Scottish Government Health Directorates Chief Scientist Office

CHIEF SCIENTIST OFFICE

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Cathelicidins as novel therapeutic antiviral agents in rhinovirus infection

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Aim
This study aimed to investigate the antiviral activity of Host Defence Peptides (HDP), which are key molecules found in the immune system. We specifically investigated their role in rhinovirus infection. Rhinovirus is linked to conditions such as viral pneumonia and can cause exacerbations of lung diseases such as asthma. It is very dangerous in young infants and the elderly. As there are no current treatments or vaccines for rhinovirus, we investigated how a) a family of host defence peptides called cathelicidins could kill rhinovirus and b) how cathelicidins could alter the surival and death mechanisms in cells that were infected with rhinovirus. We also investigated whether vitamin D, a potent inducer of natural cathelicidin peptide production in cells, could be used to treat rhinovirus.

Project Outline/Methodology
We used a range of different *in vitro* cell models of rhinovirus infection, including lung epithelial and primary blood cells, to investigate the mechanisms by which human cathelicidins, as well as cathelicidins from other mammals, affected the virus, either by directly killing it, or by causing the death of infected cells, as a possible defence mechanism against infection. We further assessed whether the virus itself could stimulate release of cathelicidins, by measuring the CAMP gene responsible for regulating cathelicidin production, as well as the production of cathelicidins themselves. We then used synthetic vitamin D to determine the extent to which it could stimulate cathelicidin production, and looked to see whether viral replication was altered in cells that had been treated with vitamin D. Finally, we looked to see whether cathelicidins could enhance the survival of cells infected with virus by affecting a process called autophagy.

Key Results
We found that cathelicidins from humans and other mammals had potent antiviral activity towards rhinovirus. We established that this was due to direct killing of the virus itself, rather than by causing death of the host cell that was infected with the virus. We determined that while vitamin D was able to induce cathelicidn production in cells, this did not translate to a significant reduction in rhinovirus and thus this would likely not be a good avenue for therapy. Finally, we found that cathelicidins could modulate the process of autophagy to a limited extent, and we demonstrated that this process suppressed viral replication in cells.

Conclusions
We conclude that cathelicidins are excellent targets for developing novel antivirals that could effectively kill rhinovirus without damaging or inducing death in host cells. We further show that cathelicidins delivered directly to a site of infection, rather than stimulating production of them by vitamin D, would be the most effective therapeutic strategy.

What does this study add to the field?
This study gives a greater understanding of how rhinovirus interacts with molecules and cells of the innate immune system. We now understand how cathelicidins kill this virus, and we believe that with further work, we can harness the potential of the cathelicidin peptides for designing new and highly effective antiviral drugs for treating this infection.

Implications for Practice or Policy
Clinical practice will not directly be affected by this study, but this project informs future work to design antiviral therapeutics, this study identified a novel mechanism by which viruses could evade the immune system. This will enable other scientists working on other infectious diseases to design more effective peptide-based drugs to treat viral infections.

Where to next?
We are currently in the process of applying for funding to look at how this virus, and influenza virus, can evade the action of these peptides and to design novel peptides that are more stable, more resistant to degradation and are better at killing these viruses.

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