The NALCN channel regulates metastasis and nonmalignant cell dissemination

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(1)簡述論文的重大發現

作者主要研究癌症轉移的相關機轉，他們發現 NALCN (鈉離子通道之一, 主要為來維持 membrane potential) 的突變與減少跟癌症轉移有相關性。接著利用 knockout mouse 的動物實驗證實：knockout NALCN 之後，小鼠體內循環腫瘤細胞(CTC)及轉移癌都會大幅增加。然而本篇最重要發現是：除了癌症細胞，正常的腸道細胞也會脫落(shedding) 跑到血液中乃至散布到其他器官。

(2)對論文內容的疑問

本研究證實了在 NALCN channel 剔除(knockout)之後會促進癌症生長與轉移。然而大部分癌症都是 NALCN 產生突變，所突變的 NALCN 或許仍保有部分功能，利用完全剔除基因的老鼠實驗也許不能完全印證。

(3)論文的缺點與評論

在缺點上，本篇主要的內容以動物實驗為主，相關的細胞功能性實驗僅有證明 knowndown NALCN 之後會降低 membrane potential，其他的功能性實驗付之闕如，因此我們無法得知改變 membrane potential 之後影響細胞的那些功能造成轉移。

目前的癌症轉移理論上，一般都認為先有原發癌症，接著腫瘤長大侵犯血管或淋巴管，部分癌細胞出現 EMT 型態改變，而得以脫離原發腫瘤順著血流轉移到其他器官。然而臨床上，大約有 3% 病患診斷癌症時找不到原發癌症。有一些理論嘗試解釋這個現象,但本研究提供一個強力證據: 正常的表皮細胞在尚未形成癌症之前，就有可能離開原生組織散布到其他器官，最終產生癌症。此一發現可能改變了我們對 metastasis 的認知。

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The NALCN channel regulates metastasis and nonmalignant cell dissemination

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We identify the sodium leak channel non-selective protein (NALCN) as a key regulator of cancer metastasis and nonmalignant cell dissemination. Among 10,022 human cancers, *NALCN* loss-of-function mutations were enriched in gastric and colorectal cancers. Deletion of *Nalcn* from gastric, intestinal or pancreatic adenocarcinomas in mice did not alter tumor incidence, but markedly increased the number of circulating tumor cells (CTCs) and metastases. Treatment of these mice with gadolinium—a NALCN channel blocker—similarly increased CTCs and metastases. Deletion of *Nalcn* from mice that lacked oncogenic mutations and never developed cancer caused shedding of epithelial cells into the blood at levels equivalent to those seen in tumor-bearing animals. These cells trafficked to distant organs to form normal structures including lung epithelium, and kidney glomeruli and tubules. Thus, NALCN regulates cell shedding from solid tissues independent of cancer, divorcing this process from tumorigenesis and unmasking a potential new target for antimetastatic therapies.

Most patients with cancer die as a result of metastasis[1], the process by which cancer cells spread from the primary tumor to other organs in the body[2]. Blocking metastasis could markedly improve the survival of patients with cancer, but how this process is triggered within the complex cascade of tumorigenesis remains unclear[3].

Because metastasis is thought to be a wholly abnormal process, restricted to malignant tissues, attention has focused on identifying genetic mutations as drivers of cancer metastasis. Although this research has unmasked genes that promote metastasis in mouse models and humans, including a variety of ion channels that induce a metastasis-like phenotype by altering the transmembrane voltage to induce changes in gene transcription[4–6], so far no recurrent metastasis-specific mutations have been identified[2,3,7].

Other cell functions implicated in the metastatic cascade include 'stem cell-like' multipotency and plasticity. Stem cell capacity has been ascribed to metastatic cancer cells because of their ability to reconstitute heterogenous malignant cell populations as metastatic tumors[8,9]. Epithelial mesenchymal transition (EMT)[2]—a type of cellular plasticity displayed during normal gastrulation and tissue healing—is also an established feature of the metastatic cascade[2,10]. What remains unclear is how cancers 'hijack' these normal cell functions to enable metastasis.

Here, we identify a single ion channel, NALCN, as a key regulator of epithelial cell trafficking to distant tissues. NALCN is responsible for the background sodium leak conductance that maintains the resting membrane potential. It regulates key functions in excitable tissues, for example, respiration and circadian rhythms[11–13], and gain-of-function mutations in the gene are associated with neurological disorders[14]. However, little is known about the role of NALCN in nonexcitable tissues. We show that NALCN regulates the release of malignant and normal epithelial cells into the blood, and their trafficking to distant sites where they form metastatic cancers, or apparently normal tissues, respectively. We thereby demonstrate that the metastatic cascade can be triggered and operate independent of tumorigenesis. These observations have profound implications for understanding epithelial cell trafficking in health and disease and identify a novel target for antimetastatic therapies.

Results

NALCN loss-of-function in cancer. We showed previously that Prominin1 (PROM1) marks basal stem cells in gastric antral glands and that their lineage forms adenocarcinomas in $Prom1^{CreERT2/LacZ}$;$Kras^{G12D}$;$Trp53^{Flx/Flx}$ ($P1^{KP}$) mice[15]. PROM1$^+$, but not PROM1$^-$, cells isolated from $P1^{KP}$ gastric adenocarcinomas ($P1^{KP}$-GAC) propagated these tumors as allografts, suggesting that PROM1$^+$ $P1^{KP}$-GAC cells are the malignant counterparts of antral gland basal stem cells (Extended Data Fig. 1). To understand how antral gland basal stem cells are corrupted during transformation, we compared their transcriptomes with those of PROM1$^+$ $P1^{KP}$-GAC cells. Ion channels

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