Dysregulated cholesterol homeostasis results in resistance to ferroptosis increasing tumorigenicity and metastasis in cancer

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1. 簡述論文概要與重大發現:

高膽固醇血症和血脂異常與乳癌的風險增加有關，並且與患者的預後不良有關。我們確定長期暴露於 27 羥基膽固醇(27HC)有助於細胞攝取和合成脂質，而這些細胞也表現出顯著的致腫瘤性與轉移能力。值得注意的是，累積的脂質對細胞施加的代謝壓力需要 GPX4(抗氧化酶)的表達，以防止細胞走向 ferroptosis，而我們發現，對 ferroptosis 產生抗性是轉移細胞的一個特徵，並進一步證明 Knockdown GPX4 減弱了 27HC resistance 細胞的致腫瘤性和轉移能力。這些發現強調了 Ferroptosis 在腫瘤生長和轉移中的重要性，並表明血脂異常或高膽固醇血症會通過選擇對 Ferroptosis 有抗性的細胞來影響癌症的發病機制。

2. 對論文內容的疑問:

在本篇研究中，作者觀察到 27HC resistance 的細胞會透過從培養基中攝取脂質或是增加脂質的合成來抑制 27HC 抗增殖的能力，但癌細胞是如何抵抗 27HC 抑制膽固醇合成來達到增加脂質的攝取的能力，這個路徑目前還不清楚。

Statin 為目前最常見的降膽固醇藥物，目前已有研究顯示 statin 會透過增加對於 GPX4 的需求來降低膽固醇，而此種機制與 27HC 類似，那在本篇研究中發現，將細胞長期置於 27HC 的環境下會使細胞產生抗性，那如果是長期服用 statin 會不會也產生一樣的現象?

3. 論文的缺點、評論:

在本篇研究中，作者證實了 27HC 可透過抑制膽固醇的合成來抑制 ER negative 的乳癌細胞增生，但長期使用 27HC 來治療反而會導致細胞產生抗藥性，造成反效果，雖然在本研究中已發現能利用 GPX4 以及 ferroptosis 的機制來克服，但目前尚未應用於人體，希望未來有機會應用在臨床治療上。

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Dysregulated cholesterol homeostasis results in resistance to ferroptosis increasing tumorigenicity and metastasis in cancer

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Hypercholesterolemia and dyslipidemia are associated with an increased risk for many cancer types and with poor outcomes in patients with established disease. Whereas the mechanisms by which this occurs are multifactorial we determine that chronic exposure of cells to 27-hydroxycholesterol (27HC), an abundant circulating cholesterol metabolite, selects for cells that exhibit increased cellular uptake and/or lipid biosynthesis. These cells exhibit substantially increased tumorigenic and metastatic capacity. Notably, the metabolic stress imposed upon cells by the accumulated lipids requires sustained expression of GPX4, a negative regulator of ferroptotic cell death. We show that resistance to ferroptosis is a feature of metastatic cells and further demonstrate that GPX4 knockdown attenuates the enhanced tumorigenic and metastatic activity of 27HC resistant cells. These findings highlight the general importance of ferroptosis in tumor growth and metastasis and suggest that dyslipidemia/hypercholesterolemia impacts cancer pathogenesis by selecting for cells that are resistant to ferroptotic cell death.

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