Neoantigen-targeted CD8+ T cell responses with PD-1 blockade therapy

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1. 簡述論文的概要與重大發現：

目前免疫治療已是癌症治療不可或缺的一環，並且越來越完善及安全，論文提及以下兩種治療，PD-1 阻斷治療主要是針對 PD-1/PD-L1 信號通路，阻止 PD-L1 與 PD-1 的結合，增強 T 細胞對腫瘤的免疫反應。PD-L1 在很多腫瘤細胞表面過度表達，會抑制周圍的 T 細胞活性。PD-1 阻斷治療可以透過解除 PD-1 受體的抑制，刺激 T 細胞針對腫瘤進行攻擊。

另一種為自身新抗原特異性 CD8+ T 細胞免疫治療主要是針對腫瘤特異性抗原，特異性 CD8+ T 細胞可以通過識別和攻擊腫瘤細胞上表達的腫瘤特異性抗原，將腫瘤細胞消滅。與 PD-1 阻斷治療不同的是，自身新抗原特異性 CD8+ T 細胞免疫治療主要針對腫瘤細胞特定的抗原，而不是細胞表面的受體。

其中此篇論文主要以新抗原靶向 T 細胞治療與 PD-1 阻斷治療組合使用，將兩種免疫治療的優勢發揮到極致，達到更好的治療效果。自身新抗原特異性 CD8+ T 細胞免疫治療可以激發患者自身免疫系統對癌細胞的攻擊，而 PD-1 阻斷治療可以消除 T 細胞對癌細胞的抑制作用，讓 T 細胞更加有效地攻擊癌細胞。這兩種治療組合使用，可以提高治療的有效性和耐受性，並在一些難治療的癌症帶來希望。

2. 對論文內容的提問：

作者為提及是否有比較不同劑量的 PD-1 阻斷劑和自身新抗原的免疫治療對患者治療效果的影響，以及 PD-1 阻斷劑的治療時間和療程對患者治療效果的影響。

3. 論文的缺點及評價：

樣本量較小且追蹤時間較短，較難看出長期的安全性。

Article

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Neoantigens are peptides derived from non-synonymous mutations presented by human leukocyte antigens (HLAs), which are recognized by antitumour T cells[1–14]. The large HLA allele diversity and limiting clinical samples have restricted the study of the landscape of neoantigen-targeted T cell responses in patients over their treatment course. Here we applied recently developed technologies[15–17] to capture neoantigen-specific T cells from blood and tumours from patients with metastatic melanoma with or without response to anti-programmed death receptor 1 (PD-1) immunotherapy. We generated personalized libraries of neoantigen–HLA capture reagents to single-cell isolate the T cells and clone their T cell receptors (neoTCRs). Multiple T cells with different neoTCR sequences (T cell clonotypes) recognized a limited number of mutations in samples from seven patients with long-lasting clinical responses. These neoTCR clonotypes were recurrently detected over time in the blood and tumour. Samples from four patients with no response to anti-PD-1 also demonstrated neoantigen-specific T cell responses in the blood and tumour to a restricted number of mutations with lower TCR polyclonality and were not recurrently detected in sequential samples. Reconstitution of the neoTCRs in donor T cells using non-viral CRISPR–Cas9 gene editing demonstrated specific recognition and cytotoxicity to patient-matched melanoma cell lines. Thus, effective anti-PD-1 immunotherapy is associated with the presence of polyclonal CD8$^+$ T cells in the tumour and blood specific for a limited number of immunodominant mutations, which are recurrently recognized over time.

We reasoned that the analysis of the spectrum of mutational neoantigen-specific T cell responses induced by immune checkpoint blockade (ICB) therapy required (1) a highly sensitive approach that could detect T cell responses to an array of hundreds of putative neoantigens presented by the diverse HLAs in relatively small patient-derived samples containing a few million peripheral blood mononuclear cells (PBMCs) or tumour-infiltrating lymphocytes (TILs) expanded from tumour biopsies[15–17]; (2) reconstitution of the antigen specificity of isolated neoantigen-specific TCRs (neoTCRs) in a time-efficient process[18,19]; and (3) assessment of T cell recognition and antitumour activity against matched patient's autologous cell lines that endogenously express the mutational neoantigens. From 11 patients with metastatic melanoma receiving PD-1-blockade-based immunotherapy, we collected PBMCs at different timepoints in their care and established TIL cultures and autologous tumour cell lines from available patient tumour biopsies. Whole-exome sequencing (WES) and RNA-sequencing (RNA-seq) analysis of the tumour cell lines, or the tumour biopsies, were performed and compared to normal control DNA obtained from the matched patient's PBMCs. These data were used to define each patient's six HLA class I alleles, detect patient-specific non-synonymous mutations

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