Mouse Mammary Tumor Virus and Human Breast Cancer

To the Editor: Wang et al. (1) described recently the cloning and sequencing of mouse mammary tumor virus (MMTV) superantigen (sag) from human breast cancers. They report that sag sequences exhibit high nucleotide homology with MMTV and that cloned sag proteins elicit in vitro activation of human T cells. This article gives the impression that an etiologic agent for sporadic cases of breast cancer has been identified by the scientific community. Sadly however, this is far from the truth and should be interpreted with caution, as a positive association between MMTV and human breast cancer is a highly controversial debate that has smoldered on and off for 60 years. Omitted in the Wang et al. article is the fact that only two independent groups have been able to repeat the original molecular observations of MMTV DNA in human breast cancers, whereas six have not (2). This may possibly have a rational explanation, such as differing geographic distribution of an etiologic agent, vector, or clustering of populations with differing infection or cancer susceptibilities. To advance the intellectual debate proponents of an infective etiology need to critically consider the following realities: (a) how does the virus cause infection of Homo sapiens given that human cells lack the necessary transferrin receptor for MMTV (3) and that MMTV is not an endogenous human retrovirus (2)? (b) for every established human oncogenic virus (high-risk human papillomaviruses, hepatitis B and C viruses, and human herpes virus type 8), immunosuppression increases cancer risk, which is not the case for human breast cancer; (c) unlike the MMTV murine model of breast hyperplasia, human breast-feeding does not predispose daughters to breast cancer (2, 4); and (d) pregnancy is protective against the risk of human breast cancer (2, 5), whereas the opposite is true for MMTV-caused murine hyperplasias. For the reasons outlined above, MMTV is not currently classified as an environmental carcinogen for humans and is unlikely ever to be categorized as such, although in fairness Wang et al. do fleetingly allude to this (1).

Scientific articles, particularly those concerning such highly contentious issues, have a responsibility to be sufficiently nonpartisan as to make the limitations of the hypothesis being examined patentely clear. This is essential to permit the impartial scientist to judge the true significance of the observations: caveat emptor!

Christine Mant
John Cason
Department of Infectious Diseases
Guy’s, King’s College and St. Thomas’ School of Medicine
Guy’s Hospital
London, United Kingdom

References

In Response: We feel compelled to respond to Mant and Cason’s Letters to the Editor because it misrepresents our work on the relationship between mouse mammary tumor virus and human breast cancer. Their stated purpose was to clarify our findings so the readers of Cancer Research would not be misguided. Their criticism was not directed against the current article (1) but against the entire concept of mouse mammary tumor virus as a possible agent in human breast carcinogenesis. As discussed in several articles by our group, causation will only be claimed by us on proving that the virus is tumorigenic in human cells, fulfilling the requisite epidemiologic and virological proofs as well (2–5). Some of the requisites set forth have already been established by us and others (2–9).

The question concerning receptors and infectivity was also discussed clearly (1). Furthermore, retroviruses can infect cells without cognate receptors using transactivation pathways, a mechanism that has not yet been well explored with mouse mammary tumor virus (10), and retroviruses are known to cross species (11).

Mant and Cason (12) quoted in their review from articles in which env sequences were not detected. One of these is not applicable to our findings, because it concerns endogenous retrovirus expression (13). Although we agree that differences in population could explain some of the results (7, 14), it is likely that differences in technology were also involved. None of the articles cited (15–17) followed our exact methodology. Four laboratories have confirmed our results, one as yet unpublished.

The question of endogenous versus exogenous sequences has been discussed in detail by us and others in previous publications (5–7).

In humans, early pregnancy is a protective factor against breast cancer risk, but gestational breast cancer is one of the most virulent. High levels of hormones may be involved (discussed in ref. 18); therefore, the mouse and human cancers have similarities. To our knowledge, no extensive studies have been made to detect a mouse mammary tumor virus–like virus in milk.

The participation of the immune system in mouse mammary tumor virus infections is unique and differentiates this virus from other tumor viruses.

We believe that repeated confirmation of our work is significant and hope that in the future more laboratories will be able to successfully adapt our methodology.

Beatriz G.T. Pogo
James F. Holland
Mount Sinai School of Medicine
New York, New York

References


Mouse Mammary Tumor Virus and Human Breast Cancer

Christine Mant and John Cason


Updated version

Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/65/3/1112

Cited articles

This article cites 20 articles, 9 of which you can access for free at:
http://cancerres.aacrjournals.org/content/65/3/1112.full#ref-list-1

E-mail alerts

Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions

To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions

To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.