Aspirin promotes RSL3-induced ferroptosis by suppressing mTOR/SREBP-1/SCD1-mediated lipogenesis in *PIK3CA*-mutatnt colorectal cancer

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1. 簡述論文的概要與重大發現

   Colorectal cancer(CRC) 是世界嚴重的惡性癌症疾病，在所有癌症中發病率排名第三，死亡率排名第二。儘管自 2000 年以來因為新的靶向藥物或免疫檢查點抑製劑的開發與取得，對幫助 CRC 患者有很大進展，但是晚期或複發性的總體預後相對地仍不理想。

   一些研究已顯示阿司匹林可作為輔助治療癌症的一種藥物，主要抗癌的機制是抑制環氧合酶 (COX)和減少發炎相關物質的產生，也會抑制 NF-kappaB、Wnt/β-catenin，並影響 mTOR 信號途徑，導致癌細胞死亡，而死亡的方式有多種，而本篇會提到的是 Ferroptosis。Ferroptosis 是一種新發現的調節性細胞死亡形式，其主要特徵是鐵積累、氧化還原系統失衡和脂質過氧化 。

   而許多 Ferroptosis 的小分子標靶藥物，再多種癌症已被用做治療癌症的策略 。最近的證據顯示，Ferroptosis 也可作為 CRC 一種新的治療目標，所以本篇研究目的是聯合使用阿司匹林和鐵死亡誘導劑以治療 PIK3CA 突變型 CRC 提供了實驗證據的基礎。

2. 對論文內容的提問：

   在總結的部份時，最後的圖的 RSL-3(Ferroptosis inducer)不會去影響 mTOR 那條路徑，可是在實驗的方式中卻有去證明 mTOR 跟 RSL-3 的關係?

   在圖 4 的時候 SCD1 和 ACC 兩個基因(跟脂質有關的基因)mRNA 都有下降且 ACC 下降的比例可能比 SCD1 還要高，那為什麼不拿 SCD1 去做實驗呢?

3. 論文的缺點與評論：

   從此篇研究中發現阿司匹林可促進攜帶 PI3K 突變的 CRC 癌細胞的鐵死亡，為未來的鐵死亡途徑作為誘導癌症死亡之療法提供了基礎的研究。如果以後證實能在人體上使用，那將會是治療費用上很大的突破。

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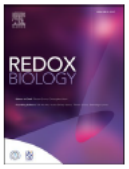

Aspirin promotes RSL3-induced ferroptosis by suppressing mTOR/SREBP-1/SCD1-mediated lipogenesis in *PIK3CA*-mutatnt colorectal cancer

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ABSTRACT

Ferroptosis, a new form of regulated cell death triggered by the iron-dependent peroxidation of phospholipids, is associated with cellular metabolism, redox homeostasis, and various signaling pathways related to cancer. Aspirin is a widely used non-steroidal anti-inflammatory drug (NSAID) and has been reported to show therapeutic benefit in cancers harboring oncogenic *PIK3CA*, which encodes the catalytic p110α subunit of phosphoinositide 3-kinase (PI3K). In this study, we found that aspirin sensitized cancer cells harboring oncogenic activation of *PIK3CA* to ferroptosis induction. Mechanistically, aspirin inhibited protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signaling, suppressed downstream sterol regulatory element-binding protein 1 (SREBP-1) expression, and attenuated stearoyl-CoA desaturase-1 (SCD1)-mediated lipogenesis of monounsaturated fatty acids, thus promoting RSL3-induced ferroptosis in colorectal cancer (CRC) cells. Moreover, genetic ablation of SREBP-1 or SCD1 conferred cancer cells greater sensitivity to ferroptosis induction. Conversely, ectopic expression of SREBP-1 or SCD1 restored ferroptosis resistance in CRC cells and abolished the effect of aspirin on RSL3-induced cytotoxicity. Additionally, the synergistic effects of aspirin and RSL3 were confirmed in a xenograft mouse model. The combined use of aspirin and RSL3 resulted in significant tumor suppression. Our work demonstrated that aspirin enhanced the cytotoxic effect of RSL3 in *PIK3CA*-mutant cancers, and the combination of aspirin and ferroptosis inducer displayed promising therapeutic effects in cancer treatment.

1. Introduction

CRC is a serious health burden worldwide, ranking third in incidence and second in mortality among all cancers [1]. As the dreadful disease becomes symptomatic at an advanced stage, primary prevention and organized screening programs are of great importance [2–4]. However, once the early critical stage is missed, CRC is difficult to control and caused approximately 935,000 deaths last year [5]. Despite great progress, such as the development of new targeted drugs [6] or immune checkpoint inhibitors [7,8] since the 2000s, the overall prognosis of patients with advanced or recurrent CRC is relatively unsatisfactory [9].

Aspirin (acetylsalicylic acid) is the cornerstone of modern therapies because of its important role in analgesia and cardiovascular prophylaxis [10,11]. In addition, epidemiological studies indicate that daily use of low-dose aspirin is associated with a reduced risk of cancer development [12,13], suggesting that it can be used as part of adjuvant therapy. Inhibition of cyclooxygenase (COX) enzymes, particularly COX-2, and reduced production of inflammatory mediators are thought to be the main mechanisms of tumor control [14]. In addition, other COX-independent mechanisms, such as inhibition of NF-kappaB [15], Wnt/beta-catenin [16,17], and the mTOR signaling pathway [18,19] are involved. A recent study showed that aspirin use is associated with a significant improvement in survival in patients with mutant *PIK3CA* CRC but not in their wild-type counterparts [20], suggesting that the benefits of aspirin treatment vary in patients with different *PIK3CA* statuses.

Ferroptosis is a newly discovered form of regulated cell death characterized mainly by iron accumulation, redox system imbalance and lipid peroxidation [21]. In mammalian cells, the system xc/glutathione peroxidase 4 (GPX4) axis plays a crucial role in limiting lipid

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