Background. The ligand-activated transcription factor, AHR (aryl hydrocarbon receptor) is an important regulator of different biological processes including angiogenesis, hematopoiesis, drug and lipid metabolism, cell motility, and immune modulation. AHR activating ligands are found in the environment (e.g., dioxin), but are also generated endogenously, for example by tryptophan catabolizing enzymes (e.g., IDO1, TDO2, IL4I1). AHR activation can lead to immunosuppression, thus limiting response to therapy. AHR activity is increased in cancer and efforts are ongoing to decipher the AHR-mediated immune modulation in the crosstalk between cancer and the tumor microenvironment.

Methods. By combining analysis of gene expression data from over 10,000 tumors in 32 different cancers and natural language processing we developed a pan-cancer AHR transcriptional gene signature (PAHR) that allows detecting the status of AHR activation in a cell and ligand independent manner. We built a plug & play pipeline using PAHR, which employs multiple machine learning methods for AHR target biomarker discovery.

Results. Using PAHR, we profiled transcriptomics and amino acid metabolic profiles of 32 different cancers that associate with the production of AHR activating ligands. Furthermore, we used PAHR to characterize AHR specific cancer subtypes showing various AHR-mediated immunosuppressive functions.

In most cancers, the AHR cancer subtypes reflected worse overall survival outcome with increasing AHR activity. Functional characterization of bladder cancer AHR subtypes showed that AHR mediates different transcriptional programs leading to similar survival outcomes using different immunosuppressive modules. Some cancer subtypes showed better survival outcome associated with high AHR activity, indicating that AHR can play both tumor promoting and suppressive roles.

Conclusions. PAHR integrative analysis detects different patterns of AHR activities across cancers with significant induction of immunosuppression in cancers leading to the development of distinct patient strata on a pan-cancer level.

We conclude that assessment of AHR-activity by way of PAHR presents as a new stratification strategy in immune oncology. PAHR will improve patient selection in clinical trials, and therapy selection of todays and future cancer immunotherapies to improve response to treatment for the individual patient.

REFERENCES


Ethics Approval. Metastatic melanoma samples were obtained from the section of dermatoncology in the National Center for Tumor Diseases (NCT), Heidelberg, Germany, under the ethics board approval S-207/2005. Participants gave informed consent before taking part in the study.