytic mechanism is the basis on which the HIV-1 enzyme inhibitors are developed. Although, several studies indicate that HIV-1 protease facilitates the cleavage of the Gag and Gag-pol polyproteins and is highly selective with regards to the cleaved amino acid precursors, however, physical parameters and main principles for substrates specificity and recognition remain poorly understood.

Method

Herein, a one-step concerted catalytic mechanism of the HIV-1 PR subtypes on its natural substrates was studied to compare the activation free energies at varying peptide bond regions (natural substrates and non-substrates) within the polypeptide sequence using ONIOM calculations.

Results and discussion

It was observed that the studied HIV-1 PR subtypes (B and C-SA) recognize and cleave at both natural substrates and non-substrates region, also the preferential peptide sequence is an important factor in the substrate recognition and specificity.

Conclusion

Based on the detailed analysis of the computed and experimental data, we proposed that future inhibitors could mimic the RH-IN natural substrate for both subtypes B and C-SA HIV-1 PR.

Keywords: HIV-1 subtypes B and C-SA PR; cleavage mechanism; Our Own N-layered Integrated molecular Orbital and molecular Mechanics (ONIOM); natural substrates; activation free energy, concerted transition state.

Presenter Biography

Zainab K. Sanusi received a master of medical science degree in 2017 from the department of pharmaceutical chemistry under the supervision of Bahareh Honarparvar and Gert Kruger. Her research involves the determination of binding free energies of HIV FDA-approved drugs using computational methods. Presently, she is pursuing her PhD degree in pharmaceutical sciences at the Catalysis and Peptide Research Unit (CPRU), University of KwaZulu-Natal, where she is applying advanced in-silico methods to unravel the reaction mechanism of HIV-1 protease.

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