Dynamic Metrics-based Biomarkers to Predict Responders to Checkpoint Immunotherapy

Can Liu¹, Hua He¹,², Yanguang Cao*¹

¹ DPET, School of Pharmacy, University of North Carolina at Chapel Hill, NC, USA; ² China Pharmaceutical University, Nanjing, China.

Objectives: Checkpoint immunotherapies have shown prominent clinical benefits but the response was only observed in 20-30% of patients. Current companion diagnosis based on PD-L1 IHC staining shows poor predictability. More precise companion diagnosis approach are demanding. Here we developed a kind of dynamic metrics-based biomarkers to discriminate responders from non-responders to checkpoint immunotherapies.

Methods: B16F10 melanoma cells (3x10⁴) were inoculated to C57BL/6 mice. Tumor-bearing mice were treated with a murine anti-PD-1 antibody (αPD1) alone and in combination with an anti-CTLA-4 antibody (αCTLA-4). Tumor size was monitored till the end to classify responders from non-responders. Profiles of peripheral and tumor immune cells (e.g. CD4+/CD8+/Treg cell population %) were also characterized. The secretory kinetics of IFN-γ from peripheral CD4+ and CD8+ T cells were quantified and the secretion parameters (e.g. magnitude, slope, lag time, time to half magnitude) were analyzed using orthogonal partial least-squares discriminant analysis (OPLS-DA) to predict responders to checkpoint immunotherapy.

Results: Both treatment groups showed improved survival and significantly slower tumor growth, among which about 60% mice displayed durable tumor regression (responders) and the remainder showed slightly or none effected tumor growth. Neither individual IFN-γ secretion parameters nor peripheral T-cell population can sufficiently predict responders. Surprisingly, combinations of several secretion parameters of IFN-γ showed high predictability of responders by OPLS-DA. Models were validated for fitting ($R^2$) and predictability ($Q^2$) by randomly permuting the samples. By integrating static cell population markers, the model was further improved with high $R^2$ (0.781) and $Q^2$ (0.64).

Conclusions: The secretion dynamics of IFN-γ by peripheral lymphocytes possess high predictabilities of responders to checkpoint immunotherapies. Such dynamic metrics-based biomarkers may potentially shift current companion diagnosis paradigm for checkpoint immunotherapies.

Figure 1 Graphical abstract of workflow

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