1293 FRAGMENTED PATTERN OF TUMOR MASS IS RELATED TO FIBROBLAST ACTIVATION MITIGATING SPATIAL INTERACTION BETWEEN TUMOR AND IMMUNE CELLS

Sukjun Kim*, Sanghoon Song, Seulki Kim, Mingu Kang, Mohammad Mostafavi, Donggeun Yoo, Chang Ho Ahn, Siraj Ali, Chan-Young Ock. *Lunit Inc., Seoul, Republic of Korea*

Background Microscopic tumor fragmentation has shown association with the immune landscape of tumor microenvironment (TME).[1] The current study aimed to further investigate the effect of the tumor fragmentation index (TFI), defined by the number of tumor fragments per total tumor area, and fibroblast infiltration on inflammatory cytokines, as well as lymphocytes maturation in TME.

Methods Tumor and stromal areas of The Cancer Genome Atlas (TCGA) H&E whole-slide images (WSI, N = 7472) across the 23 carcinoma cancer types were segmented, and cell types including lymphocytes (LC), macrophages (MP), and fibroblasts (FB) were identified using Lunit SCOPE IO, an AI-powered WSI analyzer. Independent tumor masses were isolated by the connected component labeling algorithm. Tumor fragments which are too small in size (< 968.2 μm^2) or which are not in contact with the stromal area were filtered out, then TFI (count/mm^2) was calculated.

Results In pan-carcinoma dataset, the upper 75% of TFI was 35/mm^2, which was applied for the threshold of TFI-high vs TFI-low group. The proportion of TFI-high was enriched in pancreatic adenocarcinoma (85.2%), prostate adenocarcinoma (67.2%), breast cancer (64.4%), cholangiocarcinoma (52.8%), and lung adenocarcinoma (39.9%). In the whole dataset, FB density in TME was significantly different between TFI-high and TFI-low (median 1298 [interquartile range, 987–28379] vs 475 [241–760]), whereas LC density and MP density in TME were not (LC: 339 [170–698] vs 320 [138–703]; MP: 17 [9–38] vs 22 [10–48]). Gene expression profile analysis showed TFI-high had significantly decreased levels of *IFNG* (fold change, -29%), *IL1A* (-24%), and *IL17A* (-41%) compared to TFI-low had. In contrast, there were no significant differences in PD-1/PD-L1 and CTLA4/CD28 axes (-5% ~ +8%). Cibersort analysis[2] showed that gamma delta T cells (-52%), activated memory CD4 T cells (-50%), activated NK cells (-29%), CD8 T cells (-21%) demonstrated the most significant reductions in TFI-high.

Conclusions Tumor with high fragmentation, or TFI-high is closely correlated with high fibroblast infiltration, low *IFNG* signature-related NK and T cells infiltration, but has minimal impact on overall densities of lymphocytes and macrophages, as well as PD-1/PD-L1 and CTLA4/CD28 axes.

REFERENCES

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