Potential new treatment strategy for aggressive leukemia

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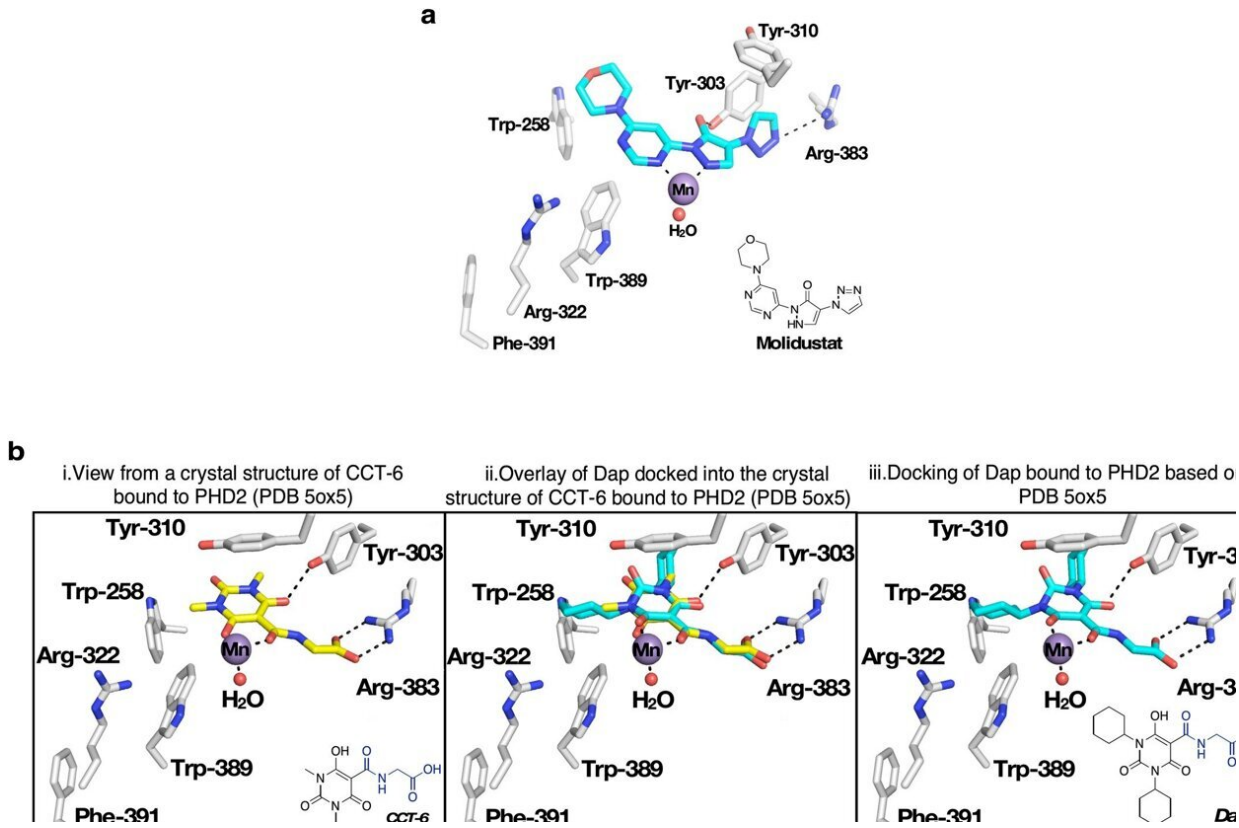

Modeling of PHD inhibitors. Credit: *Nature Cancer* (2024). https://doi.org/10.1038/s43018-024-00761-w

Scientists have found a potential treatment strategy for an aggressive type of leukemia by targeting enzymes used by cells to sense and adapt

to oxygen levels.

In findings published in *Nature Cancer*, researchers reveal that blocking these oxygen-sensing enzymes can significantly halt acute myeloid leukemia (AML) in mice and patient samples without affecting normal production of blood cells. The paper is titled "The selective prolyl hydroxylase inhibitor IOX5 stabilizes HIF-1α and compromises development and progression of acute myeloid leukemia."

The enzymes can already be blocked safely with existing drugs used to treat anemia, so the researchers hope to see their findings translated to clinical trials for leukemia. The team has also developed a new first-in-class drug which more selectively blocks the enzymes than existing drugs, and so may reduce side effects.

AML is an aggressive type of blood cancer that usually affects older adults but also occurs in children and young adults. In AML, patients experience a dramatically increased production of immature white blood cells, called blasts. This is driven by mutations in the stem and progenitor cells that usually give rise to normal blood cells. These blasts in turn damage the bone marrow and other organs with devastating consequences to the patients.

There are few treatment options for AML. Therapies have remained relatively unchanged for the last 30 years, with the majority of patients receiving chemotherapy and bone marrow transplants to control their condition. Unfortunately, many of these treatments are not effective and they cause toxic, and sometimes deadly, side effects.

The research was co-led by scientists from The Institute of Cancer Research, London, and the University of Oxford, and partly undertaken at Queen Mary University of London.

The work aimed to understand whether enzymes called hypoxia-inducible factor prolyl hydroxylases (PHDs), which sense levels of tissue oxygen in the body, could be a drug target for treating AML.

In the presence of oxygen, the PHD enzymes are active and target hypoxia-inducible factor (HIF) proteins for their destruction. Under hypoxia, when oxygen levels are low, PHD enzymes are less active resulting in increased levels of HIF.

The team had previously shown that inactivation of HIF promotes aggressive AML, and now they set out to uncover whether boosting the levels of HIF could prevent AML progression.

In this study, they achieved this by blocking or genetically inactivating PHDs. In studies in mice they showed that genetic modification to inactivate PHD enzymes increased HIF levels. This stopped the leukemia from starting or progressing, without affecting the normal production of blood cells.

They showed the same anti-leukemia effect when inactivating PHD by using existing drugs currently used to treat anemia, in mouse cells and patient samples. Notably, they generated a new first-in-class PHD inhibitor called IOX5, which selectively inhibits PHDs, without inactivating any other enzymes. They found that IOX5 significantly blocked AML progression.

The anti-cancer effect of IOX5 was further increased when combined with Venetoclax, a drug used to treat various types of leukemia. The findings provide a 'proof-of-concept' that blocking PHD enzymes is an effective strategy against acute myeloid leukemia.

Professor Kamil Kranc, at The Institute of Cancer Research, London, said, "Therapy for acute myeloid leukemia has barely changed in several

decades. There is a huge need to discover better treatments for this aggressive disease. We've shown for the first time that targeting the pathways that our cells use to respond to oxygen levels could provide a new way to treat leukemia, without impacting the normal production of blood cells within the bone marrow.

"Our next challenge is to progress the existing drugs and our new, more selective compound, to clinical trials. We're hopeful this research will pave the way towards a new era of AML treatments, and we'd like to explore whether these therapies could also be beneficial for solid tumors."

More information: Hannah Lawson et al, The selective prolyl hydroxylase inhibitor IOX5 stabilizes HIF-1α and compromises development and progression of acute myeloid leukemia, *Nature Cancer* (2024). DOI: 10.1038/s43018-024-00761-w

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