Response to Reviewer 2 Comments

Point 1: The authors have made perfect revisions according to my suggestions. I suggest it might be better if the author could add the distribution of PRGS at the scRNA level.

Response 1: We sincerely thank you for the time and effort in evaluating our manuscript. We are very grateful for the highly constructive comments that helped us improve our manuscript during the revision process. Based on your recommendations, we conducted additional experiments and added Figure S6 to the revised manuscript.

In gastric cancer, recent scRNA-seq studies[1]-[5] have provided unique insights on different aspects of gastric tumor biology. As shown in Table 1, Vikrant Kumar and colleagues performed the biggest large-scale single-cell atlas with different Lauran classifications. Single-cell library construction requires fresh tissue, so patients survival information is not available in all datasets. So we just supplement the distribution of PRGS at the scRNA level, which were discussed in lines 309-313 of the revised manuscript as follows.

We also observed that GC samples and GC samples in different Lauran classifications(Intestinal, diffuse, and mixed types) exhibited higher PRGS scores than normal samples (Figure S6A-D). We computed global PRGS scores for all cell types and found that fibroblast had the highest PRGS scores than other cell types(Figure S6D). VCAN and CTSF have been reported to be expressed by fibroblast, and PRGS(ABCA6, APOB, CTSF, VCAN) occur in many human diseases[29]-[35], but their role in GC has not been demonstrated clearly. Thus, they may be identified as new markers for GC.

Table 1 Details of baseline information in single-cell atlas

Laurens classification	Peng Zhang and colleagues	Min Zhang and colleagues	Jihyun Kim and colleagues	Vikrant Kumar and colleagues	Keyong Sun and colleagues
Intestinal	1	5	9	14	2
Diffuse	0	1	15	6	2
Mixed intestinal and diffuse	0	3	0	3	6
unknown	0	0	0	6	0
Normal	3	3	24	11	8
cell number	32332	27677	30888	200954	166533

Figure S6

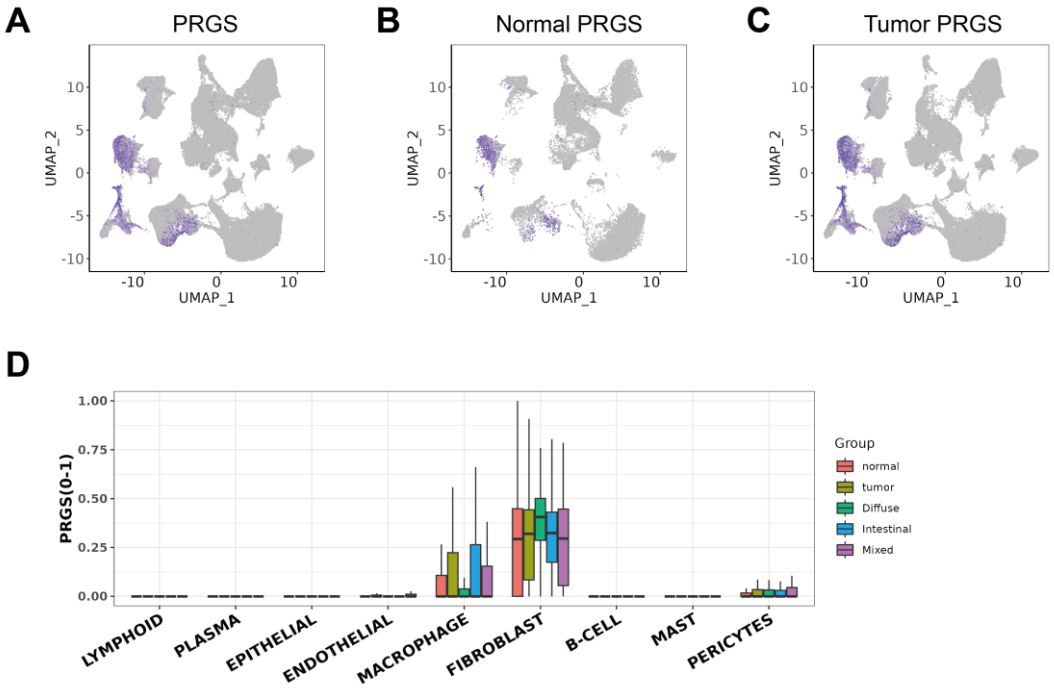

Figure S6 (A)-(C) The UMAP plot of all samples(A), normal samples(B), and tumor samples(C) according to PRGS score. (D) BoxPlot of PRGS scores for different cell types. Normal, normal samples; tumor, tumor samples; Diffuse, diffuse-type GC samples; Intestinal, intestinal-type GC samples; Mixed, mixed-type GC samples.

[1] Zhang P, Yang M, Zhang Y, et al. Dissecting the single-cell transcriptome network underlying gastric premalignant lesions and early gastric cancer[J]. Cell reports, 2019, 27(6): 1934-1947. e5.

[2] Zhang M, Hu S, Min M, et al. Dissecting transcriptional heterogeneity in primary gastric adenocarcinoma by single cell RNA sequencing[J]. Gut, 2021, 70(3): 464-475.

[3] Sun K, Xu R, Ma F, et al. scRNA-seq of gastric tumor shows complex intercellular interaction with an alternative T cell exhaustion trajectory[J]. Nature Communications, 2022, 13(1): 1-19.

[4] Kim J, Park C, Kim K H, et al. Single-cell analysis of gastric pre-cancerous and cancer lesions reveals cell lineage diversity and intratumoral heterogeneity[J]. NPJ precision oncology, 2022, 6(1): 1-11.

[5] Kumar V, Ramnarayanan K, Sundar R, et al. Single-Cell Atlas of Lineage States, Tumor Microenvironment, and Subtype-Specific Expression Programs in Gastric Cancer[J]. Cancer discovery, 2022, 12(3): 670-691.