Background

Hypoxia is prevalent in solid malignant tumors and linked to angiogenesis. Uncoordinated expression of angiogenic factors results in dysfunctional blood vessels and promotion of metastasis, associated with poor prognosis [1]. VEGFA, a major driver of angiogenesis, has been proven to be an efficacious target in multiple malignancies [2].

Aim

- Establish a score of hypoxia response based on known hypoxia-regulated genes
- Ranking of tumor types according to the magnitude of hypoxia response
- Link hypoxia response to patient prognosis
- Anticipate sensitivity of different tumor types to VEGFA-blockers

Methods

A total of 200 genes from the Molecular Signature Database [3] shown to be upregulated upon hypoxia in cell lines, were analyzed. The signature was validated using published hypoxia/normoxia cell culture data [4] and then applied to data from the TCGA consortium.

A hypoxia score was computed for each sample, based on the mean standard gene expression of the hypoxia-related genes. Next, a multidimensional framework (MDF) was built by integrating survival data, VEGFA-expression, and its correlation with the hypoxia score and used to explore the potential to anticipate sensitivity to VEGFA-blockers.

Results

Validation of the signature confirmed a significant increase of the hypoxia score under hypoxia compared to normoxia. Also, the expression of VEGFA was significantly higher under hypoxia than under normoxia (Fig. 1).

Fig. 1: Boxplots show the significant increase of the A hypoxia score and B VEGFA expression under hypoxia compared to normoxia.

Next, the score was applied to 10'550 samples across 33 tumor types, which showed a significantly higher hypoxia score in solid compared to non-solid tumors (Fig. 2A-B).

Additionally, tumors with a high hypoxia score are linked with poor survival (Fig. 3).

Conclusion

These results confirmed that hypoxia is associated with a poor prognosis and predominantly occurs in solid tumors. Furthermore, our results suggest a potential benefit of VEGFA-blockers in adrenocortical carcinoma and head and neck squamous cell carcinoma.

References


Abbreviations of the cancer types: https://pdc.cancer.gov/resources-tcga-users/tcga-code-tables/tcga-study-abbreviations.

Disclaimer

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