Immune checkpoint inhibitors (CPI) significantly improve survival and potentially cure cancer patients. Autoantigens

To identify biomarkers of autoantibodies, serum samples from 333 metastatic melanoma patients treated with different CPIs and combinations thereof were analyzed. A novel autoantibody screening array was developed, which can be used to identify CPI-related autoantibodies in patients with prior history of autoimmunity.

The mechanisms leading to CPI-induced irAEs are incompletely understood. CPIs are immune checkpoint inhibitors that target cytotoxic T lymphocyte antigen-4 (CTLA-4) or programmed death-1 (PD-1). CPIs can induce immune-related adverse events (irAEs), which may include autoimmune diseases such as rheumatoid arthritis or ulcerative colitis.

Methods

1. **Discovery of autoantibody biomarkers**
   - **Patient characteristics**
     - Table 1: Patient Characteristics
     - Fig. 1: Autoantibody profiling, data analysis and biomarker selection
   - **Best performing baseline autoantibodies**
     - Table 2: Autoantibodies associated with irAE and irAE severity
   - **Kaplan-Meier analyses**
     - Table 3: Kaplan-Meier curves of selected autoantibodies

2. **Pathway and protein-protein interaction analysis**
   - Table 4: Protein-Protein Interactions

Results

- **Discovery of autoantibody biomarkers**
  - Fig. 1: Autoantibody profiling, data analysis and biomarker selection
  - **Table 1:** Patient Characteristics
  - **Table 2:** Autoantibodies associated with irAE and irAE severity
  - **Table 3:** Kaplan-Meier curves of selected autoantibodies

- **Pathway and protein-protein interaction analysis**
  - Table 4: Protein-Protein Interactions

Conclusions

- Increased autoantibody reactivity precedes the onset of irAEs and colitis in melanoma patients.
- Autoantigens included classical tumor (MEGA4, MAGE2, MUM1, TP53p33, SPATF1, TCT2), pre-existing autoimmune (GPP130, GM130, LAMP1), and cross-reactive (GPHN, AMPH) targets.
- Pathway analysis reveals that the identified autoantigens are at the cross-road between cancer and immunity pathways including the autophagy and ubiquitination pathways.
- Novel immune checkpoint inhibitors directed against tumor antigens and normal tissue antigens could be the next generation of therapeutic agents for melanoma patients.

Further validation work in MM is ongoing.