

Immunotherapy

Major finding: CD14⁺CD16⁺HLA-DR^{hi} monocyte frequency was linked to response to anti-PD-1 in patients with melanoma.

Approach: High-dimensional single-cell mass cytometry characterizes PBMCs before and after anti-PD-1 treatment.

Impact: Monocyte frequency in PBMCs may identify patients with melanoma likely to benefit from anti-PD-1 therapy.

BLOOD MONOCYTE FREQUENCY MAY BE A BIOMARKER FOR RESPONSE TO ANTI-PD-1

Immune checkpoint blockade targeting PD-1 achieves dramatic increases in progression-free survival in a subset of patients with metastatic melanoma and other tumor types. However, many patients do not achieve durable response, and biomarkers to predict clinical response are lacking. Krieg and colleagues used high-dimensional single-cell mass cytometry and a customized bioinformatics pipeline to discover biomarkers in peripheral blood mononuclear cells (PBMC) from 20 patients with stage IV melanoma before and after 12 weeks of anti-PD-1 therapy compared with 10 healthy donors. The frequency of myeloid cells predicted responses to anti-PD-1 treatment, with responders having higher frequencies of CD14⁺CD16⁺HLA-DR^{hi} monocytes before therapy and a lower frequency of circulating T cells. Further, anti-PD-1 therapy induced a response signature in the T-cell compartment. Responders had higher numbers of CD4⁺ T cells expressing PD-1, IL4, IFN γ , IL10, IL17A, and Grz-B than



nonresponders after one cycle of anti-PD-1 treatment. Similarly, CD8⁺ T cells upregulated CTLA4, granzyme B, CD11a, and CCR4 in responders as compared to nonresponders, which also showed higher migratory capacities. Subsequent CD4 or CD8 T-cell phenotypes were of central or effector memory cells. Results were validated by using conventional flow cytometry in an independent cohort of 31 patients. Finally, a hazard model revealed that a monocyte frequency of greater than 19.38% before therapy initiation was associated with a better response, extended progression-free and overall survival. Taken together, these findings reveal that elevated monocyte frequencies may be a potential biomarker for response to anti-PD-1 treatment. ■

Krieg C, Nowicka M, Guglietta S, Schindler S, Hartmann FJ, Weber LM, et al. High-dimensional single-cell analysis predicts response to anti-PD-1 immunotherapy. *Nat Med* 2018;24:144–53.

Pancreatic Cancer

Major finding: Allelic imbalance with increased *Kras*^{G12D} gene dosage drives key PDAC characteristics.

Approach: Integrated multi-omic approaches characterize mouse PDAC cell culture resources with human data sets.

Impact: Oncogene dosage gain is critical for early PDAC progression and influences the evolutionary tumor route.

KRAS^{G12D} GENE DOSAGE DRIVES PANCREATIC TUMOR EVOLUTION AND PROGRESSION

Pancreatic ductal adenocarcinoma (PDAC) exhibits a complex genome, and so far mutational landscapes have not been linked to biological or clinical phenotypes. To better understand the genomics underlying PDAC phenotypic diversification and progression, Mueller, Engleitner, Maresch, and colleagues characterized primary PDAC cell cultures from KRAS^{G12D}-driven pancreatic cancer mouse models using exome sequencing, comparative genomic hybridization, and advanced cytogenetics. Amplifications affecting the *Kras*^{G12D} allele occurred frequently and were also observed in human PDAC precursor lesions, suggesting that upon *KRAS* mutation, additional oncogenic dosage gain is required for early cancer progression. Altogether, two thirds of tumors had allelic imbalances that increased the *Kras*^{G12D} gene dosage (*Kras*^{G12D-iGD}); these occurred through focal gain, arm-level gain, or copy number-neutral loss of heterozygosity. *Kras*^{G12D} gene dosage gain was not only linked to early progression, but also associated with metastasis, which may provide a mechanism for early dissemination of human PDAC. Tumors without increased *Kras*^{G12D-iGD} frequently showed amplification of alternative

oncogenes such as *Myc*, *Yap1*, or *Nfkb2*, suggesting that they may drive early PDAC progression when *Kras*^{G12D} is not amplified. Further, the type and level of oncogenic gain affected multiple disease characteristics including cellular histopathologic phenotypes; the most aggressive undifferentiated cancers were linked to the highest *Kras*^{G12D-iGD} dosages. Major PDAC tumor suppressor gene pathways were involved in acquisition of different types of oncogenic gains. For example, homozygous inactivation of *Cdkn2a* or *Trp53* predisposed cancers to acquire *Kras*^{G12D-iGD} whereas heterozygous loss of *Cdkn2a* allowed for amplification of the alternative oncogenes. Taken together, these findings indicate that oncogenic dosage gain is critical for early PDAC progression and can evolve along distinct evolutionary routes. The resulting dosage variation subsequently affects multiple aspects of PDAC biology. Further, these findings may extend to other *KRAS*-driven tumor types. ■

Mueller S, Engleitner T, Maresch R, Zukowska M, Lange S, Kaltenbacher T, et al. Evolutionary routes and *KRAS* dosage define pancreatic cancer phenotypes. *Nature* 2018;554:62–8.

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CANCER DISCOVERY

Blood Monocyte Frequency May Be a Biomarker for Response to Anti –PD-1

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