An immune system marker for therapy-resistant prostate cancer

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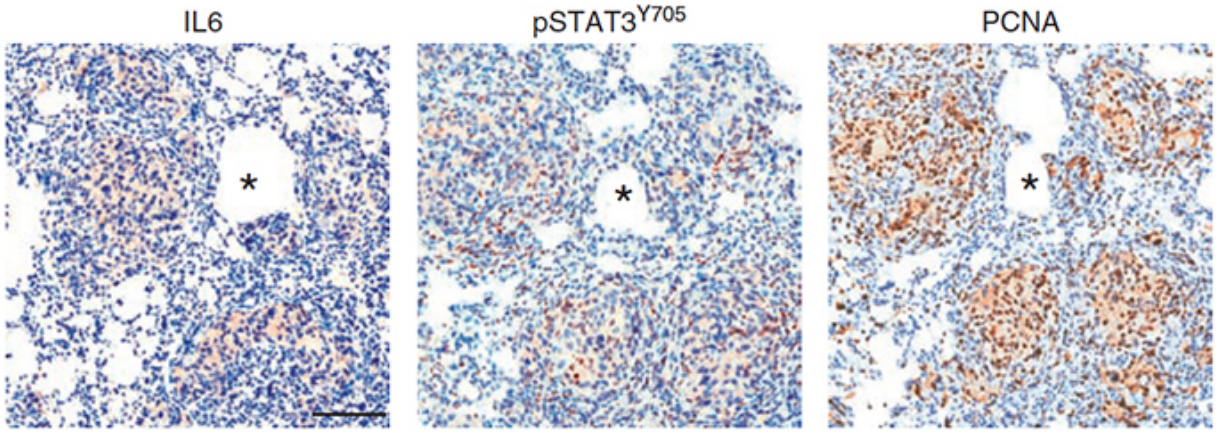


In RApidCaP, a mouse model of human metastatic prostate cancer that they developed, Trotman and colleagues have identified an immune system marker that may help to distinguish patients who will and will not respond to hormone therapy. That marker is IL-6, an immune system component whose presence is indicated in brown patches in the image at left, in a section of lung tissue (blue) colonized by prostate cancer cells. The middle image of the same section of lung tissue indicates activation of STAT3, a protein that is the downstream target of IL-6 signaling. The image at right of the same tissue section demonstrates the presence of PCNA in the invading prostate cells, a marker of metastasis. Credit: Trotman Lab/ CSHL

You are a patient who has just been treated for a serious illness but neither you nor your doctor knows how likely it is that you—in

comparison with other patients—will actually be helped by the treatment. This is often the situation with prostate cancer, one of the deadliest and most highly prevalent cancers. While hormone therapy can help, patient responses vary widely, and it's still unclear why some types of prostate cancer seem to be resistant to the therapy.

In work published today in *Cancer Discovery*, a team led by associate professor Lloyd Trotman at Cold Spring Harbor Laboratory (CSHL) shows how signaling by an immune system component called interleukin-6 (IL-6) appears to play an important role in driving particularly aggressive and therapy-resistant prostate cancer.

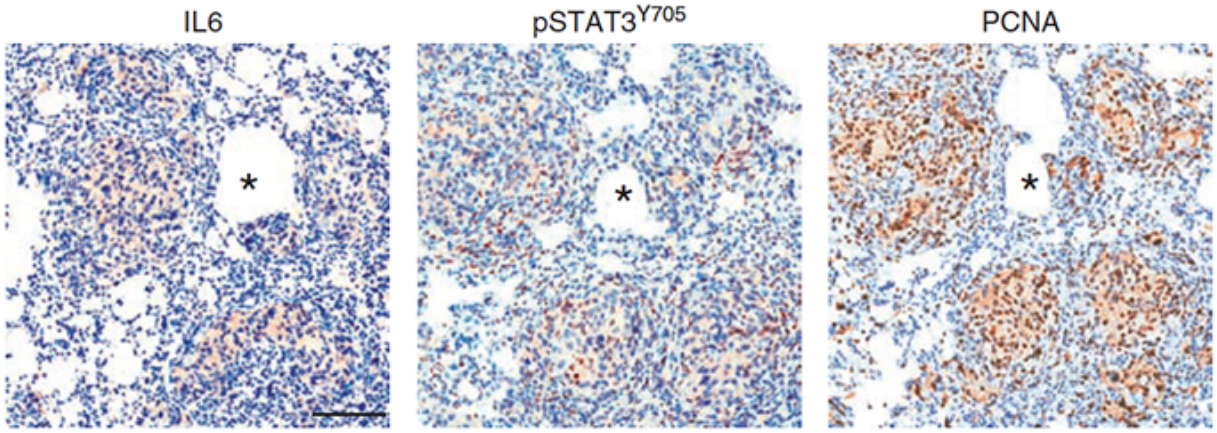
Our research suggests that IL-6 could be a marker for when the disease switches to a more dangerous state that is ultimately hormone therapy -resistant,' says Trotman.

The results could have important implications for human prostate cancer. 'The gain could be immense, because today's problem is that the variability in response of humans to hormone therapy is amazing,' Trotman says. 'For one man this therapy might be great, might reduce disease burden dramatically for many, many, years, and be an extreme benefit,' he says. 'For others there's almost no response, and it's still not clear to clinicians who is who.'

Being able to predict which patients would benefit from hormone therapy 'would be amazing,' Trotman says. 'We are really hopeful that translating the IL-6 discovery into the clinics could help us stratify patients into good responders and bad responders. For any hospital this would be a major breakthrough.'

Trotman and his team, which included Dawid Nowak, Ph.D., a postdoctoral investigator who is the paper's first author, looked for cellular signals that led to metastasis and hormone therapy resistance in a

genetically engineered mouse model for metastatic prostate cancer. They found that the combined loss of two genes, PTEN and p53—closely associated with prostate cancer metastasis—led to the secretion of IL-6. Signaling by IL-6 was then responsible for activating a powerful cancer gene called MYC, which drives cell proliferation and disease progression.



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'It suggested immediately that cell-cell communication is very, very important to make the cells resistant to therapy and very aggressive,' says

Trotman.

The involvement of the MYC pathway suggests that it could potentially serve as a target of drugs against prostate cancer, Trotman says. The team's next step is to study IL-6 signaling in humans. 'IL-6 detection in blood has been developed to a high art,' Trotman says. 'There are very good tools, which have been tested in the hospital setting.'

Provided by Cold Spring Harbor Laboratory