Oncolytic effects of the recombinant newcastle disease virus, rAF-IL12, against colon cancer cells in vitro and in tumor-challenged NCr-foxn1nu nude mice

ABSTRACT

Colon cancer remains one of the main cancers causing death in men and women worldwide as certain colon cancer subtypes are resistant to conventional treatments and the development of new cancer therapies remains elusive. Alternative modalities such as the use of viral-based therapeutic cancer vaccine is still limited, with only the herpes simplex virus (HSV) expressing granulocyte-macrophage colony- stimulating factor (GM-CSF) or talimogene laherparepvec (T-Vec) being approved in the USA and Europe so far. Therefore, it is imperative to continue the search for a new treatment modality. This current study evaluates a combinatorial therapy between the oncolytic Newcastle disease virus (NDV) and interleukin-12 (IL-12) cytokine as a potential therapeutic vaccine to the current anti-cancer drugs. Several in vitro analyses such as MTT assay, Annexin V/FITC flow cytometry, and cell cycle assay were performed to evaluate the cytotoxicity effect of recombinant NDV, rAF-IL12. Meanwhile, serum cytokine, serum biochemical, histopathology of organs and TUNEL assay were carried out to assess the anti-tumoral effects of rAF-IL12 in HT29 tumor-challenged nude mice. The apoptosis mechanism underlying the effect of rAF-IL12 treatment was also investigated using NanoString Gene expression analysis. The recombinant NDV, rAF-IL12 replicated in HT29 colon cancer cells as did its parental virus, AF2240-i. The rAF-IL12 treatment had slightly better cytotoxicity effects towards HT29 cancer cells when compared to the AF2240-i as revealed by the MTT, Annexin V FITC and cell cycle assay. Meanwhile, the 28-day treatment with rAF-IL12 had significantly ($p < 0.05$) perturbed the growth and progression of HT29 tumor in NCr-Foxn1nu nude mice when compared to the untreated and parental wild-type NDV strain AF2240-i. The rAF-IL12 also modulated the immune system in nude mice by significantly ($p < 0.05$) increased the level of IL-2, IL-12, and IFN-γ cytokines. Treatment with rAF-IL12 had also significantly ($p < 0.05$) increased the expression level of apoptosis-related genes such as Fas, caspase-8, BID, BAX, Smad3 and granzyme B in vitro and in vivo. Besides, rAF-IL12 intra-tumoral delivery was considered safe and was not hazardous to the host as evidenced in pathophysiology of the normal tissues and organs of the mice as well as from the serum biochemistry profile of liver and kidney.

Therefore, this study proves that rAF-IL12 had better cytotoxicity effects than its parental AF2240-i and could potentially be an ideal treatment for colon cancer in the near future.

Keyword: Newcastle disease virus; Apoptosis; HT29; Colon cancer; rAF-IL12