CUL3/SPOP complex prevents immune escape and enhances chemotherapy sensitivity of ovarian cancer cells through degradation of PD-L1 protein

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1. 簡述論文的概要與重大發現：

卵巢癌是最致命的婦科惡性腫瘤，卵巢癌患者容易復發和產生對化療抗藥性。研究證明，cisplatin 在卵巢癌的治療中起著至關重要的作用。免疫療法的介入對卵巢癌在內的不同癌症的治療而顯得備受關注；此篇文章中，作者通過生物信息學分析發現 CUL3 在卵巢癌組織中低表達，與卵巢癌患者的預後不良相關，也觀察到卵巢癌中 SPOP 減少。SPOP 是 Cullin-ring E3 連接酶的代表性底物識別亞基，在腫瘤發生和癌症進展中發揮雙重作用，SPOP 其高表達導致癌細胞增殖受到抑制。

作者團隊闡明了 CUL3 與其連接分子 SPOP 形成複合物，會促進 PD-L1 的泛素化和降解，導致 T 細胞增殖、活性和毒性增加，從而抑制卵巢癌細胞的免疫逃逸並減少卵巢癌細胞對 cisplatin 的抗藥性。

對論文內容的提問：

(1)經由 database 篩選過後有 20 個具有表達差異的 E3 ubiquitin ligase，當中除了 CUL3 是否有其他適合的標的物？

(2)對於 CUL3 對腫瘤的影響，其他 paper 有提出相反意見，對此後續亦須在多所討論研究。

2. 論文的缺點及評價：

此篇研究發現 CUL3-SPOP 複合物會降低 cisplatin 的抗藥性，以及影響 PDL1 的 stability，因而可以用為抑制免疫逃脫治療，也可當作預後指標，但其實際的影響機制可能需要更多的實驗來說明。

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ABSTRACT

Background Cancer immune escape is a main obstacle in designing effective anticancer therapeutic approaches. Our work was aimed to explore the function of cullin 3 (CUL3) in ovarian cancer cell immune escape and chemosensitivity.

Method Gain and loss of function assays were conducted to investigate the interactions among CUL3, speckle type POZ protein (SPOP) and programmed death ligand-1 (PD-L1) as well as their effects on ovarian cell malignant phenotypes and chemosensitivity. A mouse model of xenografted ovarian cells was further established for in vivo substantiation.

Result Poorly-expressed CUL3 and SPOP were found in ovarian cancer. Overexpression of CUL3 reduced malignant features as well as immune escape of ovarian cancer cells but enhanced chemosensitivity. Functionally, CUL3 degraded PD-L1 protein by forming complex with SPOP. Overexpression of CUL3 inhibited tumor formation and enhanced chemosensitivity of ovarian cancer cells in mice by degrading PD-L1 protein.

Conclusion All in all, CUL3/SPOP formed a complex to promote PD-L1 degradation to inhibit ovarian cancer cell immune escape and increase chemosensitivity, offering a therapeutic target for ovarian cancer treatment.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Immune system has been proved to be a crucial factor during cancer initiation and progression, including ovarian cancer.

WHAT THIS STUDY ADDS

⇒ Cullin 3/speckle type POZ protein formed a complex to promote programmed death ligand-1 degradation to inhibit ovarian cancer cell immune escape and increase chemosensitivity.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our current study offers a therapeutic target for ovarian cancer treatment.

BACKGROUND

Ovarian cancer ranks seventh among common cancer in women and eighth leading cause of cancer-related death, with 5-year survival rates less than 45%.[1] It has been well-characterized that the co-evolution of neoplastic cells and the adjacent microenvironment share close correlation with ovarian cancer progression.[2] Notably, most patients have ovarian cancer at advanced stage at the time of initial diagnosis, causing challenge for curing ovarian cancer.[3] Patients with refractory malignancies show different reaction in chemosensitivity to cisplatin, including ovarian cancer, and how resistance is resolved remains unknown.[4] In this regard, efforts are required to explore the mechanisms involved in ovarian progression for the development of novel therapeutic regimens for ovarian.

Cullin 3 (CUL3) gene encodes a key component of the E3 ubiquitin ligase complex and is capable of regulating proteasome degradation.[5] A previous report has highlighted the critical role of CUL3 in diverse processes, including autophagy, differentiation, and tumorigenesis.[6] It has been suggested that in ES2 and SKOV3 ovarian cancer cells, CUL3 depletion increased cisplatin induced cytotoxicity which could be antagonized by siCUL1.[7] Furthermore, CUL3-regulated ubiquitination of Beclin 1 has been demonstrated to inhibit autophagy and induce tumor progression in ovarian cancer.[8] More importantly, speckle type POZ protein (SPOP), a substrate recognition receptor for CUL3/RING type ubiquitin E3 complex, is capable of inhibiting proliferation and promoting apoptosis of human ovarian cancer cells by blockage of Hh signaling pathway, which provides a new approach for ovarian cancer treatment.[9 10]

Immune system has been proved to be a crucial factor during cancer initiation and progression, including ovarian cancer.[11] Ovarian cancer is an immunogenic tumor and immunotherapy is intensively required by targeting on the immune checkpoints.[12 13]