Scientists discover new lead in hunt for myeloma drug

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A molecule involved in fat transport and metabolism is key to the progression of the malignant blood cancer multiple myeloma, researchers report today in *eLife*.

The molecule—called fatty acid binding protein 5 (FABP5)—could be used as a marker to help doctors identify people with more aggressive forms of myeloma and may represent a new target for multiple myeloma treatment, which is urgently needed.

Multiple myeloma accounts for roughly 10% of blood cancers and only around half of people who develop the disease will live beyond five years. Although treatments for myeloma patients have greatly improved within the past two decades, the disease is still incurable, and most patients eventually relapse.

"Despite recent findings that multiple myeloma cells uptake and transport fatty acids, there are few treatments that specifically target molecules involved in metabolism in myeloma cells," says lead author Mariah Farrell, Research Associate at MaineHealth Institute for Research, Scarborough, US. "We wanted to study the cancer-promoting potential of the fatty acid binding proteins in myeloma cells, to determine if this could be a valid target for therapeutics."

The team began their studies in multiple myeloma cell lines by looking at relative amounts of each type of fatty acid binding protein (FABP). They found that FABP5 was the most abundant form in both mouse and human myeloma cells, and human myeloma cell lines were predicted to have a strong reliance on FABP5 for their survival.

Based on these findings, the team used two approaches to explore the FABP family's function in myeloma cells; in one experiment, they engineered the cells to lack FABP5, and in a second experiment, they treated myeloma cells with two drugs known to block FABP activity. These studies revealed that blocking FABP family members' activity hampers myeloma cell growth. By contrast, non-cancerous cells treated with the anti-FABP drug were affected to a much smaller extent.

To uncover how FABPs influence myeloma cell growth, the team studied changes in gene activity and protein production in myeloma cells where FABPs were blocked. They found many effects of FABPs in the cells, but most notably, they observed that the Myc pathway—a key survival pathway used by cancer cells—was decreased when FABP proteins were blocked. This suggests that the Myc pathway may be one way that FABPs help tumors survive.

To see whether FABP5 is linked to tumor progression in people with myeloma, the team retrospectively analyzed data from 779 myeloma patients from the Multiple Myeloma Research Foundation's CoMMpass℠ Study. They found that myeloma patients, on average, had the highest expression of FABP5; moderate expression of FABP6, FABP4, and FABP3, and essentially no expression of the other FABP subtypes. Overall, patients with higher amounts of FABP5 in their myeloma cells had significantly shorter time to disease progression and shorter overall survival.

In addition, their retrospective analysis of 414 newly diagnosed myeloma patients, showed that those who had a high-risk myeloma with poorer prognosis had higher FABP5 gene expression than those with a more favorable prognosis. Lastly, FABP5 expression was found to be increased in patients who had relapsed disease, compared with patients who were newly diagnosed.

Taken together, these studies suggest that patients with high amounts of FABP5 in their myeloma cells had a 64% higher chance of disease progression, and a two-fold increase in the risk of death, compared to patients with low FABP5 expression.

They also found that, although FABP5 has known roles in lipid metabolism, the association with myeloma progression and survival was not influenced by patient body mass index (BMI)—suggesting it could be a robust marker of myeloma risk in all patients, not only those patients whose risk might be increased by obesity.

"Overall we've found that blocking the FABPs can prevent the growth of myeloma cells, mainly by slowing the cells' proliferation. We were excited to see that clinical datasets also show that tumors expressing higher FABP5 are more aggressive compared to tumors with less FABP5, making it a key target molecule for new myeloma treatments," concludes senior author Michaela Reagan, Faculty Scientist at MaineHealth Institute for Research and Associate Professor at Tufts University School of Medicine.

"The next step is to work towards a better understanding of the activity and safety of existing FABP-blocking drugs in mouse myeloma models so we can design and develop the best candidates to take into clinical trials."

More information: Mariah Farrell et al, Targeting the fatty acid binding proteins disrupts multiple myeloma cell cycle progression and MYC signalin, *eLife* (2023). DOI: 10.7554/eLife.81184

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