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EDITORIAL – GASTROINTESTINAL ONCOLOGY

Editorial Comment on: Functions and Clinical Significance of CACNA2D1 in Gastric Cancer: "Potential for Targeted Therapy against Gastric Cancer Stem Cells Using the Clinically Available Calcium Channel Blocker"

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Despite improvements in the management of gastric cancer, the prognosis of advanced stages of the disease remains poor.[1] Therefore, promising biomarkers and therapeutic tools for the advanced stages of gastric cancer are urgently required.

A calcium ion channel is a multi-subunit protein complex that consists of a pore-forming α1 subunit and regulatory subunits, α2δ, β, and γ.[2] Four voltage-dependent calcium channel α2δ subunit coding genes have been reported, namely voltage-gated calcium channel auxiliary subunit α2δ1 (*CACNA2D1*), *CACNA2D2*, *CACNA2D3*, and *CACNA2D4*. Among these, CACNA2D1 has been reported to play essential roles in cancer stem cell-related phenotypes.[3] *CACNA2D1* is methylated in 12.5% of gastric cancer cases; however, the status has not been significantly associated with clinicopathological features in gastric cancer.[4] Interestingly, Shiozaki et al. reported that gastric cancer stem cells expressed high levels of CACNA2D1, and CACNA2D1 inhibitor amlodipine showed chemosensitizing effects in in vitro and in vivo experiments.[5]

In this issue of the *Annals of Surgical Oncology*, Inoue et al. report the expression and functional significance of CACNA2D1 in gastric cancer, indicating that CACNA2D1 plays important roles in gastric cancer against apoptosis and promotes tumor growth. They also reported that CACNA2D1 might be a promising biomarker for predicting poor overall survival and short-recurrence free survival of gastric cancer patients. Moreover, they propose that combining chemotherapy and CACNA2D1 inhibition by calcium channel blocker amlodipine might be a promising therapeutic strategy for gastric cancer.[6]

Until now, basic and clinical studies have been conducted in anticipation of an anticancer drug sensitizing effect of calcium ion channel blockers. The working mechanism of calcium ion channel blockers, such as verapamil and nifedipine, is expected to sensitize the therapeutic effect by increasing the intracellular concentration of anticancer drugs by inhibiting drug efflux pumps.[7] Furthermore, these blockers may enhance anticancer drug sensitivity by suppressing side-population cells along with cancer stem cell characteristics, such as therapeutic resistance and aggressiveness.[8]

Amlodipine, which was the focus of the study by Inoue et al. is a representative calcium channel blocker and is frequently used as an antihypertensive agent in clinical practice. Ji et al. reported that amlodipine derivatives enhanced drug sensitivity of doxorubicin-resistant human leukemia cell lines.[9] However, such promising therapeutic strategies combining cytotoxic agents with calcium channel blockers are not currently available for patients with advanced cancer due to inadequate therapeutic efficacy and side effects (hypotension and cardiovascular disorders).[10] Therefore, the development of new compounds that specifically inhibit calcium channels of cancer cells and efforts to improve drug delivery as well as reduce side effects may be necessary to apply this promising therapeutic strategy in clinical practice.

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Furthermore, Inoue et al. clarify that high expression of tumoral CACNA2D1, which is highly expressed in gastric cancer stem cells, was associated with poor prognosis and short recurrence-free survival.[6] Evaluating CACNA2D1 in resected gastric cancer tissues may allow the identification of patients with high risk of recurrence and poor prognosis. However, it is unclear whether combining calcium channel inhibitors and cytotoxic anticancer agents is an effective strategy as adjuvant treatment in gastric cancer patients. Further studies are needed to clarify the combined effect of CACNA2D1 targeting and existing anti-cancer drugs as adjuvant treatments in gastric cancer patients. Moreover, it is expected that combining calcium channel inhibitors with systemic chemotherapy only for gastric cancer patients with high CACNA2D1 levels may lead to better therapeutic outcomes than previously anticipated.

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