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Tumor-intrinsic subtypes of esophageal adenocarcinoma associate cellular phenotypes with responses to therapy

D. Blangé[1], M. Dings[1], A. van der Zalm[1], M. Lansbergen[1], M. Verzaal[2], C. Oyarce[1], S. Meijer[3], C. Waasdorp[4], M. van Mourik[1], C. Longobardi[2], E. Cuppen[5], H. Bloemendal[6], J. Koster[7], D. Zwijnenbrug[7], J-P. Medema[8], H.W.M. van Laarhoven[9], M.F. Bijlsma[10]

[1] Medical Oncology, Amsterdam University Medical Center (UMC) - locatie Academic Medical Center (AMC), Amsterdam, Netherlands, [2] Laboratory of Experimental Oncology and Radiobiology, Amsterdam University Medical Center (UMC) - locatie Academic Medical Center (AMC), Amsterdam, Netherlands, [3] Pathology, Amsterdam University Medical Center (UMC) - locatie Academic Medical Center (AMC), Amsterdam, Netherlands, [4] Laboratory of experimental oncology and radiobiology, Amsterdam University Medical Center (UMC) - locatie Academic Medical Center (AMC), Amsterdam, Netherlands, [5] Medical, Hardwig Medical Foundation, Amsterdam, Netherlands, [6] Department of Medical Oncology, Radboud University Medical Center, Nijmegen, Netherlands, [7] Center of Experimental and Molecular Medicine, Amsterdam University Medical Center (UMC) - locatie Academic Medical Center (AMC), Amsterdam, Netherlands, [8] Center for Experimental and Molecular Medicine, Amsterdam University Medical Centers UMC, Amsterdam, Netherlands, [9] Medical Oncology Dept., Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands[10] Center for Experimental and Molecular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands

Background

Effective treatment of esophageal adenocarcinoma (EAC) is hampered by a high degree of mesenchymal plasticity that contributes to acquired therapy resistance and disease recurrence. Many trials are or have been investigating new treatments, such as additional epidermal growth factor signaling inhibition, to improve patient outcome. However, patient selection methods are limited. The existence of a tissue-level molecular subtype that could be used to stratify patients has remained elusive, in large part due to an abundance of non-tumor cells confounding bulk gene expression data.

Methods

We profiled gene expression from 186 esophageal cancer samples and applied non-negative matrix factorization to identify tumor-intrinsic features. Subgroups were discovered using consensus clustering of the tumor-intrinsic gene expression signatures and single-nucleus RNA sequencing analysis.

Results

Two subtypes were identified; intestinal-like (IL) and mesenchymal-like (ML). The latter enriched following neoadjuvant treatment and during disease progression. In a separate cohort of RNA-sequenced metastatic EAC, the ML subtype was found to predict poor response to treatment. Conversely, IL subtype cancer cells were highly dependent on epidermal growth factor signalling, and sensitive to receptor tyrosine kinase inhibition. Mechanisms behind the dependence on epidermal growth factor signalling are currently elucidated using comprehensive analyses.

Conclusions

Targeting of epidermal growth factor signaling is currently only available for HER2-positive patients, about 15% of all cases. Based on our tumor-intrinsic subtypes, a larger fraction of EAC patients seem to benefit from epidermal growth factor inhibition. Therefore, the ability to assign subtype labels in the clinic will be an important step forward to identify patients who may benefit from additional epidermal growth factor inhibition.

Clinical trial identification

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Legal entity responsible for the study

The authors.

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Disclosure

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