



48° Virtual SIM 2020

Virtual Congress

“Lezioni dall’emergenza di SARS-CoV-2”
21-22 settembre 2020

“Antimicrobico resistenza: la sfida sostenibile”
18 novembre 2020

ABSTRACT BOOK

4 INTERAZIONI MICRORGANISMO-OSPITE

26 - Strigolactone Analogs Are Promising Antiviral Agents for the Treatment of Human Cytomegalovirus Infection

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INTRODUCTION: Human cytomegalovirus (HCMV) is a widespread lifelong pathogen whose infection usually doesn't produce overt manifestations in healthy individuals. On the other hand, in immunocompromised individuals, such as transplant recipients and AIDS patients, and if vertically transmitted to the fetus, HCMV can be associated with severe, even fatal, diseases. Although several drugs have been successfully employed against HCMV infection, their use is restricted because of toxicity, occurrence of serious side effects and viral resistance. Consequently, there is an urgent and unmet clinical need for less toxic, but highly effective, antiviral agents that can be safely administered against HCMV. Strigolactones (SLs) are a new emerging class of plant hormones with many and well-known functions in plant-related fields, while their roles on human cells and their potential applications in medicine are far from being fully exploited. In this context, the goal of this project is to define SLs antiviral activity during HCMV infection.

MATERIALS AND METHODS: We investigate the antiviral activity of a panel of SL analogs, called TH-EGO, EDOT-EGO, EGO-10, and GR24, in Human Foreskin Fibroblasts (HFFs) during HCMV infection via virus yield reduction assays. Focusing on TH-EGO and EDOT-EGO, we also employ attachment assays, entry assays and western blot analysis to clarify their effects during HCMV replication cycle. Furthermore, we investigate the capability of SL analogs to modulate cell-death pathways in HCMV infected cells using Annexin V analysis and *in-vitro* analysis of Caspase 3 activity. Finally, *in-silico* docking was used to predict possible viral molecular targets of SL analogs.

RESULTS: We demonstrate that TH-EGO and EDOT-EGO, and their derivatives TH-ABC and EDOT-ABC, significantly inhibit HCMV replication *in vitro*. Interestingly, SL analogs do not affect the first steps of HCMV infection - *i.e.*, attachment and entry - but dramatically impair late protein expression, including that of the HCMV tegument protein UL99 (pp28). Finally, we suggest that the SL-dependent induction of apoptosis in HCMV infected cells, during the late stages of infection, is a contributing mechanism to SL antiviral properties.

DISCUSSION AND CONCLUSIONS: These findings indicate that SL analogs TH-EGO and EDOT-EGO may be promising candidates for a new class of antiviral agents for the treatment of HCMV infections.