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THE TUMOR IMMUNE CONTEXTURE AND DNA REPAIR ENZYMES EXPRESSION IN GASTRIC CARCINOMA

Oksana Sulaieva[1], Artem Mashukov[2], Stanislav Kirkilevsky[3]

[1] Laboratory of Pathology CSD, Kyiv, Ukraine; [2] Department of Oncology, Odessa National Medical University, Odessa, Ukraine;

[3] Research Department, National Cancer Institute, Kyiv, Ukraine

OBJECTIVES

Tumor immune microenvironment (TIME) assessment is thought to be effective tool for evaluation of tumor-host interplay and prognostication of different cancers, including gastric carcinoma (GC) [1-3].
As inflammatory signaling is closely related with DNA-repair pathways, there could be the link between GC immune contexture and theranostic markers expression defining GC response to different therapies [4-5].
This study aimed to clarify the relations between TIME and expression of ERCC1, TOPO2A and PDL1 in GC of different histological types.

METHODS

In this retrospective study we assessed 50 cases (29 males and 21 females; 52.5±2.18 years old) of the locally advanced or metastatic GC naïve to preoperative chemotherapy and radiotherapy.
Among enrolled cases there were 15 diffuse GC and 35 intestinal-type GC according to Lauren's classification.
Number of CD3+, CD8+ as well as CD68 and CD163 cells was counted in tumor clusters (TC) and stroma (TS) per 1 mm^2. The threshold of 84 cells per 1 mm2 was used (as a median of CD8+ cells number) to stratify cases for High and Low intensity of TILs infiltration in both TC and TS.
ID type of TIME was defined in cases with Low CD8+ infiltration in both TC and TS.
Cases of IE immunophenotype included tumors with Low CD8+ number in TC and High CD8+ infiltration in TS compartmenti.
Cases with High CD8+ cells infiltration in TC and TS were considered as of Inflamed immunophenotype. In addition, PD-L1, ERCC1 and TOPO2A expression was evaluated immunohistochemically.

Graphs and tables

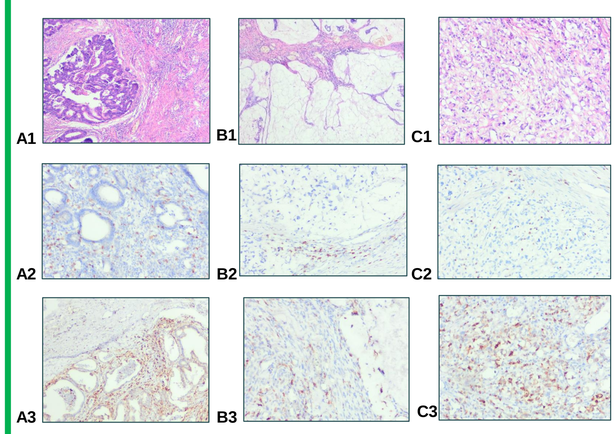

Figure 1. Histological features and immune cells infiltration of GC of different histological types.
A1 – intestinal type GC of inflamed TIME with moderate number of CD8+ cells (A2) and high count of CD68+ cells forming dense meshwork (A3) inside tumor nests. A 1– ×100, A2-3 – ×200
B1 – mucinous GC demonstrated specific TIME of IE type with low number of immune cells within tumor nests and high number of CD8+ (B2) and CD68+ cells (B3) in peritumor stroma. AB1– ×100, B2-3 – ×200
C1- diffuse type GC possessed predominantly ID TIME with low number of CD8+ cells (C2), but high amount of CD68+ cells; C1 - × 100; C2-3 ×200.

Table. Immunophenotype of GC of different histological types

Characteristics	ID TIME	IE TIME	Inf TIME	Total
Histological types of GC				
Intestinal	1 (3,2%)	5 (16,1%)	25 (80,7%)	31 (62%)
Diffuse	8 (53,3%)	5 (33,3%)	2 (13,3%)	15 (30%)
Mucinous	1 (25%)	3 (75%)	0	4 (8%)
Immune checkpoint expression				
PD-L1 positive	1 (5,6%)	0	8 (94,4%)	9 (18%)
PD-L1 negative	9 (21,9%)	13 (31,8%)	19 (46,3%)	41 (82%)
Total number	10	13	27	50

Most Intestinal GC demonstrated Inflamed TIME. In contrast, mucinous GC had IE-immunophenotype in majority of cases, whereas more than half of diffuse GC exhibited ID-TIME features.

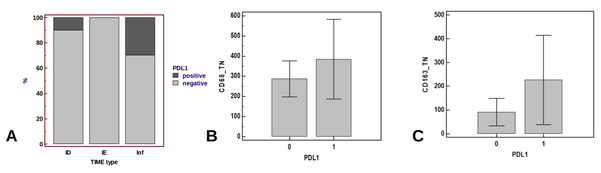

Figure 2. The rate of PDL-expression in GC of different immunophenotypes and its relationship with number of CD68 and CD163 cells.
A – demonstrates prevalence of PD-L1 expression in GC of Inflamed type. PD-L1-positivity in GC was associated with higher number of M2-macrophages, but not CD68+ cells (B and C).

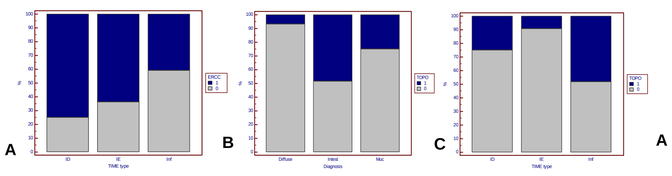

Figure 3. Differences in theranostic markers expression in GC with regard to histological type and inmmunophenotype. A – ERCC expression in GC of various immunotypes. B and C – differences in TOPO2A expression in GC cells with regard to histological and immunological features of GC.

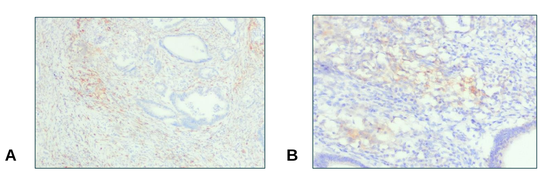

Figure 4. Relationship between high number of CD163+ cells (A) and PD-L1 expression (B) in GC. IHC. A - ×100, B - ×200.

RESULTS

GC of different histological types were associated with alternative immune response. Notably, mucinous GC (n=4) demonstrated the distinct immunophenotype associated with immune exclusion features. Intestinal GCs demonstrated predominantly enhanced infiltration by CD8+, CD68+ and CD163+ cells (P=0.002) and were associated with the higher rate of PD-L1 expression (P=0.03). In contrast, diffuse GC showed mostly immune desert phenotype and CD68+ macrophages were the most prevalent within tumor nests and stroma (P<0.001).
The highest rate of lost ERCC1 expression was found in GC with inflamed TIME (P=0,047) regardless histological type. Whereas TOPO2A expression was higher in inflamed GCs of intestinal (P=0,018), but not diffuse type. PD-L1 expression in both tumor and tumor-infiltrating immune cells was revealed predominantly in intestinal type GCs. PD-L1expression was associated with high number of CD163+ cells (P=0.03).

CONCLUSIONS

Various histological types of GC demonstrated distinct immunophenotypes that was related with different expression of DNA-repair enzymes and immune checkpoint biomarker PD-L1. This could be related with the intrinsic mechanisms linking together carcinogenesis, immunogenicity and DNA-repair machinery.

Further investigation of these mechanisms is essential for better understanding of different GC immunogenicity and resistance to therapies with regard to histopathological features.

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