ABSTRACT

Influenza RNA-dependent RNA polymerase is a heterotrimeric complex and has an essential role in the life cycle of the virus. It is responsible for viral replication and transcription. One of its subunits, the polymerase acidic protein, interacts with the PB1 subunit via a crucial protein-protein interaction at its C-terminal domain. This 3_{10} helix-mediated intersubunit interaction is required for the whole heterotrimer assembly. The N-terminal domain carries the endonuclease active site with two manganese ions. Both domains are considered promising drug targets. Current strategies to fight the influenza virus are limited to seasonal vaccines, and there are only a few anti-influenza drugs targeting mostly other viral proteins. Many used antivirals are susceptible to rapid resistance mutations development or cause severe side effects.

This thesis provides structural insights into the two domains of the PA subunit. The first part is devoted to the characterization and optimization of a PB1-derived minimal peptide interacting with the C-terminal domain. Results from this part may be considered as a starting point for the rational design of first-in-class anti-influenza inhibitors of the PA-PB1 protein-protein interaction. In the other half, we have explored the inhibitory potency of flavonoids and their derivatives against the endonuclease domain. Using X-ray protein crystallography, we have described the binding modes of those inhibitors in the PA endonuclease active site. Ultimately, we have identified the target protein of those compounds which are being broadly used as supplements during influenza viral infection.