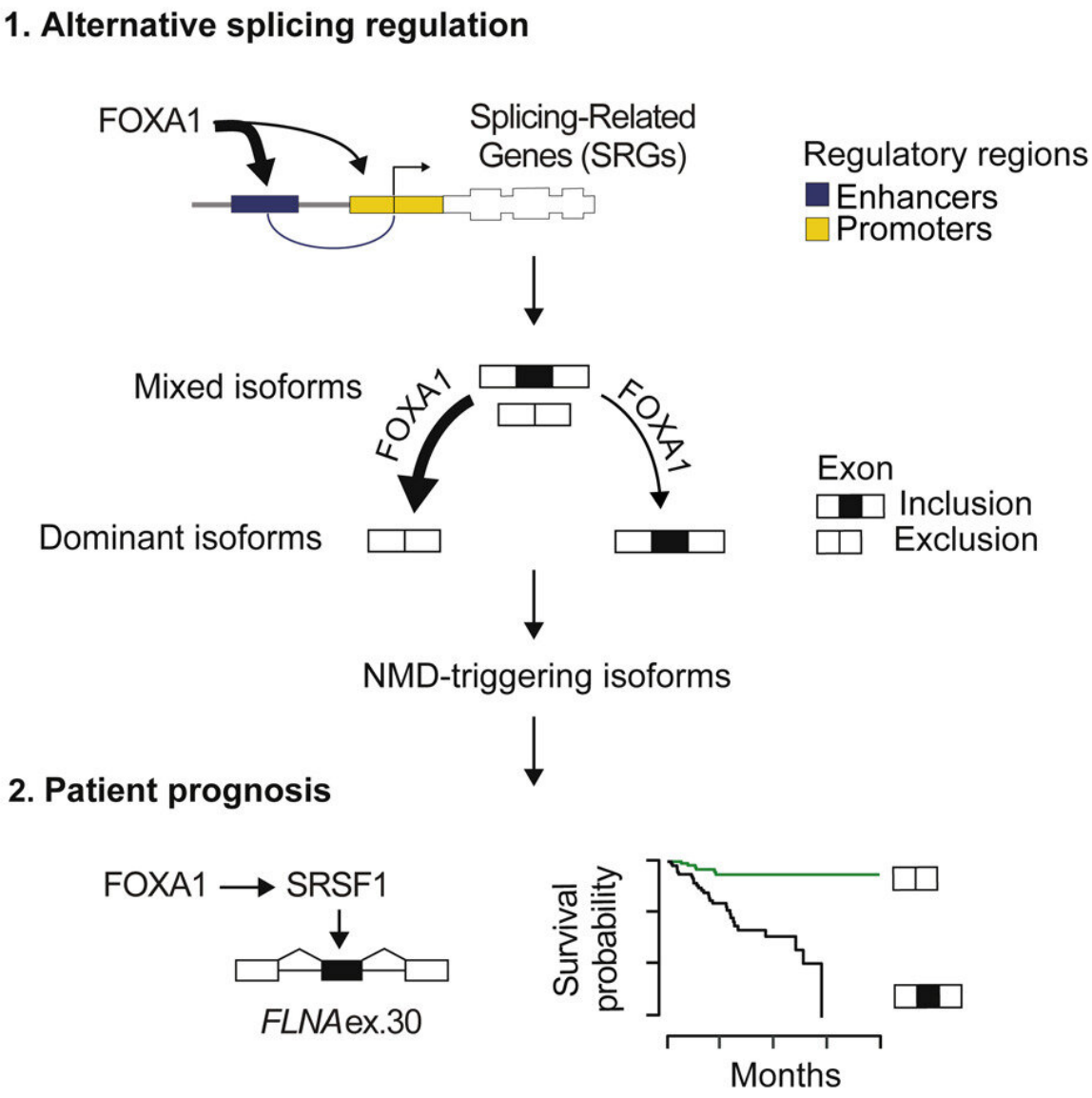
Study identifies how cancer-causing gene regulates genetic variation in prostate cancer

September 27 2022



Graphical abstract. Credit: *Cell Reports* (2022). DOI: 10.1016/j.celrep.2022.111404

Researchers from Barts Cancer Institute (BCI) at Queen Mary University of London, the Italian Institute for Genomic Medicine, and the University of Milan have identified a novel role for a cancer-causing gene in controlling an important genetic process that underpins genetic variation in prostate cancer.

The findings, published today in *Cell Reports*, reveal how the gene influences the generation of genetic variants in prostate cancer that may predict disease relapse and represent new drug targets to improve patient survival.

Co-senior author Dr. Prabhakar Rajan, Group Leader at BCI and Consultant Urological Surgeon at Barts Health NHS Trust, says that "prostate cancer is the [most common] male cancer in the world and lead cause of male cancer-related death. It is very variable in its genetic makeup, which makes diagnosis and treatment tricky, as there is not a one size fits all approach for treating patients. A knowledge of the drivers of genetic variability will help us understand the disease better, and improve treatments."

Alternative splicing is the process whereby segments of genes are shuffled to create different combinations of genetic code known as "splice variants," which provide the instructions to make proteins. Through alternative splicing, a single gene can code for multiple different proteins that are expressed at different levels and have various functions in the cell.

Alternative splicing is an important process for regulating gene

expression and generating genetic and protein diversity within normal cells; however, it is disrupted in many cancer types, including prostate cancer.

In this study, the team identified that the cancer-causing gene FOXA1 is a key regulator of alternative splicing in prostate cancer and may control the generation of splice variants that influence disease relapse and patient survival.

FOXA1 fine-tunes alternative splicing in prostate cancer

FOXA1 is a type of protein known as a pioneer transcription factor. Transcription factors can select which genes in DNA are transcribed into the instructions used to make proteins within our cells and the rate at which this occurs. As a pioneer factor, FOXA1 opens up DNA for binding by distinct transcription factors. Changes to FOXA1 have been found to drive the initiation and progression of prostate cancer.

By assessing alternative splicing in cell line models and primary cases of prostate cancer, the team found that high levels of FOXA1 limited genetic diversity towards splice variants that have a functional benefit for the cancer cells. The investigations revealed that FOXA1 favored splice variants that were present at high levels within the cells and silenced splice variants expressed at low levels, thus reducing the splicing variability in prostate cancer.

Dr. Rajan says that "this unique finding has never been shown before for a controller of alternative splicing and may mean that FOXA1 directs prostate cancer cells to act in a particular way that may be detrimental to patients."

Co-senior author Professor Matteo Cereda, Associate Professor at the University of Milan and Group Leader at the Italian Institute for

Genomic Medicine, added that "for the first time we show that an early player of transcription regulation is also responsible for the fine tuning of alternative splicing."

Potential new targets for treatment

To determine whether FOXA1-controlled alternative splicing had an impact on patient survival, the team analyzed clinical data from over 300 patients with primary prostate cancer, available via The Cancer Genome Atlas.

Although high levels of FOXA1 reduced splicing variability, the team found that FOXA1 enhanced the inclusion of genetic segments into splice variants that are strong markers of prostate cancer recurrence. Using prostate cancer cell lines, the team revealed that the inclusion of one particular genetic segment in the splice variant of a gene called the FLNA gene, which is controlled by FOXA1, conferred a growth advantage to prostate cancer cells, which may drive early disease relapse.

Dr. Rajan says that "this study illustrates how we can exploit the power of genomics to make important scientific discoveries about how genetic variability in prostate cancer is controlled. We hope our findings will have clinical impact by identifying more precise markers of disease recurrence and new potential drug targets."

The team would now like to further test whether the splice variants they have identified to be linked to cancer recurrence are useful in predicting disease relapse in reality, and to undertake experiments to determine whether targeting these genes could represent new ways to treat prostate cancer.

More information: Marco Del Giudice et al, FOXA1 regulates alternative splicing in prostate cancer, *Cell Reports* (2022). DOI:

10.1016/j.celrep.2022.111404