How a master regulator in ovarian cancer can go from helpful to harmful

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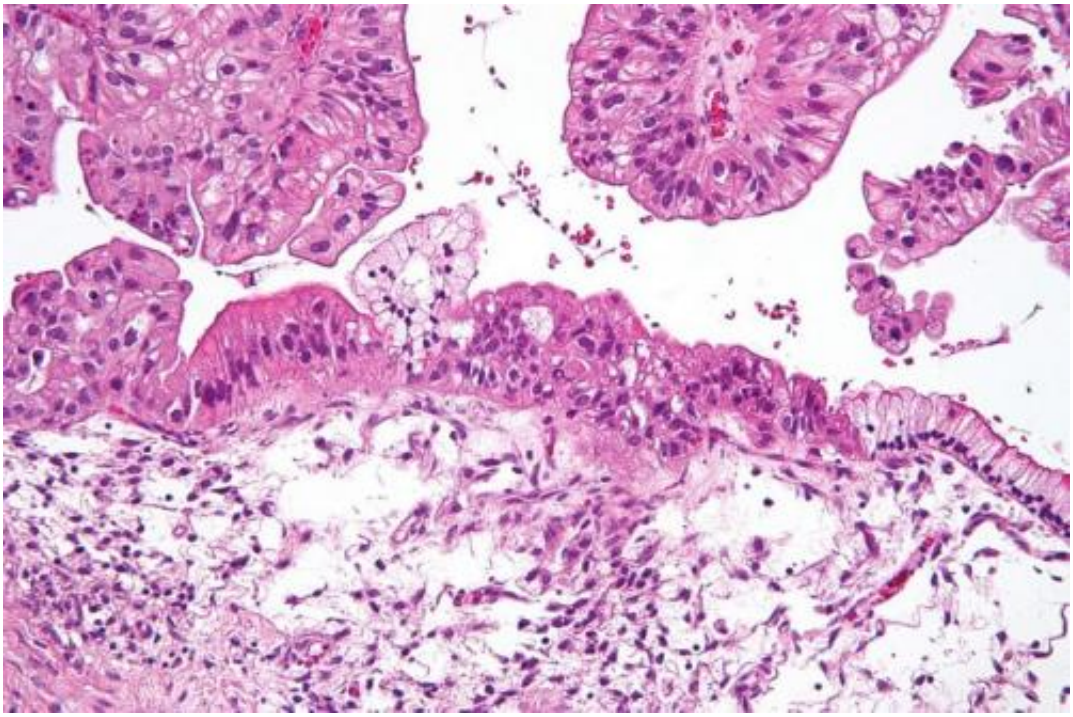

Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. H&E stain. The micrograph shows: Simple mucinous epithelium (right) and mucinous epithelium that pseudo-stratifies (left - diagnostic of a LMP tumour). Epithelium in a frond-like architecture is seen at the top of image. Credit: Nephron /Wikipedia. CC BY-SA 3.0

When it comes to our immune system, dendritic cells serve as a sort of lighthouse for T-cells. These specialized immune cells break down cancer cells into smaller pieces known as antigens. Once this happens,

they can signal white blood cells that are now able to recognize these matching antigens in cancer cells and respond appropriately.

Dendritic cells in ovarian cancer behave differently. When they receive activating signals, they can effectively present the antigens to T-cells. However, if the cells do not receive those signals, these dendritic cells spontaneously suppress anti-tumor immune responses. This differential behavior of dendritic cells could help explain why spontaneous immune pressure against ovarian cancer progression eventually fails, resulting in accelerated tumor progression.

Now, scientists at The Wistar Institute have defined the role of how a master genomic organizer influences the behavior of these ovarian-associated dendritic cells, revealing a previously unseen way in which cancer is able to manipulate our immune system. Study results were published in the journal *Cell Reports*.

A gene called special AT-rich binding protein 1 (Satb1) helps organize the genome and control phenotypes and differentiation within cells. In a prior study published in 2012, the lab of Jose Conejo-Garcia, M.D., Ph.D., professor and program leader of the Tumor Microenvironment and Metastasis Program at The Wistar Institute, found that this gene is a direct target of miR-155 - a microRNA that stimulates the immune system - in ovarian-associated dendritic cells. Conversely, when miR-155 is not stimulating the immune system, these dendritic cells produce inflammatory, tumor-promoting cytokines like interleukin-6 and galectin-1.

"We know from our previous work that Satb1 down-regulation by miR-155 supplementation is closely linked to proper immune response in tumor-bearing hosts. For this study, we wanted to know how the gene behaved when dendritic cells were transformed from a potentially immunostimulatory cell type into immunosuppressive cells," said Conejo-

Garcia, lead author of this new research paper.

Study results showed that Satb1 expression in dendritic cells is paradoxically required for proper immune response. However, Satb1 has a very narrow window in which it should be expressed. After dendritic cells mature, Satb1 should go away. If Satb1 hangs around and remains expressed, it drives immunosuppressive, pro-inflammatory behavior, which was confirmed when Satb1 was silenced in tumor-associated dendritic cells. Silencing the gene led to reduced levels of inflammation and immunosuppression, and boosted T-cell activation and immune response. In fact, 22 percent of transcripts experienced two-fold or greater changes in these immune response levels when Satb1 was silenced, underscoring the importance of this single molecule in determining the complex transcriptional programs in dendritic cells.

Among the physiological functions of Satb1 expressed with the right temporal pattern, the researchers also linked Satb1 behavior to Notch1, a gene linked to tumor cell survival and proliferation. Notch1 is activated in a Satb1-dependent manner during the transient state when Sabt1 is about to disappear as dendritic cells mature. In inflammatory dendritic cells, Notch1 expression coincides with increased levels of a molecule MHC-II, which is required for the activation of CD4+ T-cells, also known as helper T-cells. Conejo-Garcia and colleagues found that Satb1 drives Notch1 expression, while Notch1 in turn drives MHC-II expression, thus equipping dendritic cells with the capacity to activate different T-cell populations. However, if Satb1 remains overexpressed after dendritic cells are able to produce a normal immune response, it drives the production of multiple inflammatory and immunosuppressive factors that transform dendritic cells into accomplices in malignant progression and immunosuppression.

"Our studies provide new mechanistic insight into how tumors, and in particular ovarian cancer, progressively transform myeloid cells from an

immunostimulatory to an immunosuppressive cell type, which our previous studies showed to be critical to understand the evolution of ovarian cancer," said Conejo-Garcia. "Modulating Satb1 expression, either in vivo through nanocomplexes as in our study or in vitro in dendritic cell-based vaccines, could drive stronger anti-tumor immune responses and make antigen-presenting cells more resistant to tumor-induced immunosuppressive signals."

More information: *Cell Reports*, dx.doi.org/10.1016/j.celrep.2016.01.056

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