題目: ATR-mediated CD47 and PD-L1 up-regulation restricts radiotherapy-induced immune priming and abscopal responses

Abstract

Despite the wide use of radiation therapy (RT) in colorectal cancer, many patients experience progression at non-irradiated sites of disease. Thus, it is crucial to improve the abscopal effects of RT. Here, Hsieh et al. used mouse modeling and human cancer cell lines to show that RT increased the expression of CD47 and PD-L1 in a DNA repair signaling–dependent manner. Targeting CD47 and PD-L1 with anti-SIRPα and anti-PD-1, respectively, in combination with RT led to clearance of primary tumors and robust abscopal effects. This triple combination depended on host STING expression, leading to improved tumor cell phagocytosis and subsequent cross-priming of tumor antigen–specific T cells. Together, these data suggest that targeting immune checkpoints and phagocytosis during RT may help patients with colorectal cancer.

中文摘要

放射治療是現今癌症治療的主要方式之一，約一半的癌症患者在其療程中會接受某種形式的放射療法。過去研究顯示局部放療可促進免疫系統活化以攻擊遠端未受照射的腫瘤，但癌細胞可運用免疫逃脫機制抑制宿主免疫反應，導致放療之全身性療效目前仍不理想，而這背後的分子機轉目前尚不明朗。

本研究利用多種老鼠模型及人類癌症株系，發現癌細胞在放射治療後會利用 DNA 修復路徑來向上調控巨噬作用免疫檢查點 CD47 及 PD-L1 以躲避巨噬細胞攻擊，並利用長庚醫院組織銀行大腸直腸癌病患檢體，驗證放療後 CD47 表現量上升與較差之放射治療反應相關。

研究發現放療後給予 CD47 及 PD-L1 之受體 SIRPα 及 PD-1 抗體阻斷，可增強免疫系統對照射病灶及遠端腫瘤之清除能力，而此合併治療之療效是依靠宿主細胞之 STING 路徑活化，造成腫瘤吞噬作用增強及後續對 T 淋巴球抗原交互呈現功能提升，此研究顯示放療後合併巨噬作用免疫檢查點抑制劑可增進癌症放療後控制機率，可做為未來臨床試驗之重要理論基礎。