Autoantibody Profiling in Prostvac and Ipilimumab Treated Prostate Cancer Patients Reveals Potential Biomarkers of Immune-Related Adverse Events

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ACR 2017 Abstract #1182

Background

- Autoantibodies (AAB) targeting self-antigens can be found in two clinically and immunologically opposing diseases, autoimmune diseases (AID) and cancer.
- While in AID, the immune system is hyperactivated against self-antigens, many tumors develop mechanisms that allow them to evade anti-tumor immune responses.
- The development of therapeutic antibodies that modulate immune inhibitory pathways has been a major breakthrough in the treatment of cancer (1), but is associated with immune-related adverse events (irAEs), which resemble autoimmune responses (2).
- A combination of the immune checkpoint inhibitor ipilimumab (anti-CTLA-4) with the cancer vaccine Prostvac is clinically tested in metastatic castration-resistant prostate cancer (mCRPC) (2).
- Since there are no biomarkers for predicting irAEs, we investigated AAB profiles as biomarkers associated with irAE in mCRPC patients.

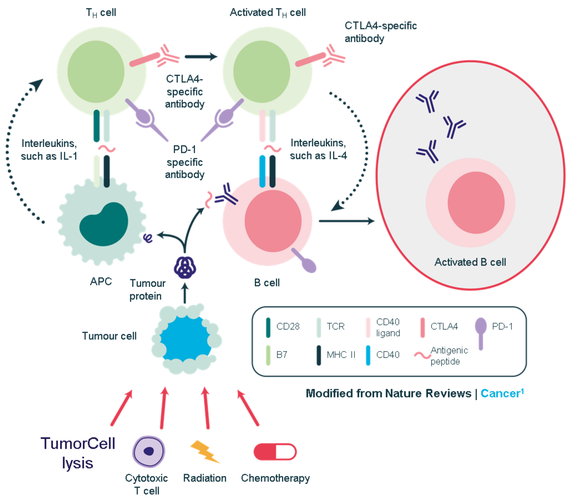

Fig. 1: Autoantibodies as biomarkers for cancer immunotherapy
Modified from (1)

Methods

Serum samples from 24 mCRPC patients treated with prostvac/ ipilimumab therapy (2) were tested for the presence of serum AABs against 842 preselected antigens. AAB levels were measured by Luminex FlexMap3D bead-based multiplex protein arrays (3). Pre- and post-treatment (month 3 and 6) samples were analyzed. IrAEs included rash, elevated aminotransferases, neutropenia, diarrhea, colitis, and endocrine irAEs (2).

Fig. 2: SeroTag immuno-oncology array to investigate biomarkers for response and irAEs

Results

Partial Least Square (PLS) regression analysis was performed to investigate if autoantibodies can serve as biomarkers of efficacy and toxicity profiles of immunotherapy in mCRPC patients.
Fig. 3 shows that a distinct AAB profile is associated with longer overall survival and the development of irAEs.

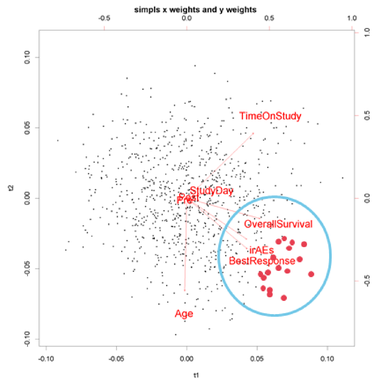

Fig. 3: PLS weights (wc*) plot components 1 vs 2 of AABs in mCRPC samples and their relationship with overall survival and irAEs.

Each dot represents one antigen.
Biomarker candidates are highlighted in red.

Autoantibody Reactivity Signatures

The development of irAEs was associated with longer overall survival on study. In total, 87 AABs were found that were significantly different in patients with irAEs and those without irAEs (SAM |d|>2.5; Pearson's correlation |r|>0.35). There were also 40 AABs in patients who do not experience irAEs.

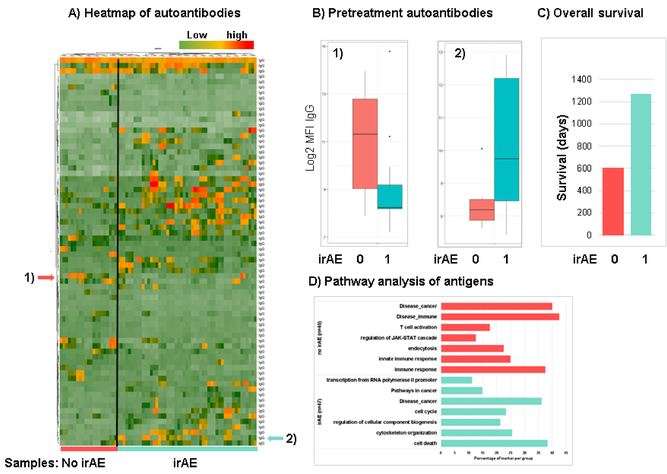

Fig. 4: Autoantibody reactivity of mCRPC patients with and without irAEs following prostvac/ipilimumab combination therapy

Conclusions

AABs that target proteins involved in cancer signaling, apoptosis, or cell cycle pathways are associated with irAEs following prostvac/ipilimumab combination therapy.
In contrast, AABs targeting immune response pathways were found in patients who do not develop irAEs and may counteract the action of inflammatory molecules.
Similarly, anti-cytokine AABs have been found in autoimmune diseases, were they appear to counteract the effects of cytokines (4). Further studies in larger sample sets are needed to confirm these findings.

(1) Kwek et al. 2012 Nat Rev Cancer. 2012 12(4):289-97.
(2) Madan RA et al. 2012 Lancet Oncol 13(5):501-8
(3) Budde P et al. 2016 Lupus. 25:812–22.
(4) Cappellano G et al. 2012 Am J Clin Exp Immunol. 1(2):136-46.