IDENTIFYING NOVEL IMMUNOTHERAPY TARGETS UNDER THE PRESSURE OF INHIBITORY CYTOKINE TGF-β

Liangzhe Wu*, Nicholas Gascoigne, Ling Wu, Vivian Tan, Manoj Krishnan, Unnikrishnan Unniyampurath, Benson Chua.
National University of Singapore, Singapore; Duke-NUS, Singapore, Singapore

Background T cell function is under regulation by some suppressive signals such as anti-inflammatory cytokines and immune checkpoint molecules in order to maintain self-tolerance and immune cells homeostasis. Transforming growth factor β1 (TGF-β1) is a pleiotropic cytokine which participates to orchestrate the negative regulation of T cell activity and is produced in large quantities within tumor microenvironment that ultimately promotes neoplastic progression, notably by suppressing the host’s T-cell immunosurveillance. 1,2 Cancer immunotherapy with aims to re-activate tumour-induced exhaustive T cells to fight against cancer cells is a hot and promising field of cancer therapy in recent years. However, despite some positive results in the past years, success of immune checkpoint blockade therapies in clinic is still limited. These have suggested that albeit several key immune checkpoint genes have been identified, there is still an urgent and unmet medical need to discover new inhibitory genes.

Methods mRNA sequencing of human CD8+ T cells, either with or without TGF-β treatment, was performed and compared for novel immunosuppressive genes discovery. CRISPR-Cas9 validation system was followed and applied in both Jurkat T cell line and primary T cells to investigate the knockout effect of the gene candidates in terms of T cell effector function, proliferation, cytotoxicity and in vivo anticancer ability.

Results Among the mRNA sequencing list, two genes – show the significant inhibitory effect to T cells. After being knocked out, T cell function would be impressively rescued in terms of cytokine secretion, proliferation, and target cell killing. In vivo study also demonstrated that adoptive transferred T cells with these genes knock out enhance the anti-cancer effect in terms of controlling tumor size and improving survival rate. On the other hand, these two genes also showed the ability to affect Treg polarization. With these genes knock out, CD4+ T cells tended to less likely to polarize to Treg population under polarizing conditions.

Conclusions Two genes, a regulator of G protein and a F actin-binding protein, are discovered to be novel T cell inhibitory genes and showed their potential to become the immunotherapy gene targets.

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REFERENCES

Ethics Approval Animal Protocols were approved by NUS IACUC (R20-1118)
Use of human primary T cells was approved by institutional review board (IRB) (H-19-026)