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REPORT**A Commentary on Modified Citrus Pectin**

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Life Extension has been at the forefront in bringing attention to important advances in medicine over the last 20 years. This month's article by Romy Fox on modified citrus pectin (MCP) continues in this tradition. This is a thought-provoking article that Life Extension members should read. My commentary on this article focuses on MCP and its relationship to the control of cancer. For the reader to understand this aspect of MCP, it is necessary that I first discuss how MCP interacts with specific cell products called carbohydrate-binding proteins or galectins.

Two core concepts— communication and balance— are critical to the worlds of humanity and biology. Communication between healthy or normal cells is vital to their many functions and survival. What needs to be emphasized is that this is also true as it relates to the function and survival of cancer cells. It has become clear that the important strategies that work for the “healthy” cell also are vital strategies for the “enemy” or cancer cell. Cell-to-cell communication, therefore, is critical to cell survival. One key aspect of this interaction relates to the ability of tumor cells to form cohesive groups. As in human interactions, there is strength in numbers when it comes to cancer cells. Clusters of tumor cells are able to survive destruction by the body's immune system because immunity functions best when dealing with a low tumor burden, i.e., tiny amounts of tumor.

Specialized proteins detected within cancer cells facilitate cancer cell cohesiveness resulting in cell clumping or clustering. This in turn hastens the growth and spread of malignancy, as depicted in the diagrams that accompany the article. These proteins are called carbohydrate-binding proteins or lectins. Of the 14 lectins so far identified, the one that appears most important in the cancer process is galectin-3.

If we can block cancer cells from clumping together and also prevent their sticking to target sites on blood vessel walls, we can develop therapies that affect cancer production, the adhesion, migration, growth, progression, and metastasis of cancer cells, and even cancer cell death (apoptosis).¹ The galectins, and especially galectin-3, are intimately involved in many, if not all, of these processes.

An in-depth review of the contemporary medical literature on galectins reveals an exciting but intricate picture. Some publications clearly indicate that increased levels of galectin-3 in the blood or in tissue are associated with the frequency of malignancy and an increased stage of tumor progression.²⁻¹⁴ Some of these articles are of landmark importance because they indicate impressive accuracy when galectin-3 testing is used to establish the presence of malignancy. This is clearly the case with thyroid cancer^{7-11,15-18} and colon cancer.^{4,5,17} Physicians and patients must be made aware of such highly significant developments, and commercial laboratory tests need to become available to translate these advances to the care of patients.

Additional medical research has involved the raising or lowering of galectin-3 levels in animal models of cancer. These studies have also established a correlation between higher galectin-3 levels and metastasis.¹⁹ Some controversy arises, however, from other articles that point out that just the opposite is seen with other malignancies. In such instances, lower or absent galectin-3 levels are associated with a more aggressive biological behavior of certain cancer types, and higher levels of galectin-3 with more mature (more differentiated) tumors that are less advanced in the stage of the cancer.²⁰⁻²² For example, in the article by Piantelli et al, a significant correlation was found between higher galectin-3 tumor levels and longer relapse-free survival and overall survival in patients diagnosed with cancer of the larynx.²³

Therefore, we must be specific in detailing the type of cancer when discussing the effects of galectin-3 levels on cancer diagnosis, tumor stage, aggressiveness, and survival. The accompanying table shows such relationships, but the reader should be aware that this is a first approach and does not include many tumor types. The biologic effects shown in this table are of major medical significance.

The literature on galectin-3 becomes more exciting in light of research that now reveals multiple functions for this protein. Most of the older literature focuses on the carbohydrate-binding properties of galectin-3. The binding takes place at the end of the molecule called the C-terminal end. The other end of the molecule, called the N-terminal, end, is responsible for another important function— protecting the tumor cell from cell death or apoptosis. When a specific amino acid (serine) in the sixth position from the N-terminal end is activated, a chemical process is begun that triggers an “anti-death” chemical sequence. In this case, the cancer cell is being protected. The cellular mechanism involves protection of the cancer cell mitochondria (the

powerplants for both normal and cancer cells) from damage due to oxidation by nitric oxide.²⁵ Thus, galectin-3 works at the N-terminal end to protect the cancer cell from cell death or apoptosis caused by nitric oxide. This cell death pathway is a key mechanism in the action of radiation therapy and also some chemotherapy drugs such as cisplatin.²⁶ To add to the excitement of such a discovery, the galectin-3 protein has also been shown to function as an on-off switch. When the N-terminal end of galectin-3 is activated, it switches off the functioning of the carbohydrate-binding end of the protein.²⁷ When the C-terminal end of the molecule is activated, it switches off the anti-apoptosis function of the N-terminal end.²⁸ Thus, galectin-3 is a multi-tasking protein with one "on" trigger to protect the tumor cell from death or an "off" trigger that allows tumor cells to bind together to form cohesive masses, to invade connective tissue including blood vessels, and to metastasize and grow. This is a key development in our understanding of the cancer process!

Modified citrus pectin enters the picture and ties up the C-terminal end of the protein blocking the tumor cells' ability to adhere and form cohesive masses or cancer cells. Modified citrus pectin, in studies by Strum et al and Guess et al, slowed the prostate-specific antigen (PSA) doubling time in men with prostate cancer.^{29,30} This could be simply due to turning off PSA production without affecting tumor cell proliferation. Other studies have shown, however, that modified citrus pectin actually decreases tumor cell growth,³¹ and that it is able to bind to galectin-3 and decrease cell adhesiveness, invasion, and metastasis.³²⁻³⁴

The central question is whether MCP, at the time it affects the functions noted above, is able to turn off the switch at the N-terminal end of the galectin-3 protein, thus weakening the tumor cell's ability to protect itself from destruction by radiation or chemotherapy. Additional studies are badly needed because of the potentially great benefit of MCP in the treatment of a multitude of malignancies. The diagnostic and staging implications for galectin-3 and other galectins and the therapeutic implications for MCP are of such magnitude as to warrant major conferences and further funding on this exciting development.

In conclusion, modified citrus pectin appears to be an important mitigating factor in cancer cell control and death.

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