Nitroxoline suppresses metastasis in bladder cancer via EGR1/circNDRG1/miR-520h/smad7/EMT signaling pathway

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論文的概要與重大發現

Bladder cancer 是全球最常見和最致命的癌症之一。Nitroxoline,是一種廣泛使用來治療尿路感染的口服抗生素。最近的研究證明，Nitroxoline 可以抑制許多癌症的 progression 和 metastasis，尤其是 bladder cancer。然而,Nitroxoline 抗腫瘤活性的機制尚不清楚。作者使用 CircRNA microarray 來探索 bladder cancer cell lines 中 Nitroxoline 介導的 CircRNA expression profile, 並且應用 Transwell assay 和 wound-healing assay 來評估轉移能力。另外用 ChIP assay 來證明 promotor 和轉錄因子的結合。進行 RNA pull down assay 以探索 circRNA 和 microRNA 之間的關聯性。結果作者發現 circNDRG1(has_circ_0085656)在 Transwell assay 和 wound-healing assay 中可以抑制膀胱癌的轉移。 ChIP 分析也顯示 circNDRG1 通過結合宿主基因 NDRG1 的啟動子而受到轉錄因子 EGR1 的調控。 RNA-pulldown assay 證明 circNDRG1 激活 miR-520h 導致 smad7 的過表達，smad7 是 EMT 的 negative regulation protein。在本篇研究結果顯示，Nitroxoline 可能通過調控 EGR1/circNDRG1/miR-520h/smad7/EMT 信號通路抑制 bladder cancer metastasis。

對論文內容的疑問

作者在篩選 mir-520h 的 target gene 時用了四個 database, 但仍有 172 個可能的 target gene, 最後是選用之前研究的 smad7, 這代表也可能有其他 mir-520h 的 target gene, 但作者並未多做說明。

論文的缺點與評論

現在許多研究漸漸使用多個資料庫來尋找可能的 pathway 和 target gene 等等, 這是基於科技發達和前人研究心血建立的資料, 優點是可以達到事半功倍的效果, 也可提高實驗成功機率, 缺點是也可能被限制住而遺漏了其他可能性, 綜觀目前 paper 大多以研究出新的 pathway 作為發表, 也希望能有一些 paper 是證明原本以為可能的 pathway 但是最後是失敗的, 這樣在研究上也許可以避免許多冤枉路。

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Research Paper

Nitroxoline suppresses metastasis in bladder cancer via EGR1/circNDRG1/miR-520h/smad7/EMT signaling pathway

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Abstract

Bladder cancer is one of the most common and deadly cancer worldwide. Current chemotherapy has shown limited efficacy in improving outcomes for patients. Nitroxoline, an old and widely used oral antibiotic, which was known to treat for urinary tract infection for decades. Recent studies suggested that nitroxoline suppressed the tumor progression and metastasis, especially in bladder cancer. However, the underlying mechanism for anti-tumor activity of nitroxoline remains unclear.

Methods: CircRNA microarray was used to explore the nitroxoline-mediated circRNA expression profile of bladder cancer lines. Transwell and wound-healing assay were applied to evaluate the capacity of metastasis. ChIP assay was chosen to prove the binding of promotor and transcription factor. RNA-pulldown assay was performed to explore the sponge of circRNA and microRNA.

Results: We first identified the circNDRG1 (has_circ_0085656) as a novel candidate circRNA. Transwell and wound-healing assay demonstrated that circNDRG1 inhibited the metastasis of bladder cancer. ChIP assay showed that circNDRG1 was regulated by the transcription factor EGR1 by binding the promotor of host gene NDRG1. RNA-pulldown assay proved that circNDRG1 sponged miR-520h leading to the overexpression of smad7, which was a negative regulatory protein of EMT.

Conclusions: Our research revealed that nitroxoline may suppress metastasis in bladder cancer via EGR1/circNDRG1/miR-520h/smad7/EMT signaling pathway.

Key words: Bladder cancer, nitroxoline, metastasis circNDRG1, microRNA

Introduction

Bladder cancer is one of the most common cancer around the world, with an estimated 81,400 new cases and 17,980 new deaths in United States in 2020 [1]. Bladder cancer is staged by the measure of depth of bladder wall invasion, including non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC) [2, 3]. NMIBC accounts for about 80% of all newly cases. Bacille Calmette-Guérin (BCG) is the recommended treatment after surgery [4]. However, some patients may not benefit from the treatment of BCG for drug resistance or unbearable side-effect [5]. Therefore, it is urgent and important to explore new drug candidates for the treatment of bladder cancer.

Nitroxoline is an antibiotic and known to treat for urinary tract infection [6]. Recently, several studies