# Researchers identify subtypes of squamous cell lung cancer

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Lung cancer is the number one cause of cancer-related deaths in the United States, with squamous cell lung cancer (SCC) being one of the common types. Despite improved knowledge of the molecular alterations in SCC, little is understood about how the alterations contribute to the development of the cancer and how potential vulnerabilities could be exploited to treat the disease. Researchers in Moffitt Cancer Center's Lung Cancer Center of Excellence took a closer look at SCC tumors to determine if their characteristics had an impact on patient outcomes. The findings were published today in *Nature Communications*.

The research team performed extensive analysis on 108 SCC tumor samples from Moffitt's Total Cancer Care Protocol. This analysis included copy number alterations, DNA mutations, RNA and protein expression patterns, and pathology. They determined that the SCC tumors could be grouped into 3 main subtypes based on their protein expression patterns. Those subtypes were termed inflamed, redox and mixed.

The inflamed subtype accounted for 40% of the tumor tissue. Those samples had higher levels of proteins associated with immune cells, especially neutrophils or myeloid cells, and an active inflammatory response. Based on RNA data, the researchers discovered that the inflamed subtype also had a high proportion of other immune cells, including memory B-cells and monocytes, and was associated with higher levels of PD-1 than the other two subtypes.

The redox subtype was noted in 47% of the tumors. The specimens were characterized by higher levels of proteins that are associated with oxidation-reduction cellular signaling pathways. The redox subtype also had a higher number of genetic and chromosomal alterations that are known to be involved in SCC development. Using these data as guides, they identified new vulnerabilities that could be possible future therapeutic targets.

The final subtype, the mixed group, represented 13% of the tumors and only displayed an increased level of four proteins. The researchers did not find any significant chromosomal alterations in this subtype but did learn that the mixed group had more mutations in the APC gene and had a greater infiltration of stromal cells than the other subtypes.

The analysis showed that the three subtypes did not correspond to better or worse patient outcomes. However, tertiary lymph node structures, more commonly found in the inflamed subtype, were associated with better outcomes.

"These findings are in line with the general lack of agreement of prognostic signatures in SCC but now strongly suggest that an active immune response, indicated by tertiary lymph node structures, is associated with better outcomes. We hope to better understand this in future studies and determine how to exploit this knowledge for new therapy," said Eric Haura, M.D., director of Lung Cancer Center of Excellence and interim chair of the Department of

Thoracic Oncology at Moffitt.

The researcher team hopes that their results will lead to an improved understanding of SCC and highlight potential therapeutic targets for each subtype. Ongoing studies are examining metabolic targets for treatment of the redox group.

"Our results show SCC can be thought of as a disease with three subtypes, the bulk (87%) of which are associated with either immune infiltration (inflamed) or oxidation-reduction (redox) biology. This line of thinking is compelling, because it indicates that the majority of patients could benefit from therapies directed against immune cell types (inflamed) or metabolic modulation of tumor intrinsic pathways (redox)," Haura added.

**More information:** Paul A. Stewart et al, Proteogenomic landscape of squamous cell lung cancer, *Nature Communications* (2019). DOI: 10.1038/s41467-019-11452-x

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