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Endogenous retroviruses expressed in human tumours cannot be used as targets for anti-tumour vaccines

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A B S T R A C T

Many tumour cells express on their surface proteins of endogenous retroviruses (ERVs) and there are suggestions to use these retroviral antigens as target for anti-tumour vaccines. However, until now there is no convincing data showing that this strategy works, in contrast, there are considerations suggesting that this strategy may be harmful if applied.

ERVs are integrated in the genome of all mammals, they are the result of an infection of germ cells with an exogenous retrovirus. Consequently, ERVs are present in the DNA of each cell of the organism and are transmitted to the offspring like all cellular genes [1]. ERVs are expressed in dependence on the species and the tissue. For example, in mice and pigs the ERVs are expressed in many tissues including tumours during the whole lifetime, whereas in humans they are strictly regulated and expression is found only in some, but not all tumours. This is confirmed by the presence or absence of antibodies specifically recognising ERVs in a given species. Pigs and mice express the ERVs early in ontogenesis, and their immune system recognises them as "self", these animals are tolerant and to not produce ERV-specific antibodies. In contrast, in humans the expression happens only in a few tumours and in the placenta and therefore only tumour patients and some pregnant women produce antibodies against human ERVs (HERVs) [1].

In humans most of the HERVs are characterised by deletion and mutations, however, in mice, cats, koalas and pigs ERVs are still active, e.g. they replicate in the living organism, *de novo* integrate into somatic cells, mutate and recombine. This may explain why for example in mice antibodies can be induced against murine retroviruses despite the fact that the animals are tolerant against the original ERVs: They lose tolerance or react against the closely related, but different recombinant or mutated viruses.

Nevertheless, HERVs are expressed in many tumour cells, they were activated during tumour development, and their immunosuppressive transmembrane envelope (TM) protein may contribute to tumour progression [1]. Based on this, several authors propose to use HERV-proteins as targets for an immunotherapy based on the fact that tumour patients develop antibodies against HERVs and on animal experiments (reviewed in [2]). However, the antibodies against HERVs in cancer patients are unable to stop tumour growth and the animal models are not comparable with the situation in humans. In one animal model injecting antibodies against the surface envelope protein gp70 and the TM protein p15E of murine endogenous retroviruses slowed the development of progressed murine leukaemia [3]. In another model, adoptively transferred T cells specific for the surface envelope protein gp70 of a murine retrovirus could treat mice bearing a chemically induced colon tumour called CT26 [4]. However, inoculation of plasmid DNA encoding gp70 or p15E of an endogenous murine virus elicited only a weak antigen-specific T lymphocyte response and resulted only in a weak protection from challenge with mouse tumours possessing these viral antigens. Systemic administration of agonistic anti-CD40 monoclonal antibodies increased the therapeutic potential of genetic vaccination, but only when given during the tumour rejection phase and not at the time of immunisation, obviously overcoming the tolerance. Furthermore, injecting mice plasmid DNA (pDNA) encoding gp70 alone failed to induce anti-gp70 antibody or anti-CT26 cytotoxic T lymphocyte (CTL) responses, however, immunisation with pDNA encoding a beta-galactosidase (beta-gal)/gp70 fusion protein induced anti-gp70 antibodies and anti-CT26 CTL responses and conferred protective immunity against CT26 cells. These results indicate that beta-gal acts as an immunogenic carrier protein that helps in the induction of immune responses and to overcome tolerance to the endogenous retrovirus [5].

Other models are human cancer cells in animals. For example, monoclonal antibodies against the envelope protein of HERV-K, which is highly expressed in human malignant breast cancer cell lines, were used to treat such human xenotransplant tumours in mice, and statistically significantly reduced growth of the tumours compared with mice treated with control immunoglobulin. Vaccinating mice with a recombinant vaccinia virus expressing the HERV-K Gag protein and applying murine renal carcinoma cells genetically altered to express E. coli beta-galactosidase and the HERV-K Gag protein, resulted in reduced tumour growth when the tumour cells were applied subcutaneously. In the case the tumour cells were applied intravenously, the formation of pulmonary metastases was reduced. Similar results were obtained when the envelope protein of HERV-K was expressed [6].

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However, the situation in humans will be absolutely different compared with these animal models. The vaccinated individual certainly will produce antibodies because humans are not tolerant against their endogenous retroviruses. It is well known that the Env proteins of some HERVs play an important role in the placentogenesis and some others such as HERV-K are also expressed in the placenta [1]. Therefore the antibodies may react with HERV proteins expressed in the placenta and interfere with gestation. In this case the cancer treatment will be certainly indispensable compared with child giving. However, it is well known that HERV-K is highly expressed in human embryonic stem cells ([7], Denner et al, unpublished). Embryonic stem cells may be disseminated in different human organs and harmed by the antiviral antibodies. Furthermore, expression of retroviral proteins has been shown on activated immune cells in different animals [8,9]. This is not well studied in humans, but obviously the immune response in the HIV-1 infected individual, not the infection by HIV-1, led to an enhanced expression of HERV-K in human immune cells [10]. In conclusion, an immune response against HERV proteins bears the risk of destroying stem cells and immune cells and therefore such anti-retroviral vaccines should not be used without further investigation in this field.

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Declaration of Competing Interest

The author declares an absence of competing or financial interests.

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