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IN BRIEF

IMMUNOTHERAPY

Bad B cells

Combination immune checkpoint blockade with anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA4) and anti-programmed cell death protein 1 (PD1) leads to higher response rates in patients with melanoma than either single agent alone. Yet, a drawback of this combination is an increase in immune-related adverse events. Until now attention has focused on T cell-mediated immune responses following immune checkpoint therapy, and the role B cells might play has been relatively unexplored. Das *et al.* found a decrease in circulating B cells and an increase in $CD21^{lo}$ B cells and plasmablasts following inhibition of CTLA4 and PD1 in patients. The $CD21^{lo}$ B cells were associated with greater clonality, activation and PD1 expression. Importantly, these early B cell changes occurred before and correlated with both the number and timing of treatment-related toxicities. Thus, detection of B cells could serve as a predictive biomarker of patients at increased risk of developing autoimmunity.

ORIGINAL ARTICLE Das, R. et al. Early B cell changes predict autoimmunity following combination immune checkpoint blockade. *J. Clin. Invest.* http://dx.doi.org/10.1172/JCI96798 (2018)

TUMOUR METABOLISM

The promoter becomes the suppressor

Somatic mutations in *IDH1* or *IDH2* are common in acute myeloid leukaemia (AML) and glioma, and result in a neomorphic enzyme that produces the metabolite R-2-hydroxyglutarate (R-2HG), which has been widely reported to have tumour-promoting activities. Su, Dong, Li et al. showed that R-2HG also has tumour suppressive effects in AML in vitro and in vivo, and in glioma cell lines. By inhibiting the RNA demethylase FTO, R-2HG increases N^6-methyladenosine (m^6A) of RNA, thus decreasing the stability of *MYC* and *CEBPA* mRNAs and allowing the observed inhibition of proliferation and survival. Cells that had high FTO were particularly sensitive to the anti-leukaemic effects of R-2HG, and those with high MYC were less sensitive.

ORIGINAL ARTICLE Su, R. et al. R-2HG exhibits anti-tumor activity by targeting FTO/m6A/MYC/CEBPA signaling. *Cell* **172**, 90–105 (2018)

GASTRIC CANCER

Risk analysis

Intestinal metaplasia (IM) is a pre-cancerous condition, and connected with an increased risk of developing intestinal-type gastric adenocarcinoma, the most common form of gastric cancer (GC). However, only a small subset of IM patients develop GC. In a 10-year prospective study, Huang, Ramnarayanan, Zhu, Srivastava et al. performed (epi)genomic profiling of 138 IMs from 148 GC-free patients to determine molecular features, including *Helicobacter pylori* (Hp) status, associated with GC progression or IM regression. Compared with GCs, IMs had low frequencies of clonal mutations. IMs with somatic copy number alterations (sCNAs), telomere erosion and epigenomic alterations were associated with GC progression, indicating that epigenomic changes observed in a subset of IMs can be targeted to reduce GC progression. Finally, Hp-positive IMs were detected by sequencing at a higher rate than by histology, and were more likely to harbour sCNAs.

ORIGINAL ARTICLE Huang, K. K. et al. Genomic and epigenomic profiling of high-risk intestinal metaplasia reveals molecular determinants of progression to gastric cancer. *Cancer Cell* **33**, 137–150 (2018)