This Month in APR

By Moon Jung Song, Section Editor

Maintenance of the viral genome may be the Achilles' tendon for virus-associated cancers

Approximately 15% of human cancers are attributed to virus infections. Examples of viruses linked to cancers include hepatitis B virus (HBV) and hepatitis C virus (HCV), which are both associated with hepatocellular carcinoma; human papillomaviruses (HPVs), which are associated with cervical cancer; human T lymphotropic virus type 1 (HTLV-1), which is associated with adult T-cell leukemia; Kaposi's sarcoma-associated herpesvirus (KSHV), which is associated with Kaposi's sarcoma and B cell lymphomas; and Epstein-Barr virus (EBV), which is associated with Burkitt's lymphoma (BL), nasopharyngeal carcinoma (NPC), Hodgkin's lymphoma, NK/T cell lymphoma and gastric carcinoma. For all these virus-associated cancers, prolonged persistent infection seems to be almost prerequisite. Numerous strategies to maintain the viral genomes in the host have been developed by the viruses. Among these, EBV establishes its renowned mechanism to maintain the viral genome as an episome during latency.

Latency is a hallmark of herpesvirus infection, keeping its genome intact, but silenced except a few genes, thereby allowing it to establish a life-long persistent infection. While herpes simplex virus-1, the prototype herpesvirus, infects non-replicating neurons for its latency, EBV faces a serious challenge to keep its genome during latency because it only infects constantly replicating B lymphocytes. Epstein-Barr nuclear antigen 1 (EBNA1) protein is expressed in virtually all types of EBV-infected proliferating cells, and is essential for replication and proper segregation of EBV latent genome in terms of tethering the EBV episome to chromosomal DNA during mitosis. Therefore, EBNA1 may serve as an attractive target for a potential molecular therapy against EBV-associated cancers.

In this issue, Oh et al. attempted to eliminate the EBV episomes from an EBV-positive gastric carcinoma cell line, SNU-719, by employing the method of siRNAs against EBNA1. The authors found that silencing endogenous EBNA1 expression in gastric carcinoma was much less efficient than silencing ectopic EBNA1 expression in HeLa cells. Previous

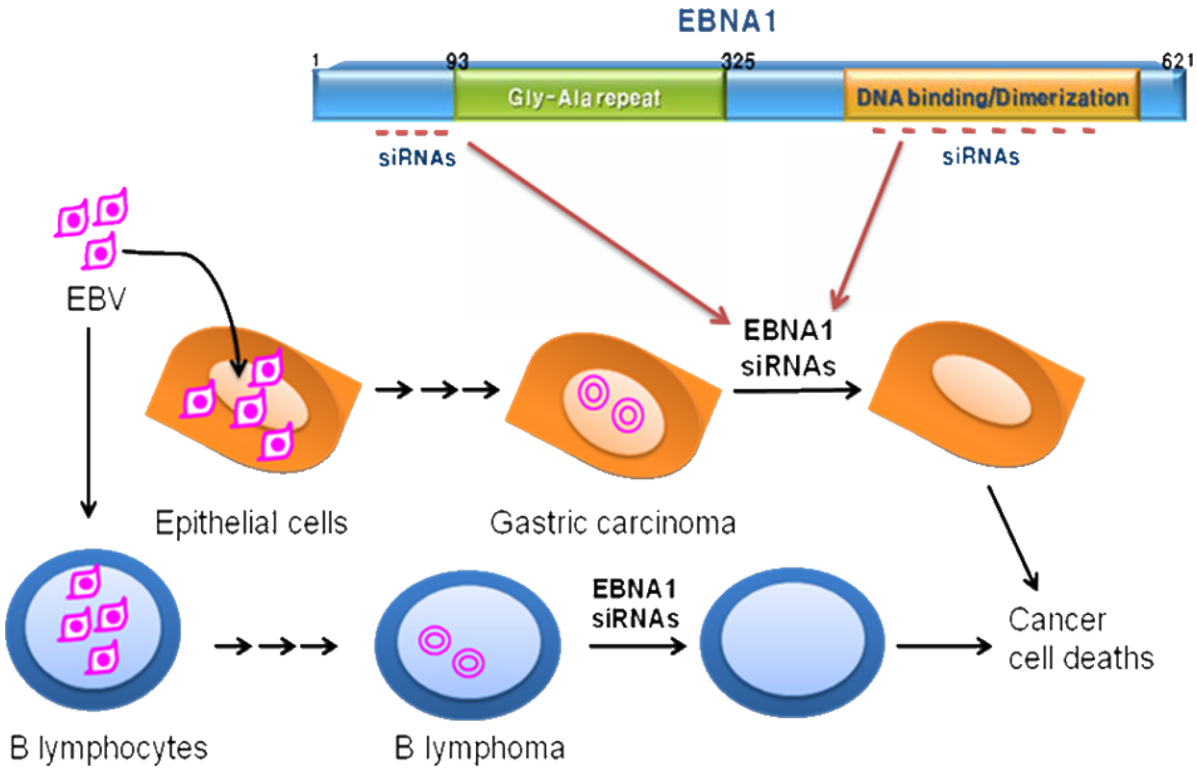

Fig. 1. EBNA1 siRNAs targeting to eliminate the persistent viral genomes in EBV-associated cancers.

reports showed similar phenomenon in NK/T cell lymphoma, BL, and NPC cell lines, and in their study EBNA1 siRNA treatments rendered cell survival and proliferation reduced (Yin and Flemington, 2006; Ian et al., 2008). Treatment with hydroxyurea, a DNA synthesis blocker, also failed to abrogate the EBV genome from SNU-719. Why was it so difficult to eliminate the EBV genome from gastric carcinoma cells? Although we do not have the direct answer, all these results are pointing to the same direction: maintenance of the viral genome may be the Achilles' tendon for virus-associated cancers.

REFERENCES

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