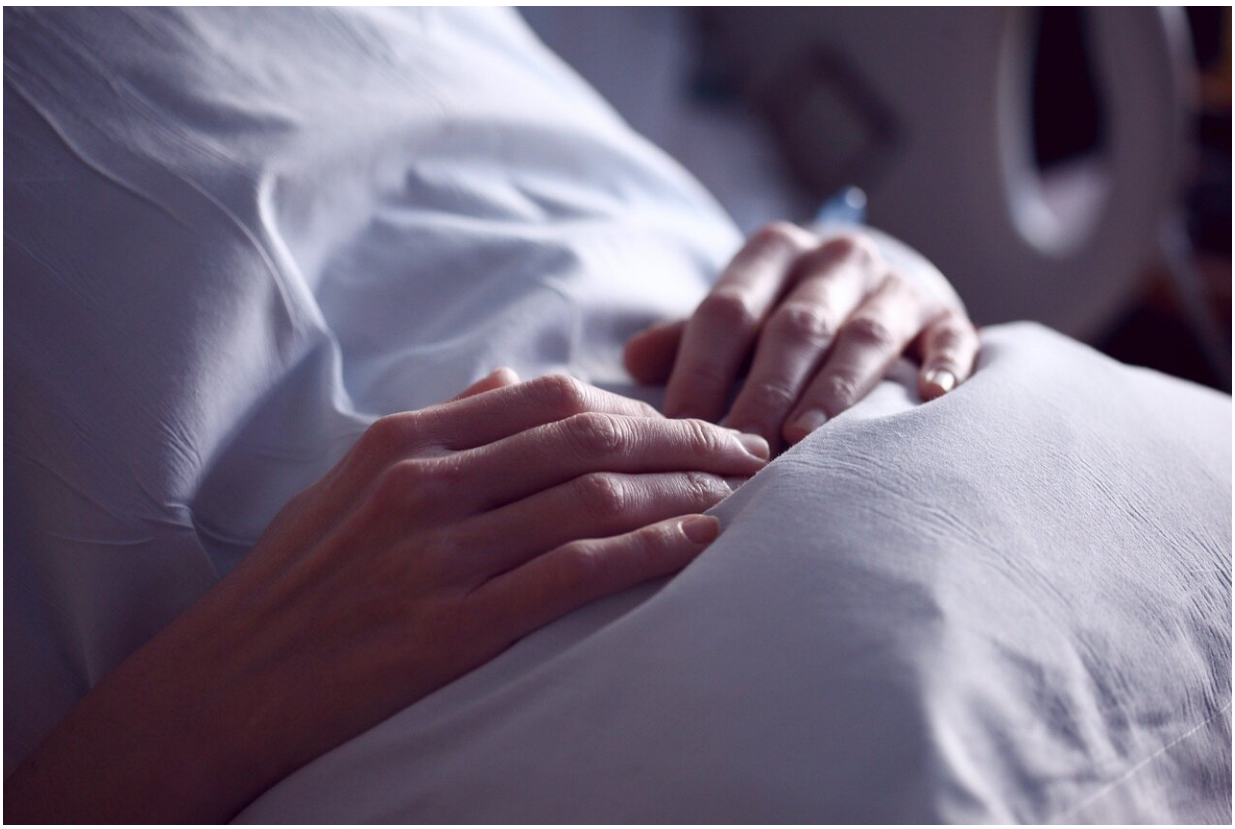
Wnt pathway dysfunction influences colorectal cancer response to immunotherapy, finds study

December 15 2023



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Colorectal cancer (CRC) presents with varying clinical characteristics due to tumor heterogeneity. Microsatellite instability (MSI), present in

10–15% of CRC cases, indicates a different clinical trajectory than microsatellite stable (MSS) patients. Notably, MSI patients tend to have better outcomes and respond well to immunotherapy, but not to chemotherapy. The reason behind this disparity and the mechanisms governing MSI remained largely unknown.

A rapid communication published in the journal *Genes & Diseases*, has shed light on the role of the Wnt signaling pathway in influencing the immune response of CRC patients.

Researchers from Nankai University discovered that abnormalities in this pathway can affect a patient's response to immunotherapy, paving the way for more tailored treatment strategies. They integrated transcriptome data from 425 CRC patients, aiming to explore the underlying mechanism of MSI.

They identified that the Wnt signaling pathway, essential for various cellular processes, showed signs of inhibition in MSI patients. The team also noted a significant down-regulation in mismatch repair enzyme gene MLH1 in these patients. Intriguingly, the expression of the MLH1 gene, crucial for DNA repair, was influenced by the activity of the Wnt signaling pathway.

In MSI patients, the canonical Wnt signaling pathway was notably suppressed, resulting in the diminished expression of the mismatch repair enzyme, MLH1. This decrease in MLH1 expression underpins defects in the mismatch repair system, a defining characteristic of MSI.

Concurrently, the study identified a down-regulation of SET, another pivotal gene, in these patients. The reduced SET expression correlated with a surge in immune infiltration and activation, hinting at an intensified immune response. Intriguingly, this research posits that MSI patients with such decreased SET expression may exhibit an enhanced

responsiveness to immunotherapy, particularly immune checkpoint blockade (ICB).

The communication indicates that dysfunction in the Wnt signaling pathway could be a driving force behind MSI in CRC. Reduced activity of specific transcription factors led to decreased MLH1 expression, impairing DNA repair mechanisms. Additionally, the role of the SET gene in modulating immune responses provides valuable insights into why MSI patients might respond better to immunotherapy.

More information: Jiyan Wang et al, The dysfunctional Wnt pathway down-regulates MLH1/SET expression and promotes microsatellite instability and immunotherapy response in colorectal cancer, *Genes & Diseases* (2023). DOI: 10.1016/j.gendis.2023.03.026

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