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NEWS

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MPS1 INHIBITION PRIMES IMMUNOGENICITY OF *KRAS-LKB1*-MUTANT LUNG CANCER

STING (stimulator of interferon genes) has an interesting role in determining resistance to immunotherapy and it is becoming increasingly clear that the activity of the cancer cell-intrinsic STING pathway defines the immunogenicity and the antitumor efficacy of immune checkpoint inhibitors. In a previous investigation, it was reported that STING expression is epigenetically silenced in *KRAS-LKB1* (*KL*)-mutated non-small-cell lung cancer (NSCLC).[1] Thus, KL cells exhibit cytoplasmic accumulation of mutant DNA owing to an autophagic defect which selects for STING silencing to protect cells from signal transduction and activators of transduction-1 (STAT1)-induced cytotoxicity, and also impairs cytotoxic T cells infiltration. This suggests that the restoration and activation of the epigenetically silenced STING could potentially represent a targeted approach to enhance immunogenicity in several solid tumors.

In a new interesting paper published in *Cancer Cell* by Kitajima et al,[2] the authors continued their investigation and explain how in *KRAS-LKB1*-mutant NSCLC, STING modulation is able to sensitize to immunotherapy. The epigenetic regulation of innate immune signaling has become a major focus to promote cancer cell immunogenicity, as it represents a potentially reversible mechanism used by tumors to evade immunosurveillance and immune checkpoint blockade-mediated T cell killing. Since cell division is required for the removal of functional epigenetic marks, DNA- or histone-demethylating agents might efficiently convert cell state from immunosuppressive to active in rapidly proliferating cancer cells. Most cancer cells show spindle assembly checkpoint (SAC)-dependent rapid proliferation and chromosomal instability. SAC abrogation by continuous monopolar spindle kinase (MPS1) inhibition, however, results in intolerable levels of genomic instability and cell death. In this investigation, the authors demonstrated that transient treatment with an MPS1 inhibitor robustly generates micronuclei via chromosome mis-aggregation in KL cells.

They were able to identify MPS1, a master regulator of the SAC, as a highly robust target to activate GMP-AMP synthase (cGAS)-STING signaling in KL cells. STING agonism induced by MPS1 inhibition causes abnormal mitosis *in vitro* and generates micronuclei, which are known potent activators of cGAS, finally inducing through a cascade pathway activation, STAT1-dependent cell death.

In a murine syngeneic *KL* model, the authors tested an MPS1 inhibitor, BAY-1217389, and decitabine, and they observed that these drugs were able to strongly activate cancer cell-intrinsic STING and enhanced T-cell recruitment, achieving prolonged activity *in vivo*. This work newly highlights the importance of STING as a potential therapeutic target and how epigenetic changes in it may cause immune resistance, suggesting a possible mechanism to restore sensitivity to checkpoint inhibitors. Further results across some patient cohorts are awaited.

ATEZOLIZUMAB FAILS AS ADJUVANT TREATMENT IN PATIENTS WITH RESECTED RENAL CELL CARCINOMA AT HIGH RISK OF RECURRENCE

Most patients with renal cell carcinoma are diagnosed in locoregional stages and standard of care treatment relies on the surgical removal of the primary tumor with partial or radical nephrectomy. Nevertheless, most patients presenting some risk factors, such as T3-T4, N1, or high-grade histology, are at a higher risk of relapse after surgery. A recent article in *The Lancet* by Pal et al.[3] reports the negative outcome of adjuvant treatment with atezolizumab as adjuvant treatment of patients with renal cell carcinoma at increased risk of recurrence after primary surgery. The trial was designed as a placebo-controlled, randomized phase III study powered to detect a 30% improvement in disease-free survival in the atezolizumab-treated arm. The study accrued 778 out of 1399 screened patients and was properly carried out according to best standard. At a median follow-up duration of 44.7 months, no differences in disease-free survival were found with a hazard ratio of 0.93 and a *P* value of 0.50.

The negative outcome of this trial contrasts with the positive results of pembrolizumab in the Keynote-564 trial,[4,5] that already showed at the first interim analysis that the primary endpoint was met. In fact, with a total 994 patients randomized and a median follow-up time of only 24 months, the pembrolizumab assigned treatment cohort showed a more favorable disease-free survival period than the ones assigned to the placebo arm with a hazard ratio of 0.68 and a *P* value of 0.002, and an absolute difference in disease-free survival at 2 years of 9.2%. These results were more recently confirmed with a longer follow-up of 30.1 months. Another study reported in September 2022 at the annual ESMO congress reported the negative outcome of the combination of nivolumab plus ipilimumab in a similar setting for the phase III CheckMate 914 trial.[6]

The positive results with pembrolizumab led to the Food and Drug Administration (FDA) and European Medicines Agency (EMA) to approve its use as adjuvant treatment of patients with renal cell carcinoma at high risk of relapse after surgical resection with curative intent. An update of the ESMO Clinical practice guidelines adds a word of caution in this regard,[7] however, considering that

disease-free survival is not a robust surrogate for overall survival (OS) in renal cell carcinoma and OS data are not mature enough to assess this specific and relevant endpoint. Despite recommending pembrolizumab as an option for adjuvant treatment in renal cell carcinoma based upon the current evidence, the ESMO guidelines underline the importance of a robust statistical analysis for OS to consolidate its current recommendation. The negative outcome of atezolizumab as single agent and the combination of nivolumab plus ipilimumab reinforces the importance of looking for valuable predictive biomarkers for a more personalized approach. More than 2500 patients gave their consent to participate in these three randomized, controlled studies and the oncological community should be indebted and thankful to them. Bringing personalized precision oncology to them to avoid unnecessary treatment of those who are already cured by surgery, avoiding significant toxicity and selecting those who may really benefit from a given therapy is a service we should strongly search and implement.

PROTEOGENOMIC MARKERS OF CHEMOTHERAPY RESISTANCE AND SENSITIVITY IN TRIPLE-NEGATIVE BREAST CANCER

The triple-negative breast cancer subtype is characterized by low expression of human epidermal growth factor receptor 2 (HER2) and negative expression of estrogen and progesterone receptors and represents between 10% and 15% of breast cancer.[8] This subtype has a highly aggressive clinical course with high mortality and frequent chemotherapy resistance. Cytotoxic chemotherapy is standard of care but is only partially effective. A better understanding of the mechanism underlying the response to chemotherapy will help to develop more efficient therapies.

Anurag et al.[9] published, in *Cancer Discovery*, an impressive article where they describe the first time to deploy microscaled proteogenomics to discover neoadjuvant chemotherapy response biomarkers in triple-negative breast cancer. The authors used biopsies from patients with clinical stage II and III enrolled in two clinical trials treated with six cycles of neoadjuvant carboplatin and docetaxel combination chemotherapy. They used paired samples, a pretreatment biopsy and an additional sample from 48 to 72 h after initiating chemotherapy. They analyzed tumor germline matched whole exome DNA sequencing (WES), RNA sequencing (RNAseq), and tandem mass tag-based proteomics and post-marker association with pathological complete response (pCR).

First, they showed that, whereas expression of immune-related pathways was reduced upon treatment at the RNA and protein level, cell cycle and metabolic pathways (including oxidative phosphorylation, adipogenesis and fatty acid metabolism) were significantly up-regulated specifically at the protein level. Elevated *MARK2* (a gene that controls the stability of microtubules) was enriched in non-pCR tumors. Therefore, metabolic pathways were up-regulated in samples without pCR (these associations were observed in the proteomic data but not at the mRNA level). In contrast, immune signaling (interferon-α and -γ response) and cell cycle (G2-M checkpoint and E2F and MYC target) pathways were elevated in pCR cases in both the proteomic and transcriptomic datasets.

Second, due to these findings they explored the signals from the immune microenvironment. Protein-derived immune stimulatory score, previously found to be well correlated with immune infiltration, as well as programmed death-ligand 1 RNA, protein, and phosphorylation levels, were significantly higher in pCR-associated samples. Non-synonymous mutation load, however, was associated with neither pCR nor immune score, suggesting increased mutation burden was not a strong determinant of immune infiltration in this Triple Negative Breast Cancer dataset.

Interestingly, they also evaluated copy number alterations, showing that expression of gene products from 8q21.3 (amplified) and 19q13.31-33 (deleted) cytobands was elevated and suppressed, respectively, in non-pCR versus pCR tumors. Four genes located at 8q21.3 (*RMDN1*, *CPNE3*, *DECR1*, and *OTUD6B*) showed higher mRNA and protein expression in non-pCR tumors. In addition, RIPK2, which may mediate metastasis in advanced breast cancer, also located in 8q21.3, was significantly higher in non-pCR tumors, but only at the protein level. Similarly, four genes located on 19q13.31-33 (*LIG1*, *PPP5C*, *BCL13*, and *NOSIP*) showed lower mRNA and protein expression in non-pCR tumors. Hallmark pathway of the genes on cytoband 19q13.31-33 showed enrichment in the DNA damage repair pathway, with *LIG1*, *XRCC1*, *POLD1*, and *ERCC2* comprising the leading-edge genes. LIG1 showed the strongest association with treatment response at the protein level followed by POLD1. Moreover, loss of LIG1 was associated with features related to poor prognosis such as higher proliferation rates, a less active immune microenvironment, and higher copy number instability. These results were validated in orthotopic patient-derived xenografts (PDX) models generated from a single patient (from pretreated breast primary tumor, from surgical sample, and from liver metastasis that appeared 1 year after treatment initiation). Consistent with previous data, they revealed a progressive loss of LIG1 at the copy number, mRNA, and protein levels as the tumor progressed to a chemotherapy-resistant state. LIG1 loss was related to carboplatin resistance, but was not significant for docetaxel treatment.

Overall, this work suggests that integrated proteogenomic characterization provides more extensive information and emphasizes its potential in the investigation of cancer treatment resistance.

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