EDITORIAL

Interaction Between Anti-Gal and Human Tumor Cells: A Natural Defense Mechanism?

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In this issue of the journal, the study by Castronovo et al. on the binding of the natural anti-α-galactosyl IgG (anti-Gal) antibody to human mammary carcinoma cell lines and to cells of primary malignant mammary lesions poses two challenging questions. (a) Is the expression of the Galα1-3Gal epitopes a common characteristic of human malignant cells? (b) Does anti-Gal bind in vivo to these cells and affect the growth and metastatic potential of tumor cells expressing the Galα1-3Gal carbohydrate epitope?

Anti-Gal is a natural IgG antibody present in unusually large amounts in the serum of healthy individuals and constitutes 1% of circulating IgG (1). Anti-Gal, which can be readily isolated from normal human AB sera by affinity chromatography, was found to be a polyclonal monospecific antibody interacting specifically with an oligosaccharide residue with the structure Galα1-3Galβ1-4GlcNAc-R (2,3). Anti-Gal is produced throughout life in humans as a result of what seems to be a constant antigenic stimulation by gastrointestinal bacteria (e.g., Escherichia coli and Klebsiella), which express α-galactosyl epitopes on their lipopolysaccharides and other cell wall components (4). A striking reciprocal evolutionary pattern in the distribution of anti-Gal and the Galα1-3Galβ1-4GlcNAc-R residue was observed in mammals. The Galα1-3Galβ1-4GlcNAc-R residue is abundant on various nucleated cells and red blood cells from non-primate mammals, prosimians (i.e., lemurs), and New World monkeys (5,6). The expression of this structure is diminished, however, on cells of Old World monkeys, apes, and humans (5,6). In contrast, anti-Gal is present in the serum of Old World monkeys and apes in amounts comparable to those found in man, but this antibody is absent from the blood of New World monkeys and various nonprimate mammals (6). The lack of Galα1-3Galβ1-4GlcNAc-R synthesis in human cells results from the diminished activity of the enzyme α1-3-galactosyltransferase, which catalyzes the following reaction:

\[ \text{Galβ1-4GlcNAc-R + UDP-Gal} \rightarrow \text{Galα1-3Galβ1-4GlcNAc-R + UDP.} \]

This enzyme was found to be active in the Golgi apparatus of many mammalian species (7-10), but it was not detected in human cells (5). It seems that the α1-3-galactosyltransferase has undergone suppression in Old World primates. This might have resulted from the exposure of ancestral Old World primates to an infectious agent, endemic to the Old World, which expressed α-galactosyl residues and exerted a deleterious effect on the animals. Such an infectious agent could have driven the ancestors of Old World primates to produce anti-Gal as a protective antibody, with concomitant suppression of the α1-3-galactosyltransferase gene activity to prevent autoimmune reactions. The ultimate direct proof for this hypothesis may be obtained by the use of cloned α1-3-galactosyltransferase cDNA in hybridization experiments with human DNA to demonstrate the presence of this gene within the human genome. Nevertheless, the present study by Castronovo et al. suggests that the α1-3-galactosyltransferase gene is indeed present in man and that this gene appears to undergo deregulation in a considerable proportion of transformed cells in patients with mammary carcinoma. This leads to the synthesis of the Galα1-3Galβ1-4GlcNAc-R epitope in malignant cells, which is recognized by anti-Gal.

The observation of Castronovo et al. is also supported by the studies of Towbin et al. (11), who showed that anti-Gal interacts with human astrocytoma and rhabdomyosarcoma cell lines. A more direct indication of the possible activation of α1-3-galactosyltransferase in certain human malignant cells emerges from the recent study of Kagawa et al. (12), who showed that a human lung carcinoma cell line can produce N-glycosylated glycoproteins (i.e., recombinant DNA interferon-β) in which a substantial proportion of the carbohydrate chains have the Galα1-3Galβ1-4GlcNAc-R epitope. The present study of Castronovo et al. thus calls for further careful analysis of various human malignancies to evaluate the tendency of such cells to express the Galα1-3Galβ1-4GlcNAc-R epitope.

In addition to the basic scientific interest in the possible deregulation of α1-3-galactosyltransferase in human malignant cells, this process may also be of considerable clinical significance. Since all humans produce large amounts of antibodies which recognize the Galα1-3Galβ1-4GlcNAc-R epitope (i.e., the anti-Gal antibodies), it may be assumed that expression of such epitopes would be detrimental to malignant cells. This assumption has been evaluated in a previous study by Castronovo et al. (13). They showed that pre-exposure of malignant murine cells to anti-Gal (these cells express an abundance of the Galα1-3Galβ1-4GlcNAc-R epitope) resulted in the subsequent in vivo trapping of the cells within the reticuloendothelial system, preventing metastasis formation. Theoretically, circulating malignant cells expressing this
The study by Castronovo et al. raises several questions with regard to the possible in vivo interaction of anti-Gal and tumor cells. Does anti-Gal bind to mammary carcinoma cells in vivo? If so, does anti-Gal mediate an inflammatory response in vivo against cells expressing the Galα1-3Galβ1-4GlcNAc-R epitopes? If no such response is observed, how do the tumor cells compartmentalize themselves away from this abundant antibody? Does anti-Gal act as a barrier against metastasis formation by cells expressing the Galα1-3Galβ1-4GlcNAc-R epitope, and if so, do the metastases of such primary tumors lack this carbohydrate epitope? Finally, the possibility exists of a transient decrease in the anti-Gal titer, which may hypothetically enable metastasis formation by cells expressing the Galα1-3Galβ1-4GlcNAc-R epitope. This possibility should be examined. Careful studies of all of these questions in patients with malignant cells capable of binding anti-Gal may provide important information concerning the contribution of anti-Gal to the immune-mediated surveillance against malignant cells in man, as suggested by Castronovo et al.

References
