Researchers make promising discovery in pursuit of effective lymphoma treatments

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Researchers at NYU School of Medicine have identified a target for slowing the progression of multiple myeloma by using currently available drugs.

Published recently in Nature Cell Biology, the study reveals a pathway that, if deactivated, may help slow the development of the disease.

"We have the ability to target this pathway with drugs that already exist," said lead investigator Michele Pagano, MD, the May Ellen and Gerald Jay Ritter Professor of Oncology in the Department of Pathology and a member of the NYU Cancer Institute at NYU Langone Medical Center, and a Howard Hughes Medical Institute investigator. "Many other lymphomas are also controlled by this pathway, so while we're optimistic that this discovery will provide a way to kill multiple myeloma cells, we're also very hopeful that this can be applied to other lymphomas and that it will have a major impact on these aggressive cancers."

Pagano and colleagues put together several new pieces of the puzzle surrounding the survival and spread of multiple myeloma cells and the Nuclear Factor kappa B (NF-κB) pathway. This complicated pathway induces transcription of genes that control inflammation, immunity, and certain developmental processes. It is also known to frequently be involved in disease.

In normally functioning cells, the NF-κB pathway turns off and on, triggered by the accumulation and then degradation, or breakdown, of a

protein called p100. When the pathway is "on," p100 is degraded, allowing for pathway-dependent gene transcription. Several hours after the pathway's activation, p100 begins to accumulate in the cell's nucleus, naturally blocking the pathway, so that the gene transcription signal is temporarily blocked and transcription is halted.

In lymphomas, including multiple myeloma, however, the NF-κB pathway remains active, providing a refuge for lymphoma cells to hide. In fact, within this active pathway, the lymphoma cells are able to evade apoptosis, or cell death, allowing them to proliferate in an uncontrolled way.

"Activating mutations in the NF-κB pathway does not generally represent the initial oncogenic event," Dr. Pagano said. "But they are necessary for the survival and spread of the cancer."

Dr. Pagano explained the steps involved with pathway's activation and deactivation in more scientific detail: The process begins in the pathway's off state, with the accumulation of p100. To clear the pathway and naturally turn it back on, a sequence of events has to happen. First, a kinase, which the team identified as GSK3, phosphorylates p100. The phosphorylation draws the attention of Fbxw7α, a subunit of a ubiquitin ligase, which binds to the portion of p100 that has been phosphorylated by GSK3. The addition of Fbxw7α to the p100 protein then causes ubiquitin to seek out p100. Ubiquitin attaches to the protein and modifies it in a way such that it is recognized by a protease whose job it is to recognize and degrade any protein that has been modified by ubiquitin conjugation. As a result, p100 is degraded in the nucleus of the cell and the pathway is cleared and activated, turning on the gene transcription signal.

These new findings lead the researchers to conclude that the intersection of GSK3, Fbxw7α and p100 may serve as a potential intervention point

for the treatment of multiple myeloma. Researchers believe if they can find a way to target the elimination of p100 they may be able to inactivate the pathway, which would eliminate the tumor cells' safe haven so that they would be susceptible to apoptosis. This would in turn promote the death of multiple myeloma cells.

According to Dr. Pagano, this strategy may not be too far from becoming a reality. There are already drugs being tested in clinical trials for Alzheimer's Disease that work by inhibiting GSK3. With the current study, the research team from NYU School of Medicine has shown that, by blocking GSK3 from phosphorylating p100, it is possible to prevent the degradation of p100, which then blocks the NF-κB pathway, thereby halting gene transcription and blocking tumor cells' safe zone. Alternatively, pharmaceutical research may find a way to target Fbxw7α, which would keep the pathway turned off in the same way.

"Cancers are persistent and tenacious," Dr. Pagano said. "There are millions of pieces to the puzzle of how they work and we've discovered a few more pieces of that puzzle. It is very possible that we can find an inhibitor of Fbxw7α since there are already drugs being tested that inhibit very similar enzymes."

Moreover, Dr. Pagano explained, it is likely that the effects observed in multiple myeloma may be generalized to other B-cell neoplasms, types of lymphomas, especially those in which the tumor cells hide out in the NF-κB pathway.

"These new findings strongly suggest that by targeting this enzyme, we will kill multiple myeloma cells and other B-cell lymphomas," he said. "And that, from a researcher's perspective, is a very exciting prospect."

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