Review of: "Sting Pathway Activation by Orally Administered Attenuated dsRNA Vaccine Virus for Therapy of Viral Diseases"

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Potential competing interests: No potential competing interests to declare.

The author provided an interesting pre-emptive vaccine development strategy using dsRNA of IBDV. There are few concerns with the strategy. 10 As the author pointed out, dsRNA activates the STING pathway via interferon activation but not IFN-gamma; dsRNA can engage cytosolic TLRs, NLRPs, and activate inflammasomes, thus by nature innate. For a vaccine to be effective, it is desirable to have pathogen, even strain or epitope-specific sensitivity, as without activation of memory cells, eventual efficacy would be transient and fade away.

2. IBDV never activated “excessive release of pro-inflammatory cytokines”; then, what did it actually activate to achieve long-term sustained immunological memory? That is not very clear from the manuscript.

3. Targeting dsRNA may have its own inherent risk of engaging RNA-sensitive inflammasomes that involve IL-1beta and IL-18; there could even be unwanted recognition and generation of autoantibodies.

4. As the author stated, HBV and HZV infections are manageable and often self-limiting, so there is a real question: Why use pre-emptive dsRNA for IBDV? What is the risk/benefit ratio?

5. “The attenuated, reversely engineered IBDV serotype R903/78 strongly induces IFN-β and IFN-λ (~30-fold and 5 to 10-fold, respectively) in the A549 human lung adenocarcinoma cell line, while IFN-γ is not induced. As IBDV did not lyse several mammalian cell lines (A549, HEK293, HepG2, U937, and THP1), it provides safety compared to lytic viruses ”

This statement feels generalized but is based on scanty evidence; most of the cell lines used are heavily modified human cancer cell lines or embryonic cell lines where IBDV may not show its lytic property, but is it non-lytic for all cell types? Also, does it have integration capacity in the host?

6. “Long-term oral administration of IBDV alone was capable of eliminating HBV without killing infected cells.” - How was that achieved? Needs some explanation.

7. As such, most examples cited by the author involve safety checks, but what is the actual change in immune profile of treated diseased patients?

Overall, the approach has a lot of potential but needs close scrutiny of efficacy, potential danger, effect on local and systemic immune profile through pre-clinical, and then clinical, studies.