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Writing Assignment #3

The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus

In their 2020 study, Gordon et al. discovered that the antiviral drug remdesivir (RDV) prevents RNA-dependent RNA polymerase (RdRp) from transcribing the Middle East Respiratory Syndrome coronavirus (MERS-CoV). Previous literature has noted how the triphosphate form of RDV (RDV-TP) has been proven to inhibit the RdRp of respiratory syncytial virus, Nipah virus, and Ebolavirus, which are all negative, single-stranded RNA viruses. Since RDV-TP is structurally similar to ATP, RDV-TP competes with ATP to bind to the RNA of these viruses, which inhibits RdRp from transcribing the rest of the sequence, and therefore, prevents protein synthesis. Although RDV-TP has shown to inhibit RNA synthesis, this medication has only been used on negative single stranded RNA viruses. Since coronaviruses are positive single stranded RNA viruses, there is speculation as to whether coronavirus RNA would respond to RDV-TP in a similar manner. In this way, researchers hypothesized that the properties of RDV-TP would inhibit the RNA synthesis of coronaviruses by inhibiting the RdRp's of MERS-CoV and SARS-CoV.

For their methods, Gordon and his team were able to isolate and propagate a stable protein complex composed of nsp 5, nsp 7, nsp8, and nsp12, which are proteins naturally synthesized by SARS-CoV and MERS-CoV (*in-vitro*). This protein complex was selected for analysis because previous tests proved that the incorporation of RDV-TP in the RNA of this protein complex was more efficient than the naturally produced, non-combined proteins. The RNA sequences and RdRp complexes for this group of proteins was then synthesized, and samples of RDV-TP were then placed in each RNA primer plate to determine whether RDV-TP had an effect on the transcription for this protein complex. In addition, EBOV RNA was placed with RDV-TP to see whether RDV-TP would affect the transcription of EBOV differently from coronaviruses.

In the results, Gordon and his team saw that the incorporation of RDV-TP in MERS-CoV and SARS-CoV strains inhibited RNA transcription, and RDV-TP effectively prevented ATP from binding onto the RdRp's of the two coronavirus strains. As a result, the protein complexes researchers studied were not synthesized. In addition, when observing RDV-TP and the EBOV, RDV-TP was also able to terminate RNA transcription of EBOV by inhibiting the action of RdRp. Therefore, RDV-TP uses the same mechanism to terminate transcription for both positive and negative single-stranded RNA viruses.

When discussing the implications, researchers were able to conclude that the properties of the antiviral drug remdesivir can potentially be used to treat SARS-CoV or MERS-CoV viruses. Although other medications are being considered for the treatment of the current COVID-19 outbreak, remdesivir is one of the first antiviral drugs that is being extensively studied. Since this study was conducted *in-vitro*, it is difficult to determine the effect of remdesivir on humans until further research is conducted. Although the full effects of remdesivir are not fully known, this study indicates that the triphosphate form of remdesivir is able to mimic ATP and cause RNA chain termination, which is a key mechanism that can be further studied.

References:

Gordon CJ, Tchesnokov EP, Feng JY, Porter, DP, Götte M. 2020. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. *The Journal of biological chemistry*, 295(15), 4773–4779.