GASTRIC CANCER METASTASES TO THE PERITONEUM IN A MOUSE MODEL

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Resume: Using gene array analysis, we found that this protective effect is linked to a significant downregulation of the expression of Fms-related tyrosine kinase 4 (FLT4), CXC chemokine receptor-4, collagen α2(IV) (COL4A2), non-receptor spleen tyrosine kinase (SYK), and Fms-related tyrosine kinase 4 (FLT4) in neoplasic foci. Because it acts at multiple crucial points during the tumor cells' attachment and diffusion process, a modest medication that inhibits p38 MAPK generally helps prevent poorly differentiated gastric cancer cells from migrating throughout the peritoneum.

Keywords: Tyrosin, gene array, p38MAPK, gastric cancer, fms-related tyrosine kinase, collagen, CXC chemokine receptor-4, neoplastic foci, multidrug resistance, chemotherapeutic resistance, spleen.

Abstract

The relatively common consequence of poorly differentiated stomach tumors is peritoneal dissemination, for which there are currently no effective treatments. It is known that the constitutive activation of mitogen-activated protein kinases (MAPKs) signaling cascades causes the malignant transformation of several cancer cell types. In this work, we use a mouse model of peritoneal carcinomatosis to show that suppression of p38 MAPK prevents the spread of gastric cancer cells, and that giving mice strong and selective p38 MAPK inhibitors such as ML3403 and SB203580 reduces the development of neoplastic foci caused by intraperitoneal injection of stomach cancer cells.

In neoplasic foci, we found that the expression of collagen α2(IV) (COL4A2), non-receptor spleen tyrosine kinase (SYK), and Fms-related tyrosine kinase 4 (FLT4) is strongly downregulated, which is linked to this protective effect, according to gene array analysis. In vivo suppression of p38 MAPK increased tumor cell sensitivity to cisplatin and was associated with a significant downregulation of multidrug resistance (MDR)-1 expression, a known indicator of chemotherapeutic resistance. In conclusion, by acting at multiple crucial points during the attachment and

diffusion process of the tumor cells, a modest medication that suppresses p38 MAPK helps prevent poorly differentiated gastric cancer cells from spreading throughout the peritoneum.

Introduction

A variety of external stimuli can activate serine/threonine kinases, or MAPKs 1, 2. The three primary subclasses of MAPKs that have been identified are p38, c-Jun NH2-terminal kinase (JNK), and extracellular signal-regulated kinase (ERK). G proteins, oncogene products, cytokine receptors, and other receptor tyrosine kinases can all activate MAPKs. Accordingly, it is proposed that MAPKs are engaged in a variety of cellular processes, including apoptosis, differentiation, cell division, and transformation, and that they are essential for the integration of numerous signaling transduction systems 1, 2, and 3.

Constitutive activation of these signaling cascades has been identified as one of the primary contributing factors to the malignant transformation of cancer cell lines. 4. It has been associated with the development of human malignancies and their potential for dissemination 5,6. Therefore, there is compelling evidence that the p38 MAPK signaling pathway is activated in tumor cell invasion related to head and neck, breast, colon, and melanoma malignancies 7,8. Human scirrhous gastric carcinoma frequently spreads peritoneally or distantly to lymph nodes after a clinical diagnosis. This kind of poorly differentiated gastric carcinoma thickens the stomach wall in a fibrous-like manner as a result of diffusely infiltrating a large area of the stomach wall. 4, 6. There are no proven treatments for peritoneal spread. Peritoneal spread, which frequently occurs even after extensive surgery, is the primary cause of the poor prognosis for patients with scirrhous stomach cancer. Additional systemic chemotherapy frequently has little effect on peritoneal dispersion because the peritoneal-blood barrier can stop drug distribution throughout the peritoneal cavity. 8.

Peritoneal gastric cancer distribution and pospho-p38 MAPK levels

Poorly differentiated stomach carcinomas have been suggested to express p38 MAPK, and the likelihood of peritoneal dissemination is associated with this expression. In line with findings from other studies, the diffuse-type, poorly differentiated gastric carcinomas showed positive staining for both the total and phosphorylated forms of p38 MAPK 9. Most of the cancerous cells have p38 MAPK expression.

Discussion

Using a mouse model of peritoneal carcinomatosis, we have shown in this work that p38 MAPK inhibition prevents non-differentiated gastric cancer cells from proliferating throughout the peritoneum. Additionally, p38 inhibition increases the

chemosensitivity of cisplatin, which may be helpful in treating chemoresistant stomach tumors, according to our research.

Early on in the invasion and metastasis of carcinoma cells, the p38 MAPK pathway plays a critical role.

In conclusion

However, the precise mechanism behind stomach cancer's peritoneal spread is still unknown. Phospho-p38 MAPK levels are elevated in poorly differentiated gastric tumors compared to differentiated malignancies. E-cadherin transcriptional suppression and cytoskeletal F-actin filament disarray have been associated with poorly differentiated gastric cancers; these findings may be connected to p38 MAPK activation. Amorphous morphology and a lack of cell-cell adhesion may be the outcomes of these effects.7. Here, we detail how the p38 MAPK pathway contributes to the spread of gastric cancer cells in humans across the peritoneum. According to this study, pharmacological inhibition of p38 MAPK limits the spread of gastric cancer cells and increases treatment sensitivity, indicating that small molecule p38 MAPK inhibitors may have anti-cancer potential.

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