Uncovering novel drug targets of polyproteins of SARS-CoV-2

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Abstract

Introduction

The Covid-19 pandemic has been successfully tackled by the quick development of mRNA vaccines. While vaccines are very effective in slowing the viral spreading, therapeutic drugs help deal with severe cases of infection. So far, only one drug has been developed against the SARS-CoV-2 Mpro. To combat the ever-increasing SARS-CoV-2 variants and prepare for future coronavirus outbreaks, a multi-target therapeutic strategy that addresses multiple viral proteins is the way forward. In this line, another therapeutic target is the Papain-like Protease (PlPro) located on the non-structural protein 3 (NSP3). NSP3 fulfils multiple crucial functions in viral replication. After the genome translation into two polyproteins, PlPro cleaves part of the polyprotein to release the functional NSPs 1-3. PlPro furthermore suppresses the human innate immune system by its deubiquitinating and de-ISGlating properties. Furthermore, NSP3 together with NSP4 forms so called double membrane vesicles (DMVs) with the ER-membrane, which are a hub for viral RNA replication.

Objectives

Structural and functional studies on PlPro and its neighbouring domains (Ubl2 and NAB) within NSP3 with the goal to perform fragment screening to explore novel small molecule binding sites for antiviral therapeutics development.

Results

Fragment screen has been successfully performed on the target domain Ubl2-PlPro, measuring ~800 different fragments that resulted in multiple promising hits. Furthermore, TSA fragment screens with ~2000 fragments were performed against Ubl2-PlPro and its neighbouring NAB domain as well as a Ubl2-PlPro-NAB. Multiple hits were identified for each domain.

Conclusion

Promising fragment hits against PlPro were determined in crystallographic and TSA fragment screen. Further experiments exploring these fragments and their potential to inhibition of PlPro are undergoing.

REFERENCES

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