Pan-cancer analysis of copy number changes in programmed death-ligand 1 (PD-L1, CD274) - associations with gene expression, mutational load, and survival.

Inhibition of the PD-L1 (CD274) - PD-1 axis has emerged as a powerful cancer therapy that prevents evasion of tumor cells from the immune system. While immunohistochemical detection of PD-L1 was introduced as a predictive biomarker with variable power, much less is known about copy number alterations (CNA) affecting PD-L1 and their associations with expression levels, mutational load, and survival. To gain insight, we employed The Cancer Genome Atlas (TCGA) datasets to comprehensively analyze 22 major cancer types for PD-L1 CNAs. We observed a diverse landscape of PD-L1 CNAs, which affected focal regions, chromosome 9p or the entire chromosome 9. Deletions of PD-L1 were more frequent than gains (31% vs. 12%) with deletions being most prevalent in melanoma and non-small cell lung cancer. Copy number gains most frequently occurred in ovarian cancer, head and neck cancer, bladder cancer, cervical and endocervical cancer, sarcomas, and colorectal cancers. Fine-mapping of the genetic architecture revealed specific recurrently amplified and deleted core regions across cancers with putative...
biological and clinical consequences. PD-L1 CNAs correlated significantly with PD-L1 mRNA expression changes in many cancer types, and tumors with PD-L1 gains harbored significantly higher mutational load compared to non-amplified cases (median: 78 non-synonymous mutations vs. 40, P = 7.1e-69). Moreover, we observed that, in general, both PD-L1 amplifications and deletions were associated with dismal prognosis. In conclusion, PD-L1 CNAs, in particular PD-L1 copy number gains, represent frequent genetic alterations across many cancers, which influence PD-L1 expression levels, are associated with higher mutational loads, and may be exploitable as predictive biomarker for immunotherapy regimens. © 2016 Wiley Periodicals, Inc.