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Editorial

Tumorigenesis Mechanisms of a Putative Human Breast Cancer Retrovirus

Brian Salmons[1]* and Walter H Gunzburg[2]
[1]Austrianova Singapore Pte Ltd, Singapore
[2]Department of Pathobiology, Institute of Virology, University of Veterinary Medicine, Vienna, Austria

***Corresponding author:** Brian Salmons, Austrianova Singapore Pte Ltd, Synapse, 3 Biopolis Drive, Singapore

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Editorial

It has long been known that viruses can contribute to, or even cause, cancer. To date, 7 virus families have been implicated in tumorigenesis include Human Papilloma Virus (HPV), Epstein-Barr Virus (EBV), Merkel cell polyomavirus, Kaposi's Sarcoma-Associated Herpesvirus (KSHV), hepatitis C virus, hepatitis B virus and also the retroviruses human T-cell leukemia virus types 1 and 2 (HTLV-1 and HTLV-2) [1]. Indeed, it was estimated that in 2002 17.8% of human cancers were caused by infection, with 11.9% being caused by one of the seven virus families listed above [2].

Mouse Mammary Tumor Virus (MMTV) has long been known to be an aetiological agent of mammary cancer in mice and for almost as long as the virus has been known, MMTV, or a highly related virus, has been speculated to play a role in human breast cancer. There has been a resurgence in interest in the potential involvement of MMTV or a highly related human mammary tumor virus HMTV in the last 20 years (reviewed by [3-5]), culminating with the detection of virus in human milk [6,7] and salivary fluid [8] suggesting a horizontal, human-to-human transmission. Certainly, the mouse virus can infect human cells in cell culture and this infection is productive in that it leads to the production of new infectious virus [9-11].

Cancer is generally accepted to result from a culmination of a number of genetic changes and insults to the host cell genomes. The generally accepted mechanism by which MMTV contributes to mammary tumorigenesis in mice is by enhancer insertion in which the virus DNA or provirus integrates in the vicinity of one or more genes controlling cell growth (proto-oncogenes), although it should be noted that this may be only one of the steps involved in frank transformation of mammary epithelial cells [12]. However, although the human homolog of Wnt-1, one of these commonly activated mouse mammary proto-oncogenes, shows elevated expression in MMTV env-positive ductal carcinoma in situ and invasive ductal carcinoma [13] and a number of other cellular genes affected by MMTV proviral insertions in mouse mammary tumors are deregulated or mutated in primary human breast tumors [14], there is, as yet, no evidence that MMTV/HMTV proviruses have inserted in the vicinity of such genes in DNA isolated from human breast cancer tissue.

Nevertheless, it is known that other retroviruses can influence the biology of cells that they have infected in more subtle ways and contribute to the tumorigenic process. An example of this is provided by the Human T-Lymphotropic Virus-1 (HTLV-1), a retrovirus that is the causative agent of a highly aggressive form of non-Hodgkin's lymphoma known as adult T cell leukemia and lymphoma. HTLV-1 encodes an oncogenic protein, Tax, which plays a central role in transforming CD4+ T lymphocytes by deregulating oncogenic signaling pathways and promoting cell cycle progression [15]. Although Tax exhibits diverse functions in host cells, it primarily targets I-κB kinase complex in the cytoplasm, leading to persistent activation of NF-κB and consequent upregulation of gene products that are required for T cell survival and cell cycle progression. This promotes T cell survival and proliferation. Moreover, enhanced survival and proliferation coupled with an interference with cell senescence, leads to immortalization and, ultimately, transformation of human primary CD4 T cells [15]. Tax thus plays a key role in initiating tumorigenicity but expression of Tax is not required later on since the hosts' immune system appears to eliminate Tax expressing cells (but not late stage tumour cells). In contrast, a second HTLV-1 encoded bZIP factor, also known as HBZ, is expressed in all ATL cells and supports the growth of human T-cell lines [16]. HBZ is encoded by the HTLV-I minus strand in contrasts to the other HTLV-1 proteins [16].

MMTV does not appear to encode a Tax protein homolog or equivalent, and there is to date no evidence supporting the notion that the virus is able to directly transform mammary epithelial cells e.g. by expressing an oncogenic protein. Thus, other features of the virus replication cycle may mechanistically be involved in the putative virus induced genesis of human breast cancer.

Much attention has been focused on the MMTV envelope protein since in the last few years evidence has been accumulating that for certain other retroviruses the retroviral envelope proteins can be directly involved in oncogenic transformation, one prominent example being that of Jaagsiekte Sheep Retrovirus (JSRV), which, like MMTV, is a beta retrovirus [17].

In the case of MMTV, an Immunoreceptor Tyrosine-Based Activation (ITAM) motif is present in the envelope protein that has been shown to be capable of transforming primary mammary epithelial cells that were grown either in three-dimensional cell culture [18,19] or in mice [20]. The ITAM domain appears to contribute to tumorigenesis by suppressing apoptosis through Src tyrosine kinase signaling and this may contribute to transformation of breast epithelial cells [21].

A cleavage product of the MMTV envelope precursor protein, known as p14, has also been implicated in the virus mediated transformation process [22]. The p14 domain is the leader sequence of the envelope precursor and it is also part of the virus Rem protein that has HIV Rev-like RNA transport activity [23]. It has been shown

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that the phosphorylation status of p14 determines whether it has pro-oncogenic or anti-oncogenic modulatory effects [22].

Gao and Zheng have pointed out that viruses associated with human tumours, including retroviruses, belong in the group of enveloped viruses that by virtue of their mechanism of cell entry are capable of mediating cell fusion [24]. Cell fusion may lead to chromosomal instability by various mechanisms including deregulation of tumor suppressors such as p53 and Rb. In support of this hypothesis, aneuploid and tetraploid tumor cells are more frequently observed in virus-positive premalignant lesions [24].

There are a number of other possible mechanisms by which an MMTV/HMTV could transform breast epithelial cells. The virus may still turn out to express other, as yet unknown, proteins that may be involved in tumorigenicity, perhaps even encoded by the minus stand like HBZ of HTLV-1 [16]. Alternatively, existing proteins may have additional functions in analogy to the envelope proteins of other viruses. Accessory factors such as the RNA transport factor Rem [22], the virus super antigen Sag and the negative acting factor, Naf, [25] may also potentially play a role. Moreover, other viruses have been linked to human breast cancer [26] and it is also conceivable that MMTV infection activates a latent human breast cancer associated virus such as EBV and HPV, possibly in a similar manner to the way that Human Immunodeficiency Virus (HIV) has an indirect role in KSHV mediated Kaposi's sarcoma [4]. Finally, interaction between MMTV/HMTV and human endogenous retroviruses may also play a role [27]. The advent of newer technologies such as next-generation sequencing methods should help elucidate the mechanisms by which MMTV/HMTV contributes to the tumorigenic process in human breast cancer.

References

1. Morales-Sánchez A, Fuentes-Pananá EM. Human viruses and cancer. Viruses. 2014; 6: 4047-4079.
2. Parkin DM. The global health burden of infection-associated cancers in the year 2002. Int J Cancer. 2006; 118: 3030-3044.
3. Holland JF, Pogo BG. Mouse mammary tumor virus-like viral infection and human breast cancer. Clin Cancer Res. 2004; 10: 5647-5649.
4. Salmons B, Gunzburg WH. Revisiting a role for a mammary tumor retrovirus in human breast cancer. Int J Cancer. 2013; 133: 1530-1535.
5. Holland JF, Melana S, Jaffer S, Etkind P, Nartey T, Lee T, et al. Human Mammary Tumor Virus (HMTV) is Deeply Involved in Breast Cancer and Metastasis. In: Proceedings of the 106th Annual Meeting of the American Association for Cancer Research. 2015; 18-22.
6. Johal H, Ford C, Glenn W, Heads J, Lawson J, Rawlinson W. Mouse mammary tumor like virus sequences in breast milk from healthy lactating women. Breast Cancer Res Treat. 2011; 129: 149-155.
7. Nartey T, Moran H, Marin T, Arcaro KF, Anderton DL, Etkind P, et al. Human Mammary Tumor Virus (HMTV) sequences in human milk. Infect Agent Cancer. 2014; 9: 20.
8. Mazzanti CM, Lessi F, Armogida I, Zavaglia K, Franceschi S, Al Hamad M, et al. Human Saliva as Route of Inter-human Infection for Mouse Mammary Tumor Virus. Oncotarget. 2015; 6: 18355-18363.
9. Indik S, Günzburg WH, Salmons B, Rouault F. Mouse mammary tumor virus infects human cells. Cancer Res. 2005; 65: 6651-6659.
10. Indik S, Günzburg WH, Kulich P, Salmons B, Rouault F. Rapid spread of mouse mammary tumor virus in cultured human breast cells. Retrovirology. 2007; 4: 73.
11. Konstantoulas CJ, Lamp B, Rumenapf TH, Indik S. Single Amino Acid Substitution (G42E) in the Receptor Binding Domain of Mouse Mammary Tumour Virus Envelope Protein Facilitates Infection of Non-murine Cells in a Transferrin Receptor 1-independent Manner. Retrovirology. 2015; 12: 43.
12. Callahan R, Smith GH. Common integration sites for MMTV in viral induced mouse mammary tumors. J Mammary Gland Biol Neoplasia. 2008; 13: 309-321.
13. Lawson JS, Glenn WK, Salmons B, Ye Y, Heng B, Moody P, et al. Mouse mammary tumor virus-like sequences in human breast cancer. Cancer Res. 2010; 70: 3576-3585.
14. Callahan R, Mudunur U, Bargo S, Raafat A, McCurdy D, Boulanger C, et al. Genes affected by mouse mammary tumor virus (MMTV) proviral insertions in mouse mammary tumors are deregulated or mutated in primary human mammary tumors. Oncotarget. 2012; 3: 1320-1334.
15. Cheng H, Ren T, Sun SC. New insight into the oncogenic mechanism of the retroviral oncoprotein Tax. Protein Cell. 2012; 3: 581-589.
16. Yasunaga J, Matsuoka M. Leukaemogenic mechanism of human T-cell leukaemia virus type I. Rev Med Virol. 2007; 17: 301-311.
17. Maeda N, Fan H, Yoshikai Y. Oncogenesis by retroviruses: old and new paradigms. Rev Med Virol. 2008; 18: 387-405.
18. Katz E, Lareef MH, Rassa JC, Grande SM, King LB, Russo J, et al. MMTV Env encodes an ITAM responsible for transformation of mammary epithelial cells in three-dimensional culture. J Exp Med. 2005; 201: 431-439.
19. Grande SM, Katz E, Crowley JE, Bernardini MS, Ross SR, Monroe JG. Cellular ITAM-containing proteins are oncoproteins in nonhematopoietic cells. Oncogene. 2006; 25: 2748-2757.
20. Ross SR, Schmidt JW, Katz E, Cappelli L, Hultine S, Gimotty P, et al. An Immunoreceptor Tyrosine Activation Motif in the Mouse Mammary Tumor Virus Envelope Protein Plays a Role in Virus-induced Mammary Tumors. J Virol 2006; 80: 9000-9008.
21. Kim HH, Grande SM, Monroe JG, Ross SR. Mouse mammary tumor virus suppresses apoptosis of mammary epithelial cells through ITAM-mediated signaling. J Virol. 2012; 86: 13232-13240.
22. Feldman D, Roniger M, Bar-Sinai A, Braitbard O, Natan C, Love DC, et al. The signal peptide of mouse mammary tumor virus-env: a phosphoprotein tumor modulator. Mol Cancer Res. 2012; 10: 1077-1086.
23. Indik S, Günzburg WH, Salmons B, Rouault F. A novel, mouse mammary tumor virus encoded protein with Rev-like properties. Virology. 2005; 337: 1-6.
24. Gao P, Zheng J. Oncogenic virus-mediated cell fusion: new insights into initiation and progression of oncogenic viruses--related cancers. Cancer Lett. 2011; 303: 1-8.
25. Wintersperger S, Salmons B, Miethke T, Erfle V, Wagner H, Günzburg WH. Negative-acting factor and superantigen are separable activities of the mouse mammary tumor virus long terminal repeat. Proc Natl Acad Sci U S A. 1995; 92: 2745-2749.
26. Glenn WK, Heng B, Delprado W, Iacopetta B, Whitaker NJ, Lawson JS. Epstein-Barr virus, human papillomavirus and mouse mammary tumour virus as multiple viruses in breast cancer. PLoS One. 2012; 7: e48788.
27. Salmons B, Lawson JS, Günzburg WH. Recent developments linking retroviruses to human breast cancer: infectious agent, enemy within or both? J Gen Virol. 2014; 95: 2589-2593.

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