New insights into how blood pressure drug may benefit patients with locally advanced pancreatic cancer

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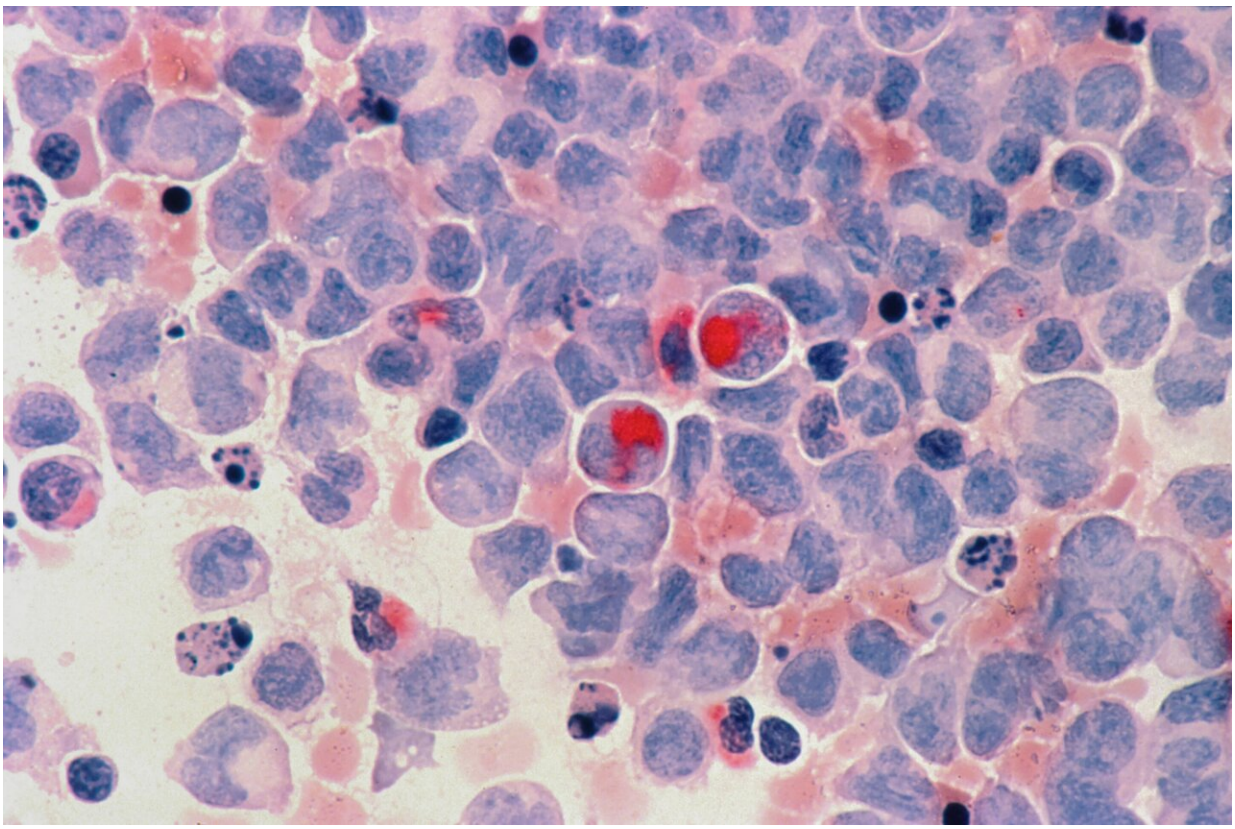

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Pancreatic cancer is highly lethal, and surgical removal of tumor tissue is currently the only potential cure for most patients. Once the cancer has

spread beyond the pancreas, treatment options are limited.

A recent phase II clinical trial led by researchers at Massachusetts General Hospital (MGH) identified a promising combination treatment regimen for patients with locally advanced pancreatic cancer, meaning that their cancer had spread, but only to nearby tissue. The trial's investigators have now uncovered the potential mechanisms behind the treatment's beneficial effects.

The combination therapy—losartan+FFX+CRT—includes the blood pressure drug losartan plus a chemotherapy cocktail called FOLFIRINOX (folinic acid, fluorouracil, irinotecan, and oxaliplatin), followed by chemoradiation. The therapy is meant to combat as much of the cancer as possible before a patient undergoes surgery to remove any remaining tumor in the pancreas—and indeed, the phase II clinical trial demonstrated that it's effective in doing so.

In this latest work, which is published in *Clinical Cancer Research*, investigators analyzed blood and tissue samples from patients undergoing this and other treatments for locally advanced pancreatic cancer. The team found that FFX+CRT improved the expression of genes linked to normalization of blood vessels and migration and maturation of various immune cells.

Losartan+FFX+CRT inhibited immunosuppression and reduced the expression of genes that promote the invasion of tumor cells into normal tissue. Also, losartan induced changes in the blood levels of various molecules involved in blood vessel health and the immune response. Lastly, tumor tisse from patients in the losartan+FFX+CRT–treated group had decreased numbers of cells that suppress the immune response and higher numbers of immune cells that are important for killing cancerous or virally infected cells.

"Our findings suggest that losartan may potentiate the benefit of FFX+CRT by reducing tumor invasion and immunosuppression. Thus, our results are important because they would not only reveal how losartan may synergize with emerging cytotoxic regimens, but also provide valuable information for overcoming resistance to immunotherapy—such as immune checkpoint blockers—that can occur in pancreatic cancer," says senior author Rakesh K. Jain, Ph.D., director of the E.L. Steele Laboratories for Tumor Biology at MGH and the Andrew Werk Cook Professor of Radiation Oncology at Harvard Medical School.

Interestingly, Jain and his colleagues found that blood levels of a molecule called soluble Tie2 increased over time in patients treated with losartan+FFX+CRT who experienced only a partial or poor response. Therefore, an increase in soluble Tie2 (which is involved in new blood vessel formation) could be an indication of tumor progression.

"Inspired by our published studies on the benefit of adding losartan, several clinical trials in patients with pancreatic cancer are currently evaluating the effectiveness of adding losartan to different cytotoxic treatment regimens or cytotoxics plus immunotherapy," says Jain. "When completed, these clinical trials will indicate whether losartan, when combined with different therapies, can improve the treatment response and long-term survival of patients with pancreatic cancer."

More information: Yves Boucher et al, Addition of losartan to FOLFIRINOX and chemoradiation reduces immunosuppression-associated genes, Tregs and FOXP3+ cancer cells in locally advanced pancreatic cancer, *Clinical Cancer Research* (2023). DOI: 10.1158/1078-0432.CCR-22-1630