Reducing resistance to chemotherapy in colorectal cancer by inhibition of PHD1

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Scientists at VIB and KU Leuven have shown that blocking the PHD1 oxygen sensor hinders the activation of p53, a transcription factor that aids colorectal cancer (CRC) cells in repairing themselves and thus resisting chemotherapy. Chemotherapy resistance remains a major clinical issue in the treatment of CRC. These findings indicate that PHD1 inhibition may have valuable therapeutic potential. The study was published in the leading medical journal *EMBO Molecular Medicine*, which features molecular biology-driven research.

Chemotherapy remains the most widely used cancer treatment, and much attention has been paid to the mechanisms underlying chemotherapy resistance. Sofie Deschoemaeker (VIB/KU Leuven) and a research team led by Massimiliano Mazzone (VIB/KU Leuven) recently investigated the interplay between p53 and the PHD family of oxygen sensors and their potential role in the response of CRC to chemotherapy.

Blocking PHD1 prevents p53 activation upon chemotherapy

The proteins PHD1, PHD2 and PHD3 are oxygen-sensitive enzymes known to be involved during cell damage and metabolic stress, such as that induced by chemotherapeutic treatment. The transcription factor p53 is a well-known cell stress sensor that, when mutated in cancer cells, can be activated to promote DNA repair in those cells, reducing chemotherapy's effectiveness. Prof. Mazzone's team found that

inhibiting PHD1, but not PHD2 or PHD3, prevented p53 activation and improved the response of CRC to multiple chemotherapeutic agents.

The study's novel insight into the molecular mechanisms underlying chemotherapy resistance adds another layer of complexity to the role of PHD1 in cancer.

Robbing cancer cells of their ability to heal

Sofie Deschoemaeker: "We demonstrated that PHD1 can affect the way colorectal cancer responds to the three most common chemotherapeutic drugs used to treat CRC today. By blocking PHD1, we rob CRC cells of their ability to harness p53 to the cell-repair yoke, even when this protein is mutated (as often occurs in CRC). That means the CRC cells are exposed to the full DNA damage caused by these genotoxic drugs, resulting in greater cell death and thus a better response to the chemotherapy and, ultimately, an improved outcome."

The research, which appeared in *EMBO Molecular Medicine*, opens the door to the design and validation of PHD1-specific inhibitors in colorectal cancer patients, with the aim of increasing their sensitivity to currently used chemotherapeutic treatments.

More information: "PHD1 regulates p53-mediated colorectal cancer chemoresistance," Deschoemaeker et al., *EMBO Molecular Medicine* 2015

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