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# New studies suggest ways to improve cancer care by inhibiting oncogenes, boosting tumor-suppressor activity

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Two new studies by cancer scientists at The Ohio State University Comprehensive Cancer Center - Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC - James) suggest new approaches for treating cancer by inhibiting overactive cancer-promoting genes and by enhancing the activity of sluggish tumor-suppressor genes. The findings were reported in the journals *Nature Communications* and *Nature Genetics*.

The *Nature Communications* paper focused on oncogenes that are activated by glucocorticoid receptor (GR) in triple-negative breast cancer (TNBC). The integrative study combined extensive genomic datasets in TNBC cells and breast cancer gene expression datasets from more than 2,000 patients.

The findings showed that when GR is stimulated by the anti-inflammatory dexamethasone, it is able to recognize and bind to a DNA sequence termed the "glucocorticoid response element." This in turn activates genes associated with drug resistance and poor patient outcomes. However, when GR is stimulated by an experimental anti-inflammatory called compound A (a selective GR modulator), GR binds to an entirely different DNA sequence and no longer activates genes associated with drug resistance or cancer promotion.

"Dexamethasone is a glucocorticoid anti-inflammatory that is often administered to patients to ease the side effects of chemotherapy," says OSUCCC - James researcher Qianben Wang, PhD, associate professor of molecular virology, immunology and medical genetics. Wang was principal investigator for both studies.

"This study suggests that dexamethasone should be used cautiously as a coadjuvant in the treatment of TNBC and some other solid tumors," Wang says. "Safer glucocorticoid anti-inflammatories are needed, and the development of those agents should be done with an awareness of their genomic effects.

"Along with our study published in *EMBO J* early this year, this work suggests that we need to develop better primary and co-adjuvant therapeutics for use during the treatment of hormone-related cancers that avoid this effect of activating oncogenes via stimulation of hormone receptors such as male hormone receptor (androgen receptor) and GR," Wang comments.

The *Nature Genetics* study, jointly supervised by Wang and a second principal investigator, Wei Li, PhD, associate professor of biostatistics and molecular and cellular biology at Baylor College of Medicine, focused on tumor-suppressor genes, which normally protect cells from becoming cancerous. The work suggested that tumor-suppressor gene activity might be enhanced in normal cells by prolonging a step in the gene-expression process called the transcription-elongation phase.

Cells make proteins using the information encoded by a gene's DNA. Cells access that encoded information by copying genes in the form of RNA. For this to happen, the DNA helix first opens down the length of the gene. Then an enzyme moves along the unwound DNA strand, reading the DNA sequence and producing a corresponding strand of RNA. Production of the RNA strand is called the elongation phase of gene transcription.

The new study, done using publicly available genomic and mutation data and genomic data generated in the Wang lab from human tumor and normal tissues, found that when an epigenetic mark called H3K4me3 is present as a broad fingerprint over genes that are widely conserved across normal cell types, it likely marks tumor-suppressor genes. When the broad fingerprint of this marker narrows for a particular gene in cancer cells, it may indicate tumor-suppressor genes with reduced expression.

The researchers also learned that the broad fingerprint is associated with enhanced transcription elongation leading to stronger tumor-suppressor gene expression.

"This epigenetic signature offers a way to discover new tumor-suppressor genes that is independent of gene mutations," Li and Wang say. "The findings also suggest that reduced expression of tumor-suppressor genes may contribute to cancer development or progression and that we may be able to recover tumor-suppressor gene expression by enhancing transcription elongation."

Source:

Ohio State University Wexner Medical Center

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