MedicalXpress

Insight into chromatin therapies for breast cancer could aid personalized medicine

February 7 2018

Most traditional chemotherapy for cancer has dangerous side effects, but new research is finding ways to develop 'targeted agents' that reduce the side effects and are better tailored to individual patient needs. While these innovations are exciting, a new study shows how certain cancer inhibitors need to be examined more carefully to better understand fine-grained effects and counter-effects, which could yield more effective and safer therapies.

Under the direction of Gerald V. Denis PhD, researchers at Boston University School of Medicine (BUSM) have long studied a family of three closely related proteins, called BET bromodomain proteins, comprised of BRD2, BRD3 and BRD4, which regulate gene expression. They were the first (in the 1990s) to show how these proteins function in human cancer.

According to the researchers, new inhibitors of these proteins have generated a lot of excitement in cancer research because they may work well to block growth in diverse cancer types and seem to be less toxic than traditional chemotherapies. However, they also have known for a long time that the three proteins don't always work together.

"The field of the bromodomain proteins is fascinating" said the study's first author Guillaume Andrieu, PhD, post-doctoral research associate at BUSM. "A decade ago, the first drugs targeting the BET proteins were discovered. Since then, researchers have identified them as promising targets for cancer therapy, notably in lymphomas, but also in breast and

prostate cancer. Yet, the contribution of each BET protein to cancer progression remains an obscure area as strategies aiming to block all of them at once have only been developed so far."

"In this study, we show that sometimes individual BET bromodomain proteins even oppose each other. Therefore, any of the pan-BET inhibitors that are currently available, which block all three, could have unexpected side effects or leave us working in the dark about their exact mechanisms of action," explained Denis, associate professor of medicine and pharmacology at BUSM and corresponding author of the study. "It has been established for several years now that BET proteins also exert protective roles in the body, notably by restricting viral infections including HIV," added Andrieu. "Therefore, it is urgent to develop new strategies to specifically target them to avoid deleterious effects."

Using human breast cancer cell lines that model estrogen receptor positive and triple negative tumor types, the researchers exposed them to a pan-BET inhibitor and compared what happened when they blocked expression of the three genes individually. They saw four patterns of expression important for 'epithelial-to-mesenchymal transition' (a program that tumor cells often activate to metastasize and to resist to treatments): one for the inhibitor and one for each of the individual genes, with surprisingly little overlap among them. "The results clearly show that the three proteins work independently and confirm our long stated concern that current pan-inhibitors are not sufficiently selective among the three. Based on this research, there are promising avenues to explore for more fine-tuned experiments and treatments," said Denis.

Denis believes this discovery should be seen in light of personalized medicine because some patients have high level expression of one or more BET proteins, some are intermediate and some are low. "Targeted drugs and patient profiling help oncologists understand which patients are most likely to benefit from tailored approaches, and which patients

should be directed to alternate therapies. Personalized medicine is the most important innovation in cancer therapy since methotrexate was discovered in the 1950s as a chemotherapeutic drug for cancer, so it's important that the field move forward both quickly and carefully."

Cancer clinical trials using BET inhibitors are currently recruiting for leukemias, lymphoma, multiple myeloma, metastatic prostate cancer, lung cancer, glioblastoma and subtypes of breast cancer, including triple negative breast cancer. "Our findings are urgently relevant to all of these trials, because the fundamental mechanisms we explored are shared across many cancer types," said Denis.

These findings appear in the journal *Molecular Cancer Research*.

Provided by Boston University School of Medicine