Estrogen signaling impacted immune response in cancer

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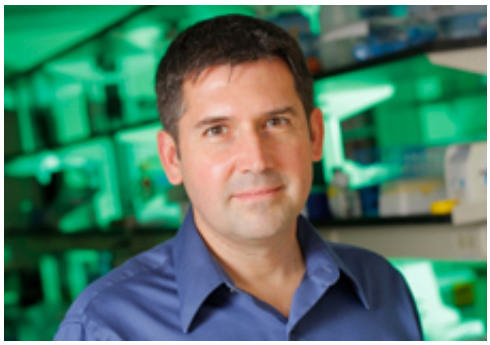

José Conejo-Garcia, M.D., Ph.D., is professor in the Tumor Microenvironment and Metastasis program at The Wistar Institute. Credit: The Wistar Institute

While the role of estrogen signaling in tumor development is well understood in breast and ovarian cancer, its role in anti-tumor immunity has not been extensively studied. However, new research from The Wistar Institute showed that estrogen signaling was responsible for immunosuppressive effects in the tumor microenvironment across cancer types.

These findings pave the way for combining immunotherapeutic treatments with anti-estrogen drugs that may significantly extend survival. Study results were published in the journal *Cancer Discovery*.

"We know about estrogen's effects directly on tumor cells, but the tumor microenvironment plays a critical role in determining malignant progression as well as response to therapy," said José R. Conejo-Garcia, M.D., Ph.D., professor in the Tumor Microenvironment and Metastasis program at The Wistar Institute and lead author of the study. "Both estrogen receptors are expressed on most immune cells, so we knew there had to be a larger role that estrogen played in cancer development."

Estrogen hormones bind to two high-affinity estrogen receptors (ER? and ER?), and when a tumor is ER-positive, it could receive signals from estrogen that promote its growth and enhance its role in malignant progression. Because of this, ER-positive breast cancer is often treated with anti-estrogen therapy like tamoxifen, which has been shown to have both positive and negative effects. While it decreases estrogen signaling in the tumor, it can increase estrogen signaling elsewhere in the body. The same therapeutic strategy has been tested in ovarian cancer, but results showed only mild effectivity with about 31 percent of ovarian cancers being ER? and about 60 percent being ER?.

Conejo-Garcia and colleagues found that estrogen signaling is closely linked to both the accumulation and activity of myeloid-derived suppressor cells (MDSCs), a set of immune cells associated with tumors treatment resistance. Estrogen enables immunosuppression in a two-pronged approach involving MDSCs. First, the estrogen drives the mobilization of MSDCs. Then, at the same time, it makes a subset of the MDSCs more immunosuppressive in vivo. Estrogen supplementation accelerated the growth of multiple models estrogen-insensitive tumors in immunocompetent animals, while ablating estrogen production by resecting the ovaries boosted anti-tumor immunity and delayed malignant progression . Importantly, differences in tumor progression disappeared in immunodeficient mice, demonstrating that estrogen-mediated acceleration of tumor growth depends on dampening protective anti-tumor immunity.

They also demonstrated how ER? is responsible for enhancing the activity of multiple pathways that are already associated with cancer development. This estrogen receptor activated the STAT3 pathway, which has already been linked to cancer cell survival and the expansion of MDSCs in cancer-bearing hosts. It was also able to activate this

pathway by enhancing the activity of JAK2 and SRC, two proteins linked to cancer development and immune response.

These cancer pathways are activated in a variety of inflammatory cancers in non-tumor cells, such as breast cancer, ovarian cancer, and melanoma. Since estrogen is present not just pre-menopausal women but men and post-menopausal women as well, the authors propose that investigating anti-estrogen therapeutic strategies could lead to new treatments for a variety of cancers. This strategy could halt the mobilization of MDSCs and tumor initiation.

"Estrogens have a profound effect on anti-tumor immunity and tumor-promoting inflation that is completely independent from their direct activity on tumor cells," Conejo-Garcia added. "With the continued development of emerging immunotherapies to treat cancer, we believe that combination strategies could significantly extend the survival of cancer patients independently of estrogen receptors in tumor cells alone."

Wistar's business development team is seeking a dedicated licensing partner to develop the use of anti-estrogen therapeutics in a broad range of oncology indications not traditionally associated with estrogen receptor antagonist therapy.

More information: N. Svoronos et al, Tumor Cell-Independent Estrogen Signaling Drives Disease Progression through Mobilization of Myeloid-Derived Supressor Cells, *Cancer Discovery* (2016). DOI: 10.1158/2159-8290.CD-16-0502