邵峰团队揭示细胞焦亡在肿瘤化疗中发挥重要作用

Feng Shao'team revealed the Chemotherapy drugs induce pyroptosis through caspase-3 cleavage of a gasdermin

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【Nature 系列】7 月 6 日，北京生命科学研究所的邵峰院士带领团队在《Nature》期刊发表了最新研究成果，揭示了一种 Gasdermin 家族蛋白——GSDME 引起细胞焦亡的机制，并证实这一焦亡通路是部分化疗药物产生毒副作用的重要原因之一，对于癌症化疗研究和临床应用具有重要的指导意义。

细胞焦亡（pyroptosis 或 pyroptotic cell death）或炎性坏死是一种程序性细胞坏死，是机体重要天然免疫反应。具体表现为细胞不断胀大直至细胞膜破裂，导致细胞内容物的释放进而激活强烈的炎症反应 。

最新研究发现，化疗时，细胞内的 caspase-3 会剪切 GSDME，使其释放 GSDME-N 片段造成细胞膜穿孔，从而诱导细胞发生焦亡。考虑到 GSDME 在正常细胞广泛表达，当敲除 GSDME 的健康小鼠接受化疗药物后，其表现出的化疗副作用（包括组织损伤和体重减轻等）相比于野生型小鼠会显著减轻。这意味着，由 caspase-3、GSDME 介导的细胞焦亡是化疗对正常组织造成副作用的关键机制。

相比之下，GSDME 蛋白在大多数类型的癌细胞中均不表达。只有表达了 GSDME 的癌细胞才会被化疗药物或 TNFα 诱导进入细胞焦亡。在许多不表达或表达极少 GSDME 蛋白的癌细胞中，GSDME 基因的启动子区域被甲基化，使其处于转录抑制状态。如果对其施以 DNA 甲基化酶抑制剂 decitabine，则会上调 GSDME 蛋白的水平，增加化疗药物对癌细胞的杀伤力。

该研究发现由Gasdermin家族蛋白GSDME介导的细胞焦亡很可能是传统化疗药物产生毒副作用的重要原因，为癌症治疗提供了新思路，这也是首次展示细胞焦亡在天然免疫之外的生理病理过程中发挥重要功能；同时该研究成果还发现 caspase-3 也可以（通过活化 GSDME）诱导细胞坏死（焦亡），打破了 caspase-3 激活必然导致细胞凋亡的经典概念。

Chemotherapy drugs induce pyroptosis through caspase-3 cleavage of a gasdermin

化疗药物造成由 caspase-3、GSDME 介导的细胞焦亡

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Pyroptosis is a form of cell death that is critical for immunity. It can be induced by the canonical caspase-1 inflammasomes or by activation of caspase-4, -5 and -11 by cytosolic lipopolysaccharide1, 2, 3. The caspases cleave gasdermin D (GSDMD) in its middle linker to release autoinhibition on its gasdermin-N domain, which executes pyroptosis via its pore-forming activity4, 5, 6, 7, 8, 9. GSDMD belongs to a gasdermin family that shares the pore-forming domain4, 6, 10. The functions and mechanisms of activation of other gasdermins are unknown. Here we show that GSDME, which was originally identified as DFNA5 (deafness, autosomal dominant 5)11, can switch caspase-3-mediated apoptosis induced by TNF or chemotherapy drugs to pyroptosis. GSDME was specifically cleaved by caspase-3 in its linker, generating a GSDME-N fragment that perforates membranes and thereby induces pyroptosis. After chemotherapy, cleavage of GSDME by caspase-3 induced pyroptosis in certain GSDME-expressing cancer cells. GSDME was silenced in most cancer cells but expressed in many normal tissues. Human primary cells exhibited GSDME-dependent pyroptosis upon activation of caspase-3 by chemotherapy drugs. Gsdme−/− (also known as Dfna5−/−) mice were protected from chemotherapy-induced tissue damage and weight loss. These findings suggest that caspase-3 activation can trigger necrosis by cleaving GSDME and offer new insights into cancer chemotherapy.