**Cancer immunotherapy via synergistic coactivation of myeloid receptors
CD40 and Dectin-1**

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**Presenter:** Pei-Wen Chen **Date/Time:** 2024/03/14, 15:10-16:00

**Commentator:** Dr. Chih-Peng Chang **Location:** Room 601, Med College Building

**Background:** Therapies like immune checkpoint blockade (ICB) and CAR T cell therapy have transformed cancer treatment, but some tumors are highly resistant to T cell therapies due to tumor microenvironment (TME). These resistant tumors often lack T cells but have abundant myeloid cells, which can both suppress and support immune responses. While myeloid cells typically hinder immune surveillance, they also possess tumor-fighting capabilities. Targeting these myeloid cells poses challenges, including avoiding the activation of compensatory immunosuppressive pathways and preserving their immune-stimulating functions.

**Objective/Hypothesis:**

To successfully target myeloid cells by preventing the activation of compensatory immunosuppressive pathways and concurrently preserving their immunostimulatory capabilities.

**Results:**

Analyzing human pancreatic ductal adenocarcinoma (PDA) tumors revealed ***CD40*** as a highly expressed TNF receptor in myeloid cells. Combining CD40 activation with **Dectin-1**, a pattern recognition receptor (PRR) of myeloid cells, demonstrated potent antitumor immunity in mouse PDA models. Mass cytometry analyses revealed changes in the myeloid compartment induced by β-glucans (BG) targeting Dectin-1 and aCD40, **shifting tumor-associated macrophages (TAMs) away from a tumor-promoting state**. While transcriptional analysis identified up-regulation of the *Pdcd-1*, *Cd274*, and the *Ctla4* immune checkpoints, the addition of immune checkpoint blockade or chemotherapy did not enhance the efficacy of BG/aCD40. T cells were necessary for tumor control, as depletion of CD4+ and CD8+ T cells abrogated treatment effectiveness, and cured mice showed T-cell-dependent immunological memory. However, T cells were not acting as cytotoxic effectors in BG/aCD40 therapy since the activity of BG/aCD40 therapy persisted after knocking out MHC class I and perforin. Further analysis identified ***Ifng*** to be among the most highly expressed cytokines by T cells in BG/aCD40-treated tumor. Knocking out Dectin-1 (*Clec7a*) in a PDA mouse model abrogated BG/aCD40 efficacy, confirming its crucial role. **BG/aCD40 therapy increased intratumoral TAMs**, influenced by aCD40-associated IFN-γ–STAT1 signaling. Depletion and targeting experiments highlighted the essential role of Ly6C+ monocyte-derived TAMs and CSF1R-dependent TAMs in optimal antitumor activity.

**Conclusion:**

Co-activation of myeloid cells using a CD40 agonist (aCD40) in combination with PRR agonists (BG) synergized to invoke productive immunosurveillance in mouse models of pancreatic cancer.