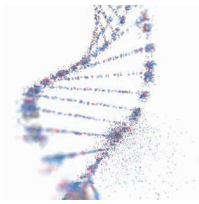
Etiology

Major Finding: Patient age at diagnosis influences the mutational landscape and clinical prognosis of tumors.

Concept: Oncogenic processes differ in activity in age-stratified patients, underlying clinical outcomes.

Impact: This study reveals genetic alterations with prognostic value in specific contexts of patient age.

AGE AT DIAGNOSIS IMPACTS MOLECULAR AND CLINICAL PROPERTIES OF TUMORS



Cancer is commonly described as a disease of aging, as the risk of cancer increases with age in the majority of tumor types. However, processes underlying the complex relationship between cancer and aging are not well understood. To explore the mechanisms by which age influences the molecular and clinical features of cancer, Li and colleagues performed a comprehensive pan-cancer analysis of age-associated molecular differences in the somatic mutational landscape of over 20,000 tumors from The Cancer Genome Atlas, the International Cancer Genome Consortium/TCGA Pan-Cancer Analysis of Whole Genomes, and the AACR Project Genomics Evidence Neoplasia Information Exchange databases. Through univariate analysis followed by multivariate modeling, associations were identified between genetic properties of tumors and the recorded age of patients at diagnosis, considering associations present in pan-cancer and tumor type–specific analyses. Age was positively associated with measures of mutation accumulation, such as single-nucleotide variant (SNV) density and genomic instability, with mutations accumulating at an estimated 0.077 mutations per megabase per year. Analysis of mutational signatures to evaluate the relative activity of various oncogenic processes associated with age in specific tumor types suggested that different mutational processes were preferentially active in age-stratified patients, as exemplified in melanoma, in which younger versus older patients frequently involved UV damage or DNA replication errors, respectively. Age-associated copy-number aberrations (CNA) in cancer driver genes were associated not only with changes in mRNA abundance but also with patient survival, as evidenced by the prognostic value of the loss of the tumor suppressor gene *SUFU* in younger but not older patients with glioblastoma. In addition to age-associated CNAs, specific SNVs associated with age influenced mRNA abundance and altered survival outcome, as observed with SNVs in the tumor suppressor gene *ATRX*, which was associated with improved survival in older patients but reduced survival in younger patients with low-grade glioma. In summary, this work characterizes the impact of age on the mutational landscape of cancer, highlighting molecular bases of age-related cancer health disparities. ■

Li CH, Haider S, and Boutros PC. Age influences on the molecular presentation of tumours. Nat Commun 2022;13:208.

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Microbiome

Major Finding: High fiber consumption and lack of commercial probiotic use improves response to checkpoint inhibitors.

Concept: High fiber consumption is associated with a high immune response in the tumor microenvironment.

Impact: Close monitoring of dietary fiber and probiotic use in patients receiving immunotherapy is suggested.

LOW COMMERCIAL PROBIOTIC USE AND A HIGH FIBER DIET IMPROVES IMMUNOTHERAPY RESPONSE

The gut microbiome modulates response to immune checkpoint blockade (ICB), but how dietary fiber intake and commercial probiotics affect this interaction is unclear. To address this, Spencer, McQuade, Gopalakrishnan, McCulloch, Vetizou, Cogdill, and colleagues profiled the fecal microbiome of patients with melanoma and assessed ICB response. *Ruminococcaceae* was significantly more abundant in patients responding to anti-programmed death 1 (anti–PD-1) or other systemic therapies compared to nonresponders; however, overall gut microbiome composition was not found to be significantly different between the groups. Investigation into any reported use of commercially available probiotics in this patient cohort indicated no significant difference in progression-free survival (PFS) in those taking probiotic supplements. However, in contrast to patients taking commercial probiotics, patients treated with ICB who had a high fiber intake at or above 20 g/day did demonstrate alterations to PFS such that for every 5 g increase in daily fiber intake, a 30% lower risk of cancer progression or death was observed. To confirm these findings in preclinical models, germ-free mice received a fecal microbiota transplant from a complete responder patient and were subsequently challenged with melanoma and treated with anti–PD-L1 therapy. Mice from this cohort that were also given commercial probiotics demonstrated significantly impaired antitumor response and larger tumors as well as a significant reduction in the number of activated and interferon-γ^+, $CD8^+$ T cells, suggesting an impaired T-cell immune response. In mice receiving anti–PD-1 treatment, a high-fiber diet led to more delayed tumor growth and significantly higher T-cell activation compared with a low-fiber diet. In line with the preclinical findings, ICB-treated patients who reported sufficient fiber intake and did not take probiotics have significantly longer PFS than any other group. Overall, this study supports that improving dietary fiber intake could improve outcomes in patients on ICB, but use of commercially available probiotics could have unintended effects, suggesting dietary habits and supplement use should be carefully considered and monitored in patients. ■

Spencer CN, McQuade JL, Gopalakrishnan V, McCulloch JA, Vetizou M, Cogdill AP, et al. Dietary fiber and probiotics influence the gut microbiome and melanoma immunotherapy response. Science 2021;374:1632–40.

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