Regorafenib shown to augment antitumor effect of anti-PD-1 immunotherapy in advanced gastric cancers

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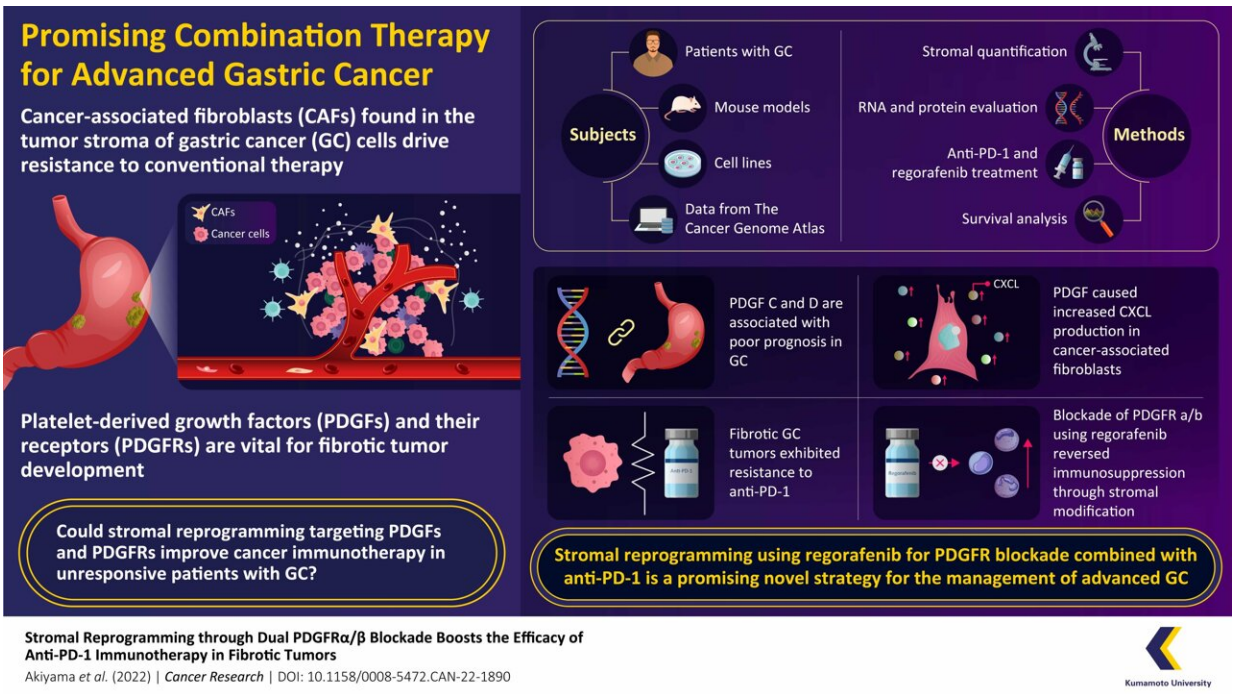

Credit: *Cancer Research* (2022). DOI: 10.1158/0008-5472.CAN-22-1890

Fibrotic cancers such as gastric cancers are highly resistant to conventional therapies like immune checkpoint inhibitors. Cancer-associated fibroblasts (CAFs) are an important part of the tumor microenvironment contributing to this resistance. Now, researchers from

Kumamoto University, Japan, have demonstrated that regorafenib and anti-PD-1 work synergistically to target CAFs, in turn modifying the cancer stroma and reducing fibrotic tumor growth.

Gastric cancer (GC) is highly prevalent and the third leading cause of death worldwide. Conventional treatments include molecular targeted therapy to block GC progression and novel immunotherapies. Unfortunately, patients with advanced GC exhibit a poor response to these therapies.

Diffuse-types GCs (DGCs) are characterized by abundant stroma (matrix surrounding tumor cells), severe fibrosis (accumulation of thick fibrous tissues), and the rapid progression and resistance to conventional treatment strategies. Moreover, high stromal aggregates have been directly linked to poor prognosis and treatment response in patients with GC.

An important component of fibrotic cancer stroma is cancer-associated fibroblasts (CAFs), which are responsible for rapid GC progression and resistance to standard therapies. Apart from CAFs, the tumor stroma also contains several immune cells, but their mutual interaction is poorly understood. The interaction between platelet-derived growth factors (PDGFs) and PDGF receptors (PDGFRs) amplifies the growth of fibroblasts in GC. However, the mechanisms underlying fibrotic tumor formation and the impact of CAFs on the stromal microenvironment in advanced GC also remains ambiguous.

In a new study published in *Cancer Research* on December 21, 2022, a team of researchers including Professor Hideo Baba and Professor Takatsugu Ishimoto from Kumamoto University, Japan, explored the mechanism underlying tumor fibrosis. Discussing the aim of their study, Professor Ishimoto remarks, "The current study investigated the underlying mechanism of PDGF-PDGFR-mediated fibrosis and the

effect of stromal remodeling by PDGF-PDGFR signaling inhibition on the immune microenvironment."

To begin with, the team investigated resected tissue samples from patients diagnosed with GC and found that a high quantity of stroma correlated with advanced stages and poor prognosis of GC. Based on the established fact that PDGF-PDGFR interaction promotes GC progression, the team examined their roles in CAF formation and GC prognosis. Interestingly, they found that high levels of PDGF C and D ligands led to poor prognosis of GC. Further investigations revealed that PDGF-PDGFβ interaction in DGC stroma also contributed to poor prognosis.

Next, the team measured the expression levels of PDGFα and β in various CAF cell lines of GC origin. They found that transforming growth factor β1 (TGFβ1) stimulated PDGFβ expression and thus enhanced fibrotic growth in DGC stroma. In vitro as well as fibrotic mouse model studies demonstrated that CAFs stimulated by PDGFs produced specific chemokines that recruit immunosuppressive cells into tumors. As a result, tumors could easily evade the immune system and become resistant to immune checkpoint inhibitors. CAF growth was significantly inhibited by anti-PDGFR antibodies, further validating the role of PDGFRα/β in tumor fibrosis and progression.

Additionally, transcriptomics and RNA sequencing analyses of CAFs revealed that regorafenib—a multikinase inhibitor that can block both PDGFRα/β and suppress PDGF mediated CAF growth—strongly blocked the expression of chemokines involved in leucocyte migration into the cancer environment, both in vitro and in vivo.

This finding underscores the potential of regorafenib in reversing CAF-associated immune suppression by remodeling the fibrotic stroma. Based on these findings, the team evaluated the impact of combining

regorafenib and immune check point inhibitors (e.g., anti-PD-1), in treating GCs in mouse models. As expected, regorafenib enhanced the anti-tumor activity of anti-PD-1 in fibrotic tumors. This combination led to an increase in tumor infiltrating immune cells in the cancer stroma, thus reducing the number of tumor fibroblasts. This synergistic effect of two treatment modalities is a breakthrough in the therapeutic management of GCs.

Summarizing their findings and the future impact of this study, Professor Ishimoto shares, "Our findings provide molecular evidence that the stromal amelioration induced by PDGFRα/β inhibition is a promising strategy for use in combination therapy with immune checkpoint inhibitors. This study lays the foundation for future clinical research that will hopefully lead to the development of immune checkpoint inhibitors for intractable cancers with advanced fibrosis."

More information: Takahiko Akiyama et al, Stromal reprogramming through dual PDGFRα/β blockade boosts the efficacy of anti-PD-1 immunotherapy in fibrotic tumors, *Cancer Research* (2022). DOI: 10.1158/0008-5472.CAN-22-1890

Provided by Kumamoto University