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Host-directed broad-spectrum antiviral drugs

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Viruses completely depend on cellular factors to multiply. In spite of their unique coding features, different viruses are shown to depend upon some common host factors. Consequently, it should be possible to develop broad-spectrum antivirals by targeting them. In the presentation, the author will give an summary of the concept of host-targeting, broad-spectrum antiviral drugs and our work on natural products. The author will specially specialise in metabolites isolated from myxobacteria, one among the highest producers of natural products with host-targeting properties.

With viral infections this is not possible. There are currently very few antiviral drugs and those that exist are specific to one type of virus, requiring a diagnostic process before being able to apply treatment. The development of broad-spectrum antivirals would speed up the prescription of treatments, which in many cases, is essential to beat the disease, and would provide a first line of defence against new viruses. "Antiviral drugs on the market today are aimed at specific components of a virus, usually viral enzymes necessary for the multiplication of the virus in infected cells", explains Georgios Koutsoudakis, researcher of Juana Díez's group and first author of the study. Bearing in mind that viruses of different families are genetically quite different, direct action antivirals are tailored to a specific type of virus.

Moreover, its potential as an inhibitor of HCV is just as good as an anti-HCV drug already present on the market. This compound is SoraphenA, a product extracted from soil myxobacteria that is targeted at the cellular enzyme Acetyl-Coenzyme A Carboxylase (ACC), a protein involved in the synthesis of lipids within cells. The great advantage of this compound is that because its antiviral activity is mediated by a cell component, it is effective for various genotypes of HCV and is little susceptible to developing drug resistance.

Given that not only HIV and HCV but many other viruses, including the emerging Dengue virus, West Nile virus and Chikungunya virus, depend on the lipid cellular metabolism to multiply, it is possible that the antiviral activity of SorA will go beyond HIV and HCV, which is something that the laboratories of Dr. Díez and Dr. Meyerhans are already testing.

The concept of broad-spectrum antivirals targeting host cells and obtained from nature as well as the characteristics of the inhibition of HCV mediated by SorA are published in two articles. It is still very early to speak of SorA in treatment. From an antiviral compound being effective in cell cultures to it coming to be used on patients is very long process. But the experimental discoveries so far are very promising.

The development of medicine with broad-spectrum antiviral activities may be a long pursued goal in drug discovery. It has been shown that blocking co-opted host-factors abrogates the replication of the many viruses, yet the event of such host-targeting drugs has been met with scepticism mainly thanks to toxicity issues and poor translation to in vivo models. With the arrival of latest and more powerful screening assays and prediction tools, the thought of a drug which will efficiently treat a good range of viral infections by blocking specific host functions has re-bloomed. Here we critically review the state-of-the-art in broad-spectrum antiviral discovery. We discuss putative targets and treatment strategies, with particular specialise in natural products as promising starting points for antiviral lead development.

Viral infections affect millions of people every year and are a global public health threat. Infections with viruses like HIV or HCV can become persistent and may produce severe diseases as AIDS or hepatocellular carcinoma, respectively. (Re-)emerging viruses like WNV, DENV or CHIKV are spreading without proper control mechanisms. Thus, there are no effective vaccines and the treatment options against most virus threads are still limited. In this context, the development of new antivirals remains an important issue. Viruses need cellular host factors to complete their life cycles. Hundreds of these host-factors have been identified. Interestingly, several viruses use the same host factors so that chemical inhibition of these may lead to broad-spectrum viral inhibition. Broad-spectrum host-acting antivirals (HAAs) may increase the barrier to resistance development and reduce the complexity of co-infection treatments. In this thesis a high-throughput anti-HIV screening was applied to a myxobacteria metabolites library. Compounds with high anti-HIV activity and low toxicity were identified as hits and 2 of them (ratjadone A and soraphen A) were selected for further research. Ratjadone A inhibits the CRM1-mediated nuclear export and soraphen A inhibits the de novo fatty acid synthesis. Both drugs inhibit HIV and we described the mechanisms of inhibition of both compounds. The data presented in this thesis suggest that the use of host-acting antivirals as a broad-spectrum therapy is a feasible option.

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