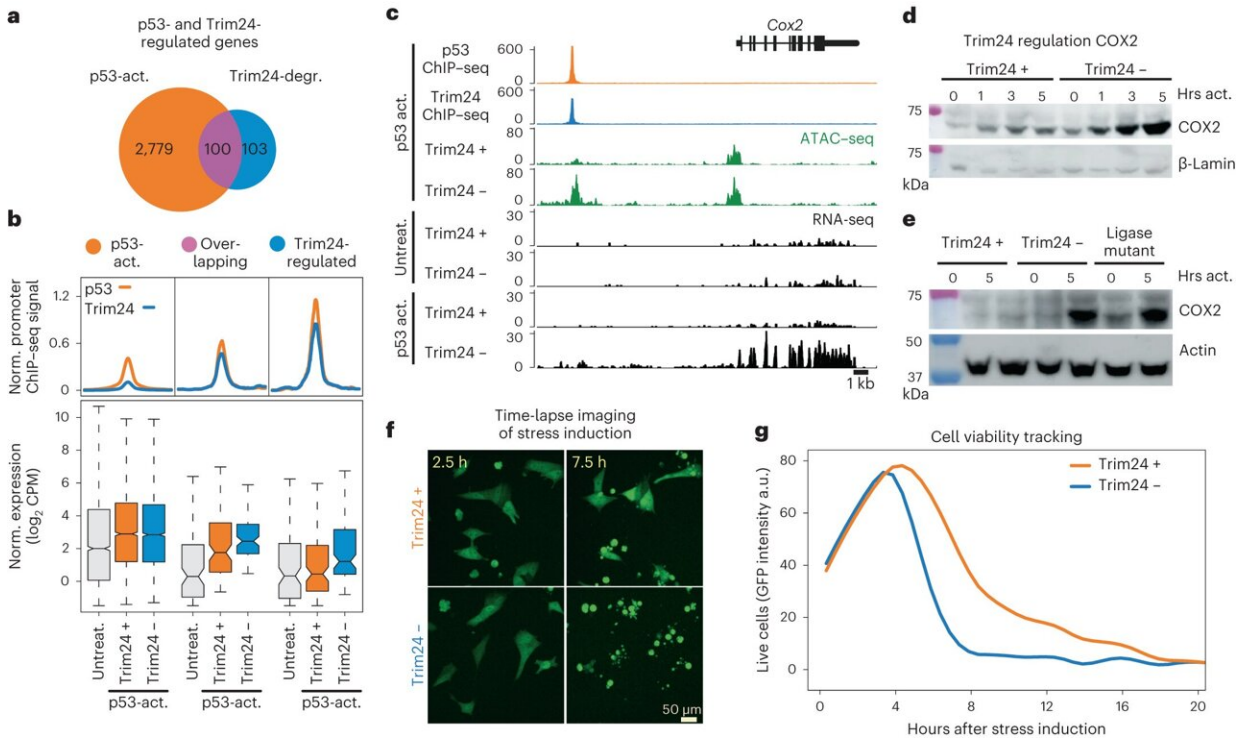
Zeroing in on the workings of tumor suppressor protein p53, the 'guardian of the genome'

June 30 2023



Trim24 regulates a subset of p53 target genes. a, Number and overlap of genes that change upon p53 activation compared with uninduced cells and upon Trim24 degradation in p53-active conditions. b, p53 and Trim24 ChIP–seq signals (top) in promoter peaks of differentially expressed genes as in a, alongside gene expression (bottom) in uninduced and p53-activated conditions with and without Trim24. Averages from triplicate experiments are shown. Center median to first and third quartile, whiskers to 1.5 multiplied by interquartile range. c, Representative Trim24-regulated gene Cox2. p53 and

Trim24 binding and accessibility are shown, with RNA-seq tracks under either uninduced or p53-activated conditions and with or without Trim24 loss. d, Western blot of COX2 protein expression after p53 activation (hours after activation (Hrs act.)), with and without Trim24. e, Western blot of COX2 protein expression after p53 activation, with and without Trim24 and in the ligase-null mutant (C52/55A) Trim24 variant line. f,g, Live imaging of GFP-expressing mES cells, measuring cell viability across a 20-h period following stress induction with or without Trim24 degradation. Representative images at 2.5 and 7.5 h after stress induction are shown (f), and cell viability as a function of Trim24, quantified for 20 h following stress induction (g). Credit: *Nature Structural & Molecular Biology* (2023). DOI: 10.1038/s41594-023-01021-8

The tumor suppressor protein p53 has been dubbed the "guardian of the genome" because it protects the DNA from stress or long-term damage by regulating the expression of numerous genes involved DNA repair, cell division and cell death. Now, FMI researchers have homed in on some of the mechanisms that regulate the activation of p53 target genes.

By stopping cells with mutated or damaged DNA from dividing, p53 helps prevent the development of tumors. The protein acts as a transcription factor that can be rapidly induced in response to various forms of cellular stress, resulting in immediate activation of genes involved DNA repair, cell division and cell death.

Unlike many other transcription factors, p53 can bind closed chromatin—a tightly packed form of DNA and proteins that suppresses gene expression by making the genome inaccessible to transcription factors. But it's unclear how p53 engages closed chromatin and opens it up to activate target genes.

Luke Isbel, a postdoctoral fellow in the Schübeler lab, and his colleagues investigated how p53 binds to DNA in mouse embryonic stem cells and

human tissues. The researchers found that the protein binds tightly packed stretches of DNA in both the mouse and human genome, yet its ability to loosen chromatin and turn on genes is regulated by another protein called Trim24. The study is published in the journal *Nature Structural & Molecular Biology*.

Trim24 localizes to p53 sites in closed chromatin, the researchers found. In the absence of Trim24, about half of 203 p53-regulated genes became strongly activated by p53.

The findings suggest that Trim24 typically limits p53 activity in closed chromatin, the researchers say. Because the levels of Trim24 are elevated in breast cancer and other types of tumors, the team speculates that the protein might limit the ability of p53 to function as a tumor suppressor in cancer cells.

More information: Luke Isbel et al, Readout of histone methylation by Trim24 locally restricts chromatin opening by p53, *Nature Structural & Molecular Biology* (2023). DOI: 10.1038/s41594-023-01021-8

Provided by Friedrich Miescher Institute for Biomedical Research