

1 **Intraperitoneal cancer-immune microenvironment promotes peritoneal**
2 **dissemination of gastric cancer**

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19 **Abstract**

20 A solid tumor consists of cancer and stromal cells, which comprise the tumor microenvironment
21 (TME). Tumor-associated macrophages (TAMs) are usually abundant in the TME, contributing
22 to tumor progression. In cases of peritoneal dissemination of gastric cancer (GC), the
23 contribution of intraperitoneal TAMs remains unclear. Macrophages from peritoneal washings of

1 GC patients were analyzed, and the link between intraperitoneal TAMs and GC cells was
2 investigated to clarify the interaction between them in peritoneal dissemination. Macrophages
3 were predominant among leukocytes constituting the microenvironment of the peritoneal cavity.
4 The proportion of CD163-positive TAMs was significantly higher in stage IV than in stage I GC.
5 Co-culture with TAMs potentiated migration and invasion of GC. IL-6 was the most increased in
6 the medium of in vitro co-culture of macrophages and GC, and IL-6 elevation was also observed
7 in the peritoneal washes with peritoneal dissemination. An elevated concentration of
8 intraperitoneal IL-6 was correlated with a poor prognosis in clinical cases. In conclusion,
9 intraperitoneal TAMs are involved in promoting peritoneal dissemination of GC via secreted IL-6.
10 TAM-derived IL-6 could be a potential therapeutic target for peritoneal dissemination of GC.

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12 **Keywords:** gastric cancer; tumor-associated macrophages; tumor microenvironment;
13 peritoneal dissemination

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15 **Introduction**

16 Gastric cancer (GC) is one of the most common malignancies worldwide, and the third leading
17 cause of cancer-related deaths(1). Peritoneal metastasis is a frequent mode of metastasis of
18 GC(2,3), which leads to a serious clinical condition, resulting in dismal consequences(4).
19 Nevertheless, there is no definitive therapy for the peritoneal spread of GC, mainly because the
20 mechanism of peritoneal metastasis has yet to be fully understood, and the appropriate target
21 has not been identified. Thus, to overcome this disease entity, we still need to explore and
22 understand the complexity of peritoneal metastasis to develop novel strategies.

23 In recent years, it has been reported that TME plays a pivotal role in cancer