

# 低氧/厌氧产品应用案例——胰腺癌

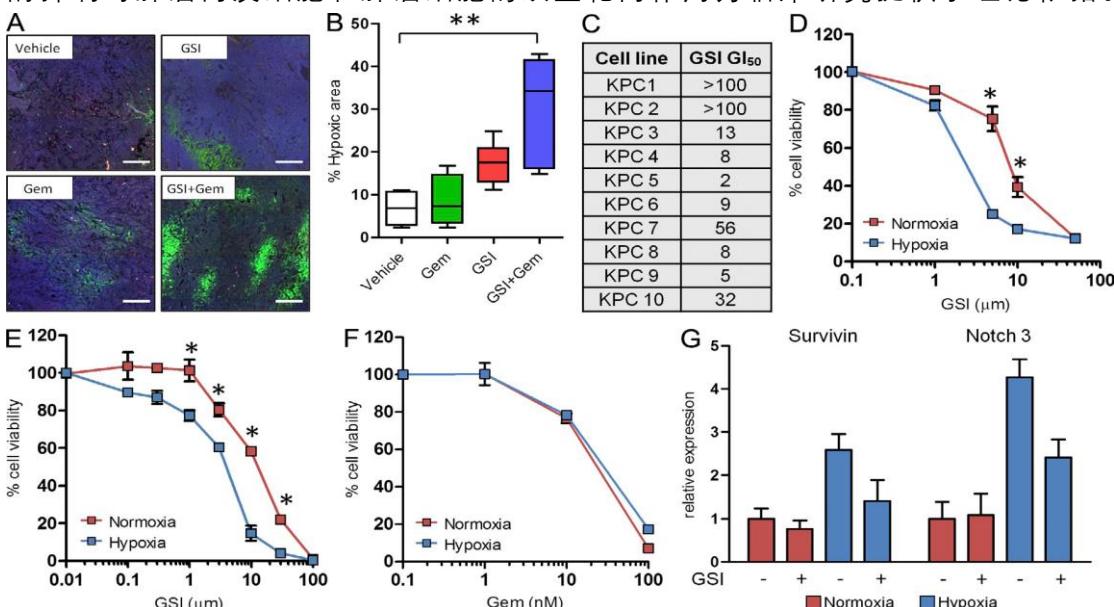
文章题目: Gamma secretase inhibition promotes hypoxic necrosis in mouse pancreatic ductal adenocarcinoma

## 抑制分泌酶的分泌促进小鼠胰腺导管腺癌低氧性坏死

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工作站使用情况: Ruskinn, invivo2 500, 1% O<sub>2</sub> and 5% CO<sub>2</sub>

**主要内容:** Notch 通路拮抗剂已被证明可以预防小鼠模型中胰腺癌前病变的进展，但尚未确定其对已建立的 PDA 肿瘤的潜在益处。本文证明γ分泌酶抑制剂 MRK003 在晚期 PDA 的 KPC 小鼠模型中有效抑制瘤内 Notch 信号。虽然 MRK003 单药治疗不能延长 KPC 小鼠的寿命，但 MRK003 联合化疗药物吉西他滨延长了小鼠的生存期，可联合杀死肿瘤内皮细胞，协同促进广泛的缺氧坏死。这些结果表明 PDA 的血管性质可以作为一种治疗易感性，而 γ 分泌酶抑制对肿瘤内皮细胞和肿瘤细胞的双重靶向作用为临床研究提供了理论依据。



**Figure 5 : Treatment-induced hypoxia acutely sensitizes tumor cells to MRK003.** (A) Representative immunofluorescence images of pimonidazole hydrochloride (Hypoxyprobe-1) staining with areas of hypoxia shown in bright green after 3 d of treatment. (B) Levels of hypoxia in tumors treated with the combination treatment (n=6) compared with vehicle (n=4; \*\*, P=0.006) and gemcitabine (n=4; P=0.02) cohorts. Combination treatment was compared with GSI (n=6; P=0.07). GSI treatment was compared with vehicle (P=0.01). (C) A panel of 10 KPC cell lines were tested to determine the GI<sub>50</sub> values when treated with GSI under normoxia (units=μM). (D) KPC cell lines were examined for effects of GSI under normoxic and hypoxic conditions. The graph shown is representative of 10 cell lines. (E) Human PDA cells were examined for effects of GSI under normoxic and hypoxic conditions. The graph shown is representative of the HPAF cell line. This experiment was performed in triplicate on two separate occasions (\*, P < 0.001). (F) KPC cell lines were examined for the cytotoxic activity of gemcitabine under normoxic and hypoxic conditions. (G) qRT-PCR of survivin and Notch3 under hypoxia, and after incubation with MRK003.

低氧(1% O<sub>2</sub>)条件下,GSI+GEM处理的KPC小鼠肿瘤缺氧显著增加，而对照组缺氧几乎无法检测到(A,B);而与常氧(20.9%O<sub>2</sub>)相比,低氧下MRK003(γ 分泌酶抑制剂)对KPC肿瘤细胞(D,毒性增加5倍)和人胰腺癌细胞(E)的毒性均明显增加，且明显降低了Survivin和Notch3等几种NICD靶基因的mRNA表达(G),但GEM对PDA细胞株的细胞毒性敏感性却几乎没有变化(F),。

PDA: 胰腺导管腺癌

NICD: NICD可转位到细胞核，激活Notch靶基因的转录。

GSI和GEM: 分泌酶抑制剂和吉西他滨。

Vehicle: 赋形剂处理，赋形剂对照组小鼠要注射除主要活性成分以外的所有东西。



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