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Tumor infiltrating lymphocytes in gastric cancer: Unraveling complex interactions for precision medicine

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Abstract

This editorial will focus on tumor immunity and the factors that alter the tumor immune micro-environment. The role of tumor infiltrating lymphocytes (TILs) will also be discussed in detail, including the types, mechanism of action, and role. Gastric cancer (GC) often presents in the advanced stage and has various factors predicting the outcomes. The interplay of these factors and their correlation with the TILs is discussed. A literature review revealed high intra-tumoral TILs associated with higher grade, HER2-, and *Helicobacter pylori* negativity. Moreover, stromal (ST) TILs correlated with lower grade and lesser recurrence risk in GC. High TILs in ST and invasive border also correlated with mismatch repair deficiency status. Further characterization of the CD3+, CD8+, and other cells is also warranted. In the future, this complex correlation of cancer cells with the immune system can be explored for therapeutic avenues.

Key Words: Tumor infiltrating lymphocytes; Gastric cancer; *Helicobacter pylori*; HER-2-neu

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Core Tip: Tumor infiltrating lymphocytes (TILs) are an essential component of the tumor microenvironment. The association of TIL levels with outcomes of malignancies is an upcoming field. This correlation may be utilized to explore the new immuno-oncological therapeutic avenues.

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INTRODUCTION

Gastric cancer (GC) often presents at an advanced stage, making successful treatment a daunting challenge. Immunotherapy is considered for treating GC because of the high tumor mutation burden[1]. Hence, a more in-depth understanding of tumor immunity in GC is needed. The tumor cells may be eliminated by these immune cells or escape detection. In the elimination phase, the cells, like natural killer cells, with the help of dendritic cells and CD4+ T-cells, recognize and eliminate tumor cells. However, the less immunogenic tumor cells can escape the immuno-surveillance.

Based on the presence of immune cells, tumors can be classified into inflamed and non-inflamed[2]. These inflammatory cells may contribute to pro- or anti-tumor activities. Amongst these cells, the tumor-infiltrating lymphocytes (TILs) are the significant determinants of the host immune response to tumor cells. TILs have recently gathered much attention because of their presumed role in carcinogenesis and therapeutics[3]. The “Hallmarks of Cancer” proposed by Hanahan *et al*[4] now include inflammatory infiltrates into the tumors as one of the components. This is because of their roles in tumor progression and escape from the host immunity. The new technological advancements mean improved assessment of tumor infiltrates and identification of genetic signatures expressed in the tumor micro-environment (TME). TILs and their functions have now become a leading topic of research. We can discover the prognostic relevance of TILs, which can help predict outcomes and guide therapy. The complex correlation of cancer cells with the immune system can be explored for therapeutic avenues.

TILS IN GC

The magnitude of TIL infiltration is thought to be related to the control of cancer growth, progression, and metastasis. In addition, it may be predictive of the response to cytotoxic treatment[5]. Still, various studies have shown conflicting results[6,7]. The prognostic role of TILs in GC needs further clarification. TILs, as a natural component of the immune system, can offer a tailored approach to battling GC. It is critical to understand the heterogeneity of TILs and their interaction with the tumor microenvironment. TILs differ according to their location in the tumor. These include intratumoral (IT), stromal (ST), and invasive border (IB)[8]. An analysis of the studies of IT TILs revealed robust hazard ratios (HRs) for overall cancer survival (OCS) than for other TILs. Studies of the pan-T-cell IT TILs, such as CD3/TIL, CD4, and CD8, in GC tissues revealed association with survival (CD3: HR = 0.65, 95%CI: 0.5-0.8; CD4: HR = 0.7, 95%CI: 0.55-0.9; CD8: HR = 0.65, 95%CI: 0.5-0.85). Higher CD8+ cells demonstrated the greatest overall survival (OS) improvement. In contrast, TILs with high FOXP3+ expression significantly correlated with decreased OCS (HR = 1.89, 95%CI: 1.5-2.3). The transcription factor FOXP3, presenting with the CD4+, CD25+, and FOXP3+ phenotype, is responsible for the T regulatory (Treg) cells. Treg cells promote immune tolerance in the TME by suppressing the anti-tumor T-cells. This can explain this association of decreased OCS with high FOXP3+ cells[9,10]. A meta-analysis of around 2900 cases demonstrated a significant association between higher pan T-cell marker (+ve) TILs and better survival[11]. It implies the role of adaptive immunity in the anti-tumor response. TILs have also shown apoptosis in GC models[12]. Interestingly, a higher number of TILs in patients with microsatellite instability (MSI) or Epstein Barr virus (EBV) associated GC correlated with better treatment outcomes and longer OS, prompting the association of TILs with other factors[13-15].

ASSOCIATION WITH OTHER FACTORS

Recent advances in cancer research have shed light on the intricate relationships between *Helicobacter pylori* (*H. pylori*) infection, mismatch repair (MMR) status, HER2 amplification, and TILs in the context of GC. These connections have brought a deeper understanding of this complex disease and are opening new avenues for targeted therapies and precision medicine.

H. pylori: A pervasive culprit

H. pylori is a bacterium that colonizes the stomach lining and has long been implicated as a significant risk factor for GC. Chronic *H. pylori* infection can lead to the development of chronic gastritis, which, over time, may progress to atrophic gastritis, intestinal metaplasia, dysplasia, and ultimately GC. This journey from infection to malignancy underscores the need for early detection and eradication of *H. pylori* in at-risk individuals. *H. pylori* infection triggers an inflammatory response in the stomach lining, contributing to the initiation and progression of GC. This chronic inflammation damages DNA and leads to the recruitment of TILs, which are a part of the immune system's response to the infection.

MMR status: A genetic determinant

In the realm of GC, MMR status is a crucial genetic determinant. MMR proteins are responsible for correcting DNA replication errors and ensuring genomic stability. Deficiencies in MMR (dMMR), typically characterized by MSI, can result in genetic mutations and increased susceptibility to cancer development.

The association between MMR status and GC is multifaceted. Individuals with MSI-high gastric tumors tend to have a more favorable prognosis due to the increased presence of TILs. These TILs, often enriched in MSI-high tumors, are believed to have a more potent anti-tumor effect.

HER2 amplification: A target for therapy

HER2, a member of the epidermal growth factor receptor family, is known for its role in several cancers, including breast and GC. HER2 amplification or overexpression in GC represents a specific subset of cases that can be targeted with precision therapies.

Trastuzumab, a monoclonal antibody targeting HER2, has been approved to treat HER2-positive GC. Notably, HER2-positive tumors often exhibit increased TIL infiltration, pointing to the interplay between HER2 and the immune response.

The path forward: Precision medicine and targeted therapies

Understanding the interplay between *H. pylori* infection, MMR status, HER2 amplification, and TILs in GC is vital for tailoring therapies to individual patients. Precision medicine in GC is evolving, with targeted therapies like trastuzumab for HER2-positive cases and immunotherapies that aim to enhance TIL activity showing promise. Hoilat *et al*[16] reviewed the association between *H. pylori* infection, mismatch repair, HER2, and TILs in GC. The study addresses the critical question of the TIL-associated predictive factors. They included 503 surgically treated stage I-III GC patients. Analysis of the TILs was done following standardized international TILs working group recommendations to determine IT, ST, and IB compartments. Immunohistochemistry (IHC) stained tissue tumor arrays were utilized to calculate immune cell density (CD3, CD8, and CD163). They also determined dMMR and HER2-status by IHC. *H. pylori* infection was evaluated by histology and by quantitative polymerase chain reaction in a subset. dMMR was found in 34.4%, HER2+ status in 5%, and *H. pylori* infection in 55.7%. TILs were subdivided into the IB, IT, and ST compartments. Median TIL levels were higher in IB and ST than in the IT compartment. They also found a correlation with the grade of the tumor. Grade 3 tumors were associated with high IT TIL ($P = 0.038$), whereas ST-TIL with grade 1 ($P < 0.001$). ST and IB TILs were seen to be higher in dMMR tumors. dMMR was also associated with high CD3 and CD8 densities. HER2- was associated with high IT-CD8. Also, *H. pylori* negative status correlated with higher IT-TIL ($P = 0.009$). It was also associated with high CD8 density in IT and ST compartments ($P = 0.001$). High TIL levels were associated with dMMR and *H. pylori*-negative status. Low CD8/CD3 ($P = 0.001$ in IT and $P = 0.002$ in ST compartment) and high CD3/CD163 ($P = 0.002$) predicted lower recurrence and longer survival.

These studies demonstrate that further research is required to identify *H. pylori* infection status because of the effect on the immune microenvironment, which can predict immunotherapy response. Molecular profiling and IHC can help determine the molecular subtypes of GC, guiding personalized treatment plans. The complex relationships between MMR status, HER2 amplification, and TILs in GC pave the way for more precise, effective, and individualized treatment approaches. While challenges remain in optimizing therapies for different subsets of patients, these insights represent a significant step towards conquering this relentless disease. As research progresses, we can look forward to a future where TILs may be used as prognostic and predictive factors in not only GC but also other malignancies. This warrants further studies on TILs.

CLINICAL IMPLICATIONS

TILs and their subtypes can be used in GC for predictive and prognostic purposes. The complex interplay of TILs with factors like MMR, HER2, and *H. pylori* infection demonstrates that they form an integral part of the immune response to the tumor cells. Further studies will clarify these factors' role in predicting response to therapy.

CONCLUSION

In conclusion, TILs represent a promising avenue in the battle against GC. It is incumbent upon the medical and scientific communities to come together and realize the full potential of TILs, ensuring that their immense promise becomes a reality for all those affected by this devastating disease and other malignancies.

FOOTNOTES

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