cGAS–STING drives the IL-6-dependent survival of chromosomally instable cancers

Christy Hong, Michael Schubert, Andréa E. Tijhuis, *et al.*

Student: Yu-Ting Lee
Advisor: Michael Chan Date : 2022/11/25

(1)簡述論文的重大發現

cGAS/STING pathway 最早是從 DNA 病毒感染所發現。當細胞被病毒感染，viral DNA 進入細胞質而被 cGAS 所捕獲，進而誘發發炎反應。除了病原菌的 DNA，DNA 傷害產生的 self DNA 或 mitochondrial DNA 進入細胞質中也會出現一樣的反應。 Chromosomally instablility (CIN)是指染色體在分裂過程中無法維持其形態或結構，導致 Daughter cells 中染色體破裂或是染色體數量改變，是癌症很重要的一個特色。

過往研究中已證實 CIN 的癌症細胞容易出現 DNA 破壞，核內的 DNA 釋出到細胞質。細胞質內的 dsDNA 可以與 cGAS 結合，接著活化在 ER 或 Golgi 上的 STING protein 進而誘發細胞凋亡以及 Type I interferon.

研究團隊在進行 knockout cGAS 的細胞實驗中，原本預期 knockout cGAS 之後的細胞，其 Apoptosis 會中止，然而卻觀察到相反的結果。研究團隊大膽假設 cGAS/STING 路徑活化除了誘發 Apoptosis 及 innate immunity 之抗癌功能外，同時也有促進癌細胞生長的反面作用。

本研究最後證實，cGAS/STING 路徑也會活化 IL6 receptor, STAT3 及 NF-kB non-canonical pathway.此路徑與維持癌細胞生長有關.在動物實驗中進一步證實，使用 IL-6 receptor 的抑制劑可明顯壓制癌症生長

(2)對論文內容的疑問

本研究證實了在 CIN cancer 中，cGAS－STING 會驅動 IL6 receptor 路徑，而維持癌細胞生長。研究團隊沒有進一步釐清與說明的是 cGAS－STING 活化之後，細胞選擇 apoptosis 或是 survival 的關鍵為何 ？ 或許未來值得深究。

(3) 論文的缺點與評論

在這篇研究中，透過十分嚴謹的邏輯與步驟將 cGAS/STING pathway 與 IL6 receptor, STAT3 及 NF-kB non-canonical pathway 連結起來，其大膽假設與邏輯推論的過程值得我們學習。研究結果與 CIN 多出現在癌症晚期之現象提供連結，另外價值就是 IL6 receptor 抑制劑(抗發炎藥物,治療自體免疫疾病及新冠肺炎產生的免疫風暴）居然可以治療 CIN 癌症，此發現違反目前的主流想法。

在缺點上，作者認為 CIN 活化 cGAS/STING 是透過 cytosolic DNA，所以沒有做太多的琢磨。事實上不只 CIN, 有許多種方式也可以產生 cytosolic DNA 進而活化 cGAS/STING, 但尚未有人提出相同 cGAS－STING 有維持癌細胞生長的觀察或研究。CIN 是否還有其他機制活化 cGAS/STING 將來可以深究。

Article

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Christy Hong[1], Michael Schubert[1,6,7], Andréa E. Tijhuis[1,7], Marta Requesens[1,2,7], Maurits Roorda[3], Anouk van den Brink[1], Lorena Andrade Ruiz[1], Petra L. Bakker[1], Tineke van der Sluis[4], Wietske Pieters[5], Mengting Chen[3], René Wardenaar[1], Bert van der Vegt[4], Diana C. J. Spierings[1], Marco de Bruyn[2,3]✉, Marcel A. T. M. van Vugt[3]✉ & Floris Foijer[1]✉

Chromosomal instability (CIN) drives cancer cell evolution, metastasis and therapy resistance, and is associated with poor prognosis[1]. CIN leads to micronuclei that release DNA into the cytoplasm after rupture, which triggers activation of inflammatory signalling mediated by cGAS and STING[2,3]. These two proteins are considered to be tumour suppressors as they promote apoptosis and immunosurveillance. However, cGAS and STING are rarely inactivated in cancer[4], and, although they have been implicated in metastasis[5], it is not known why loss-of-function mutations do not arise in primary tumours[4]. Here we show that inactivation of cGAS–STING signalling selectively impairs the survival of triple-negative breast cancer cells that display CIN. CIN triggers IL-6–STAT3-mediated signalling, which depends on the cGAS–STING pathway and the non-canonical NF-κB pathway. Blockade of IL-6 signalling by tocilizumab, a clinically used drug that targets the IL-6 receptor (IL-6R), selectively impairs the growth of cultured triple-negative breast cancer cells that exhibit CIN. Moreover, outgrowth of chromosomally instable tumours is significantly delayed compared with tumours that do not display CIN. Notably, this targetable vulnerability is conserved across cancer types that express high levels of IL-6 and/or IL-6R in vitro and in vivo. Together, our work demonstrates pro-tumorigenic traits of cGAS–STING signalling and explains why the cGAS–STING pathway is rarely inactivated in primary tumours. Repurposing tocilizumab could be a strategy to treat cancers with CIN that overexpress IL-6R.

CIN is poorly tolerated by untransformed cells, yet occurs frequently in cancer, which suggests that cancer cells have developed adaptations to overcome aneuploidy-imposed stresses that include proteotoxic stress, metabolic stress and an inflammatory response[6]. Modulating these stress pathways may therefore provide an Achilles' heel of cancers with a CIN phenotype. Indeed, exacerbation of proteotoxic stress or metabolic stress can be more toxic to aneuploid cells than to euploid cells in vitro[7]. However, effective approaches to exploit CIN-induced inflammation have not yet been identified and none has been validated in vivo.

Cells with CIN depend on cGAS and STING

To explore the effect of modulation of the inflammatory response in cells displaying CIN, we investigated the cGAS–STING pathway in triple-negative breast cancer (TNBC) cells. To induce micronuclei formation and to activate cGAS–STING signalling in human BT549 TNBC cells, cells were treated with the MPS1 inhibitor reversine[8] or the WEE1 inhibitor AZD1775 (ref. [9]). Both treatments significantly increased the frequency of mitotic abnormalities (Fig. 1a,b and Extended Data Fig. 1a) and micronuclei (Extended Data Fig. 1b,c). MPS1 inhibition mostly produced micronuclei that included centromeres, which reflects whole chromosome missegregation events. By contrast, WEE1 inhibition mostly produced micronuclei without centromeres (Extended Data Fig. 1d,e), which indicates that structural chromosomal abnormalities resulted from WEE1-inhibition-induced replication stress[10] (Extended Data Fig. 1f). Approximately half of the micronuclei were positive for cGAS (Extended Data Fig. 1b,c), which coincided with strong activation of cGAS signalling. This was quantified by the steep increase in both intracellular and extracellular cGAMP (Extended Data Fig. 1g), which is a direct readout of cGAS activation[11]. In line with this notion, MPS1 inhibition also promoted perinuclear localization of STING (Extended Data Fig. 1h,i), a downstream player of cGAS signalling that is activated by cGAMP[12,13]. Moreover, MPS1 inhibition led to increased phosphorylation

[1]European Research Institute for the Biology of Ageing, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands. [2]Department of Obstetrics and Gynaecology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands. [3]Department of Medical Oncology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands. [4]Department of Pathology and Medical Biology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands. [5]Division of Tumor Biology and Immunology, Netherlands Cancer Institute, Amsterdam, The Netherlands. [6]Present address: Division of Cell Biology and Cancer Genomics Center, Netherlands Cancer Institute, Amsterdam, The Netherlands. [7]These authors contributed equally: Michael Schubert, Andréa E. Tijhuis, Marta Requesens. ✉e-mail: m.de.bruyn@umcg.nl; m.vugt@umcg.nl; f.foijer@umcg.nl