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The Janus-Faced Nature of Cancer Immunity

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ABSTRACT

In this study, we demonstrated that the immune response in cancer patients could sometimes inhibit, but other times enhance tumor cells' growth.

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Cancer, viruses, bacteria, and chemicals are threatening our bodies every day. The weapon our body uses to fight these threats is our immune system. When triggered by the presence of something it perceives as foreign (and therefore danger), our immune system will produce antibodies targeting that threat. An antibody is a specific type of protein capable of binding to its target and plays a crucial role in the body's attempt to eliminate that target. When an antibody response is triggered, you do not produce just one antibody, but rather a mixture of slightly different antibodies, all of which can bind to the target, such as a particular type of cancer cell, virus, bacteria, etc. This is called a polyclonal antibody response. It is part of what is known as the immune surveillance system and is usually considered to be helpful.

It is generally thought that the immune response to cancer cells helps reduce the occurrence and progression of tumors. Although cancer cells are "self", they usually have a mutation in a cell surface protein (sometimes a growth factor receptor). These proteins, which have become "non-self" through mutation, can trigger a polyclonal antibody response. In this case, since the cancer cells were initially considered to be "self", the resulting antibodies are called autoantibodies. Some of these polyclonal autoantibodies are thought to function as agonists, while others may serve as antagonists. An agonist is something that binds to a receptor and activates the receptor to produce a biological response. Whereas, an antagonist binds to the receptor but blocks the normal biological response,

and may cause an action opposite to that of the agonist. We wanted to study the effect of these agonist and antagonist autoantibodies on the growth of cancer cells.

Unexpectedly, we discovered that the plasma of breast cancer patients contained autoantibodies against a specific cell surface growth factor receptor. There is limited information about how such autoantibodies interact with their target growth factor receptor and how these interactions affect tumor growth. Since it is difficult to determine any single antibody's role in a polyclonal mixture, we first needed to isolate individual autoantibodies from breast cancer patients. To do this, we selected and isolated antibodies. We then chose one of these antibodies that appeared to be an agonist and a second antibody that seemed to be an antagonist for further study.

To study the effect of these agonist or antagonist autoantibodies on breast cancer cells, we first incubated our two individual autoantibodies with breast cancer cell lines for three days. The results showed that the agonist autoantibody increased cancer cell growth, while the antagonist autoantibody decreased cancer cell growth. We then studied whether these antibodies could influence breast cancer cell growth in animals. Breast cancer cells were injected into mice. When the tumor mass was palpable, the mice were treated by injecting the purified agonist or antagonist autoantibody twice weekly for one month. The results showed tumor growth was increased in mice receiving the agonist antibody but decreased in mice receiving the antagonist antibody. We also showed that when agonist antibodies bind to their target growth factor receptor, they trigger downstream signaling similar to that seen when the natural ligand binds to the receptor. This explains why agonist antibodies can affect tumor behavior.

Conceptually one can imagine that the immune response to cancer has two consequences. The first is generally recognized and involves a surveillance role that inhibits the occurrence and development of tumors. The second, more obscure possibility, is that under certain conditions, the immune response may be deleterious, and stimulate rather than inhibit tumor growth. Given these autoantibodies' polyclonal nature, the net effect may depend on the relative representation of individual autoantibody clones. Our work indicates that a preponderance of agonist autoantibodies to a cancer cell's growth factor receptor would be harmful to the patient. Therefore we suggest that antibodies to surface proteins on cancer cells is another parameter that should be routinely measured. Agonist autoantibodies are a previously unknown driving force for cancer cell growth. Further research into the association between these antibodies and growth factor receptors in cancer is necessary. It has the potential to open new opportunities in both cancer diagnosis and treatment.