華中農業大學
HUAZHONG AGRICULTURAL UNIVERSITY

Synthetic dosage lethality in the human metabolic network is highly predictive of tumor growth and cancer patient survival

人类代谢网络合成剂量致死对肿瘤生长及癌症患者存活进行高效预测

报告人: 谈自主
学院：生命科学技术学院

SDL：通过两个基因之间的相互作用（基因A低表达，基因B 超表达）使细胞致死

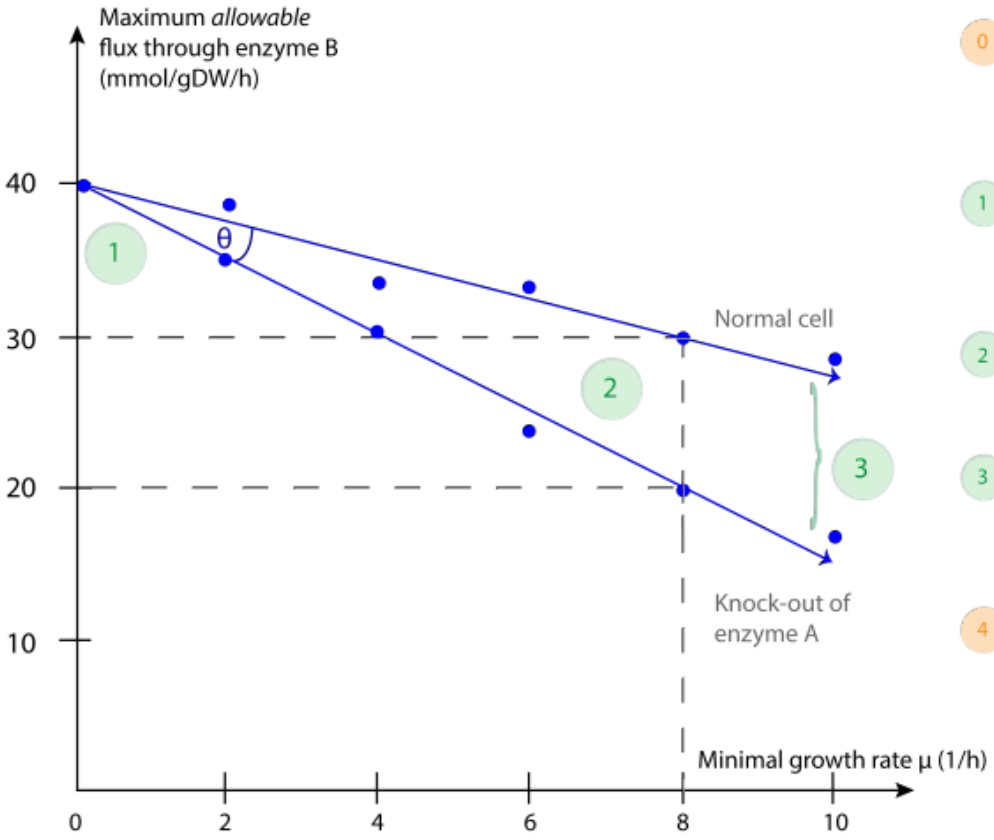
method：敲除基因A，逐渐增加基因B的表达量，比较与正常细胞的生长情况

reason:致癌基因对于细胞的生长和功能是必须的，因此很难直接对致癌基因进行改造，但可以通过改造与致癌基因具有SDL效应的相关基因，且这些基因对于细胞的生长是非必须的，从而达到抑制癌细胞的生长

- 1，识别剂量致死效应
- 2，癌细胞对SDL的防御
- 3，SDL对肿瘤细胞大小的影响
- 4，SDL增加病人的存活率
- 5，SDL的累积效应
- 6，SDL的类型

识别剂量致死效应（IDLE）

1. 对于给定的某对基因（AB），计算野生型的最大生长速率，然后计算敲除基因A后的最大生长速率。
2. 在这两种生长模式下，分别测定基因B的表达量
3. 从0开始逐步增加生长速率至最大生长速率（共10步），测定每次增加时，基因B的表达量
4. 若随着生物量的增加，基因B的表达量降低，则可通过增加基因B的表达量，从而达到抑制细胞生长的作用



0 Create a metabolic model *m* and a metabolic model *m'*, in which a specific enzyme A is knocked out (i.e. allowable flux = 0). Compute the maximum growth rate μ_{max} with FBA.

1 For *m* and *m'*, set the minimum growth rate = 0 and the maximum growth rate = μ_{max}. Now compute the maximum allowable flux through enzyme B.

2 Increase the minimal growth rate (here using 6 steps) in both models and again compute the maximum allowable flux through B.

3 The angle θ measures the vulnerability of the growth rate to an increased flux through enzyme B in the knock-out cell, compared to the normal cell.

4 At the same growth rate (μ = 8 1/h), the maximum allowable flux through enzyme B is lower in the knock-out cell, compared to the normal cell. Therefore, this growth rate can only be reached when the flux through enzyme B is ≤ 20 mmol/gDW/h. Enzyme pairs (A, B) are considered a "high-impact" SDL pair, when θ > 15°.

Figure S1: The IDLE method. IDLE measures the 'vulnerability' of the growth rate to a flux increase through enzyme B. This reference model *m* is compared with a model *m'* that computes this vulnerability when additionally enzyme A is knocked out. This difference can be quantified as the angle Θ between the vectors in the *m* and *m'* models. To accommodate for differences in flux scaling, the computation is done using relative differences.

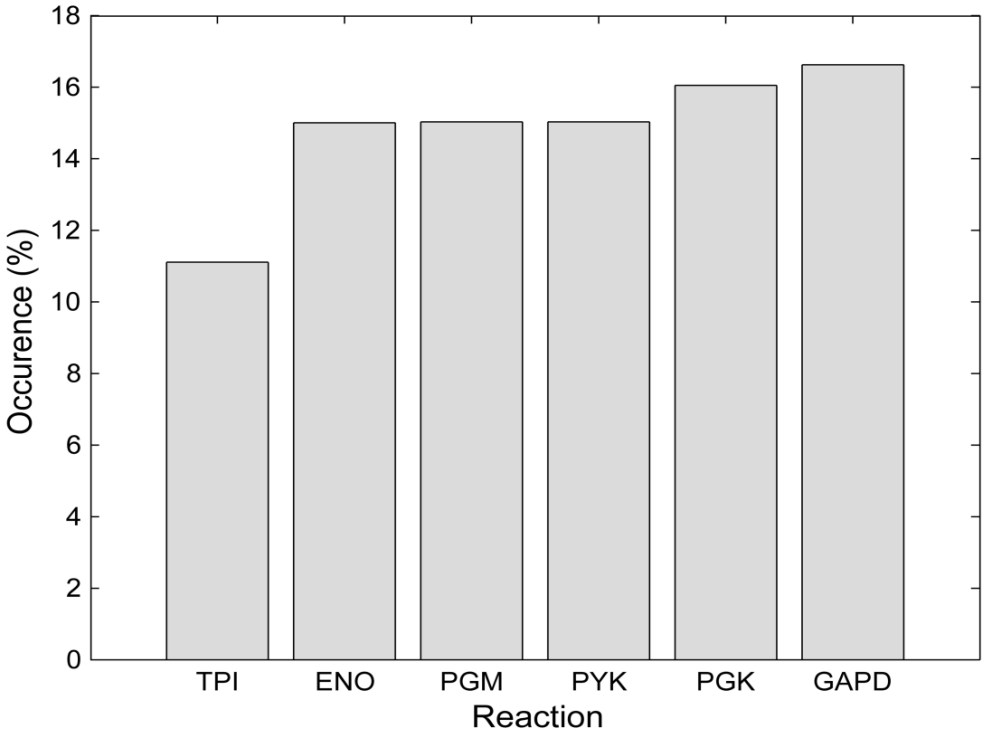
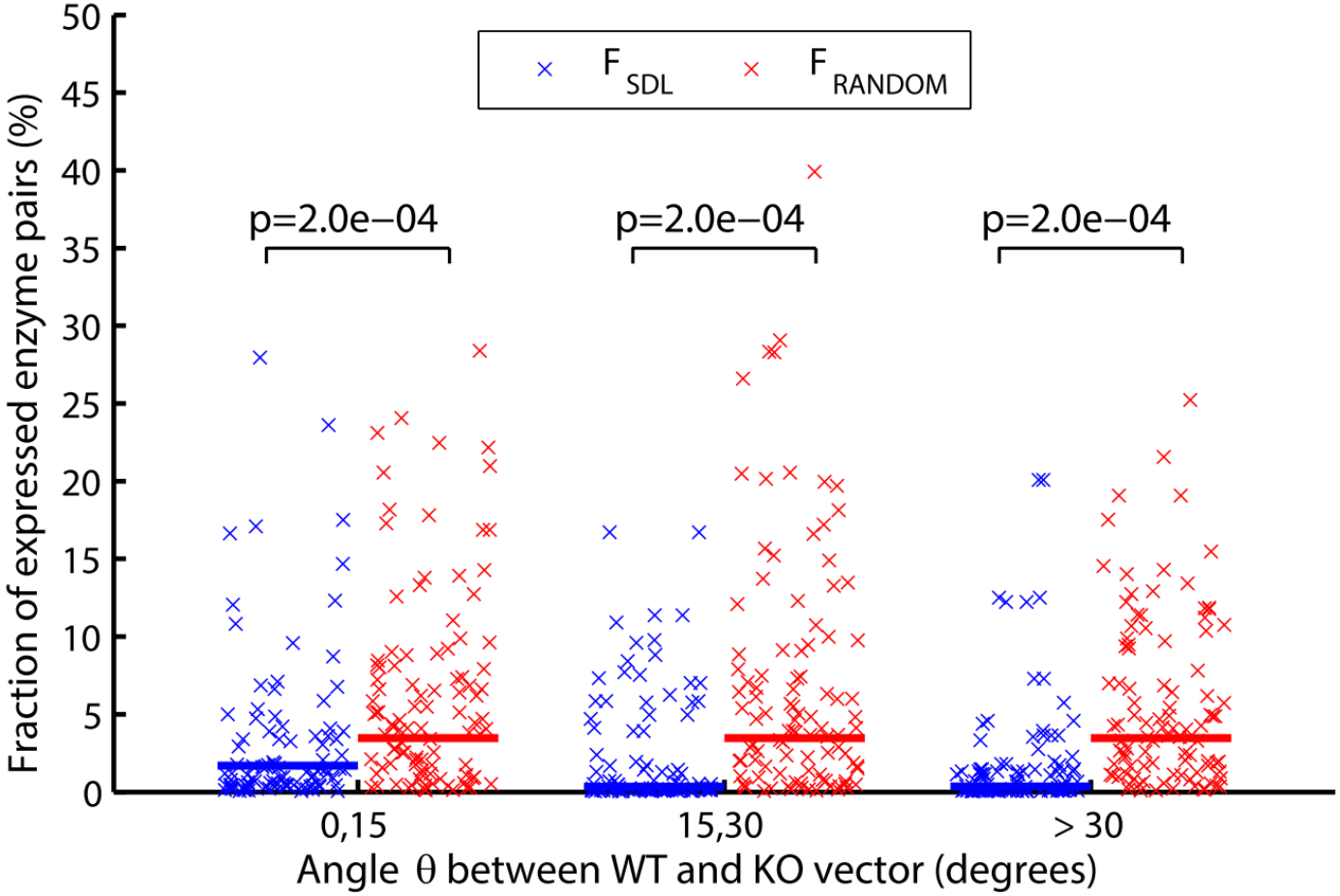


Figure S2 | Six reactions in the glycolysis pathway constitute major hubs in the SDL network. Together, they occur as the knock-out partner in nearly 90% of the SDLs with $\Theta > 15^{o}$.

癌症细胞对SDL的防御

当酶（A，B）具有合成剂量致死效应时，其在癌细胞中出现的频率应比普通细胞中出现的频率低。

一共分析了7362个人的基因表达水平，与正常人相比，确定哪些基因表达量较低，哪些基因表达量较高，计算具有SDL的数量，并用F_{SDL}表示其频率。再随机选取5000对酶，并用F_{RANDOM}表示其在病人中出现的频率。结果显示，F_{SDL}远小于F_{RANDOM}。表明具有SDL效应的酶在病人体内出现的频率更低。


F SDL
F RANDOM
p=2.0e−04
p=2.0e−04
p=2.0e−04
Fraction of expressed enzyme pairs (%)
50
45
40
35
30
25
20
15
10
5
0
0,15
15,30
> 30
Angle θ between WT and KO vector (degrees)

SDL对肿瘤细胞大小的影响

SDL抑制了肿瘤细胞的生长，因此具有SDL的肿瘤细胞可能比不具有SDL的肿瘤细胞更小。

共分析了1587个具有乳腺癌病人的癌细胞大小。并把这些病人分为四类。

1，具有超表达的酶B以及不同表达量的酶A（低表达）

2，没有超表达的酶B，但有不同表达量的酶A（低表达）

3，具有低表达的酶A以及不同表达量的酶B（超表达）

4，没有低表达的酶A，但有不同表达量的酶B（超表达）

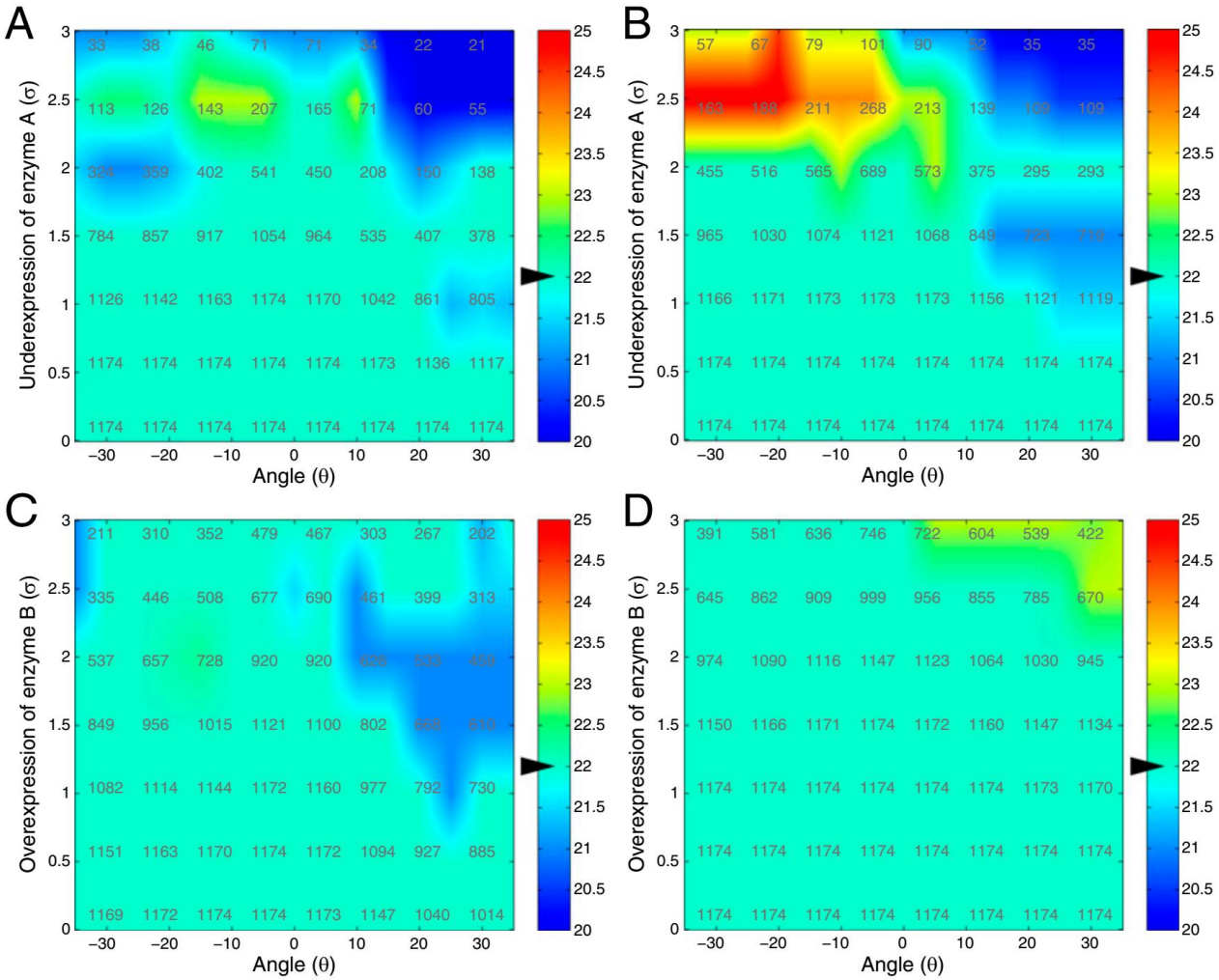


Fig. 3. Median BC tumor size (in millimeters) for patients with ER^+ disease. Arrowheads denote the median tumor size for all patients with ER^+ BC (22 mm). The number of patients that express at least one enzyme pair are denoted inside the figures. (*A*) Patients with at least one active SDL ($A^{\downarrow}$, $B^{\uparrow}$) with constant overexpression of enzyme B. (*B*) Patients whose disease only underexpresses enzyme A ($A^{\downarrow}$, B) of the SDL. (*C*) Patients with at least one active SDL ($A^{\downarrow}$, $B^{\uparrow}$) with constant underexpression of enzyme A. (*D*) Patients whose disease only overexpresses enzyme B of the SDL (A, $B^{\uparrow}$).

SDL能增加病人的存活率

既然SDL能减小肿瘤细胞的大小，那么它是否与癌症患者的存活时间有关？

对乳腺癌患者存活时间进行数据分析，发现具有SDL的患者比仅具有低表达的酶A或高表达的酶B存活时间更长，且差异极显著（$P < 3 \times 10^{-4}$）

此外，对上皮性卵巢癌患者存活时间进行分析，同样得到了上述结论。

在研究没有低表达的酶A，只具有超表达的酶B时，发现酶B的过量表达反而会增加癌细胞大小，减少癌症患者的存活时间。

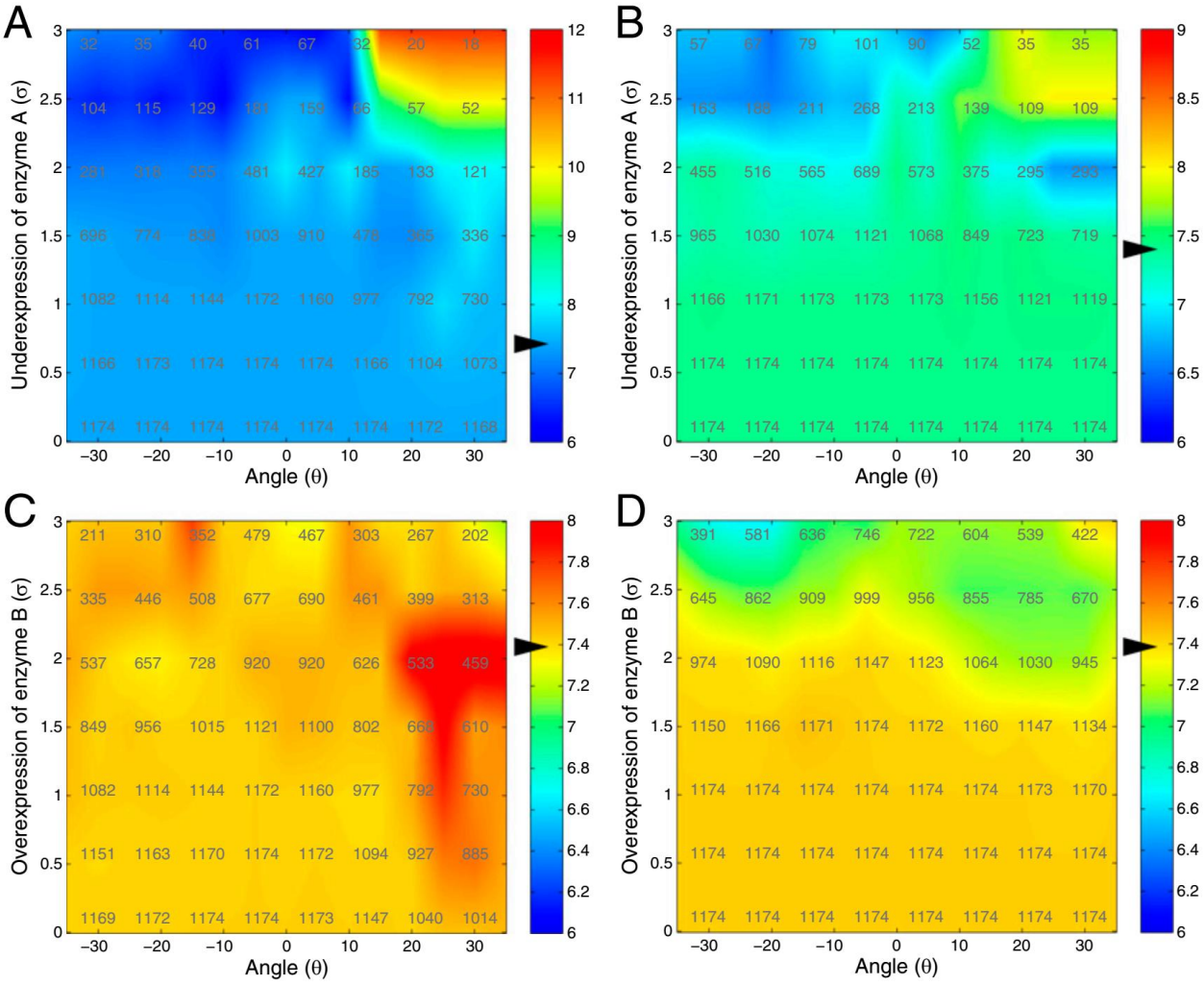


Fig. 4. Median ER^+ BC survival time (in years). Arrowheads denote the median survival for all patients with ER^+ BC (7.4 y). The numbers of patients whose disease expresses at least one enzyme pair are denoted inside the figures. Note that the axis of figure a scales differently. (*A*) Patients with at least one active SDL ($A^{\downarrow}$, $B^{\uparrow}$) with constant overexpression of enzyme B. (*B*) Patients whose disease only underexpresses enzyme A ($A^{\downarrow}$, B) of the SDL. (*C*) Patients with at least one active SDL ($A^{\downarrow}$, $B^{\uparrow}$) with constant underexpression of enzyme A. (*D*) Patients whose disease only overexpresses enzyme B of the SDL (A, $B^{\uparrow}$).

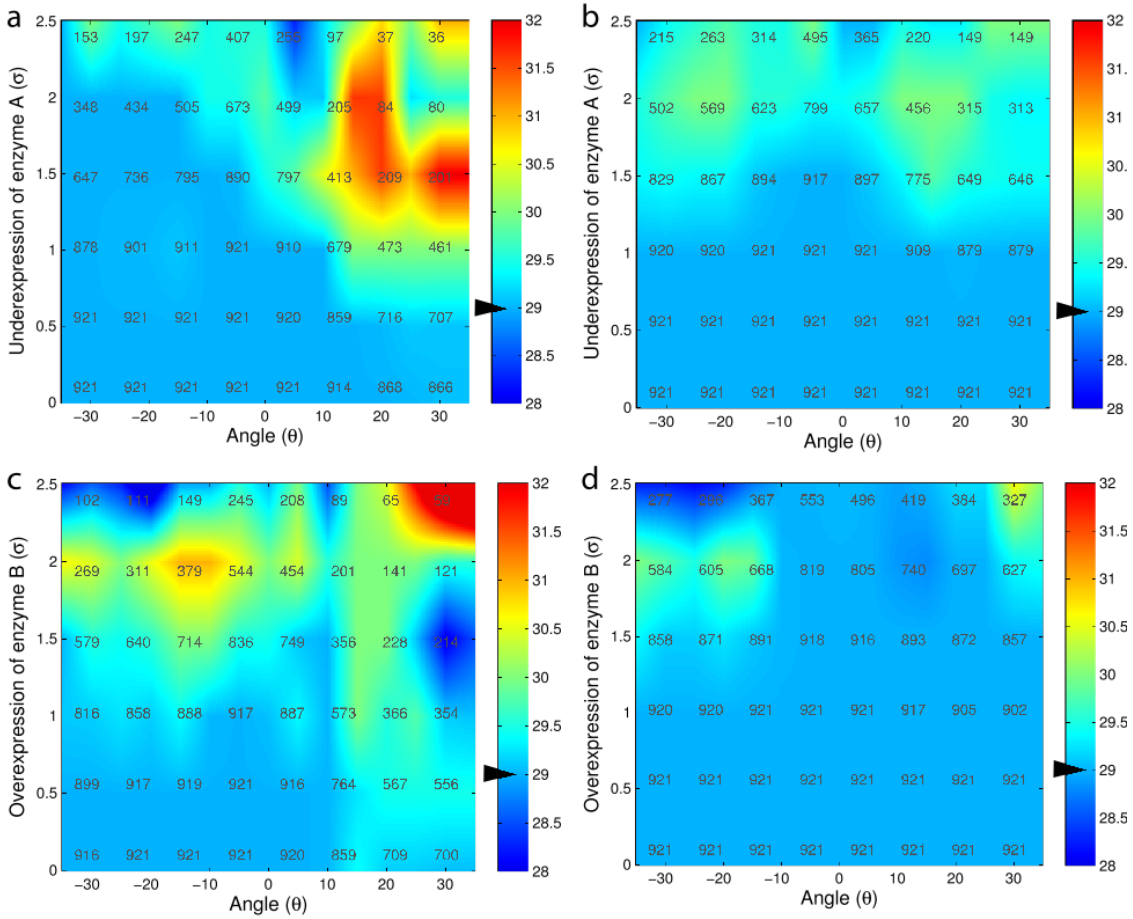


Figure S5 | Median overall survival time for serous epithelial ovarian cancer patients (months). The arrowhead denotes the median survival time for all patients (29.0 months). **a)** Patients with at least one SDL ($A^{\downarrow}$, $B^{\uparrow}$) active, with constant overexpression of enzyme B. **b)** Patients that only underexpress enzyme A ($A^{\downarrow}$, B). **c)** Patients with at least one SDL ($A^{\downarrow}$, $B^{\uparrow}$) active, with constant underexpression of enzyme A. **d)** Patients that only overexpress enzyme B (A, $B^{\uparrow}$).

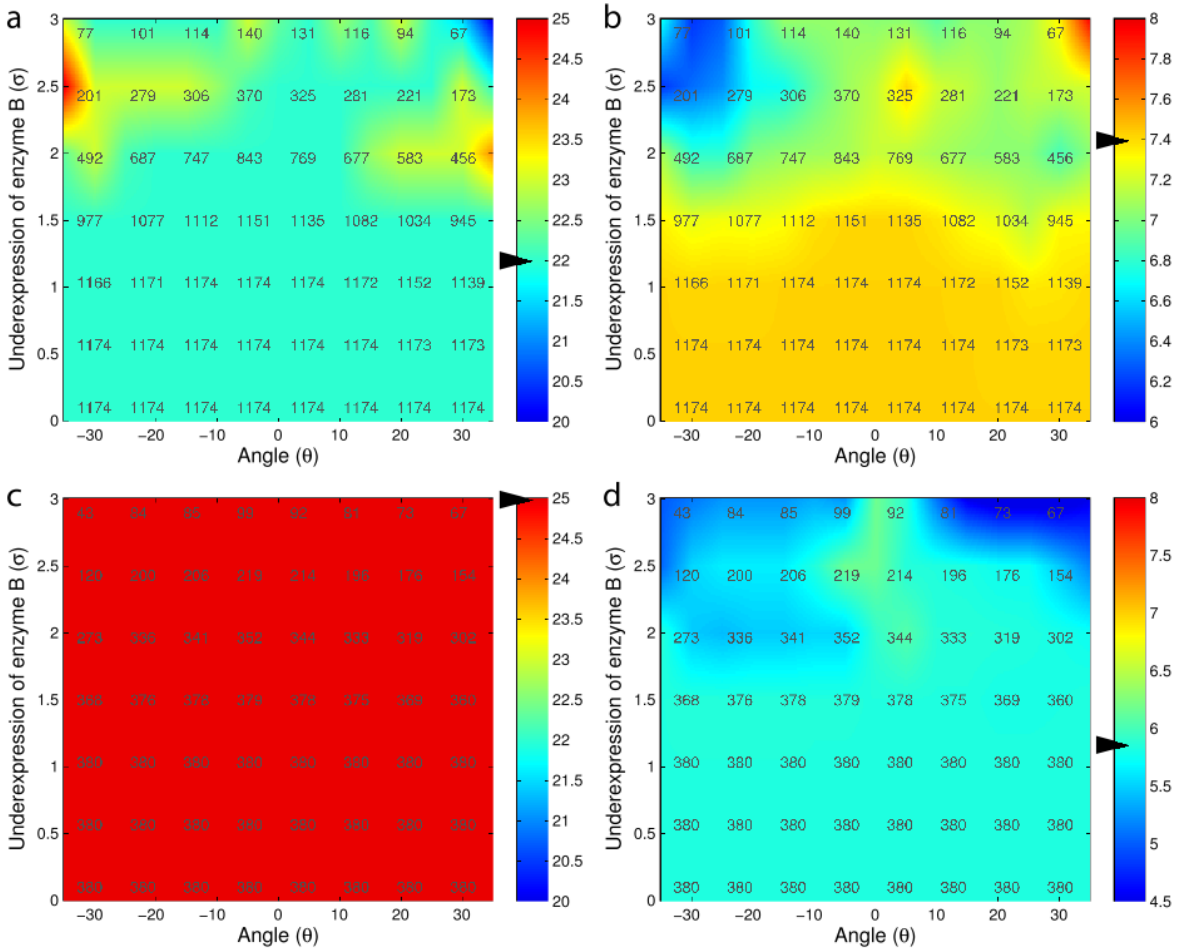


Figure S4 | Median breast cancer tumor size (mm) and survival time (years) for patients that under express enzyme B. **a)** Tumor size for ER+ patients that underexpress at least one of the enzymes B in the SDL (A, B). **b)** Survival times for these ER+ patients. **c)** Tumor size for ER- patients that underexpress at least one of the enzymes B in the SDLs (A, B) **d)** Median survival times for these ER- patients.

SDL的累积效应

因为SDL能增加病人的存活率，那么SDL的数量是否会影响病人的存活？

分析1174例乳腺癌患者，921例卵巢癌患者。一共分为三组。

1，具有1-3个SDL

2，具有4-8个SDL

3，具有8个以上的SDL

结果显示，具有SDL越多的病人，存活时间越长，表明SDL具有累积效应。

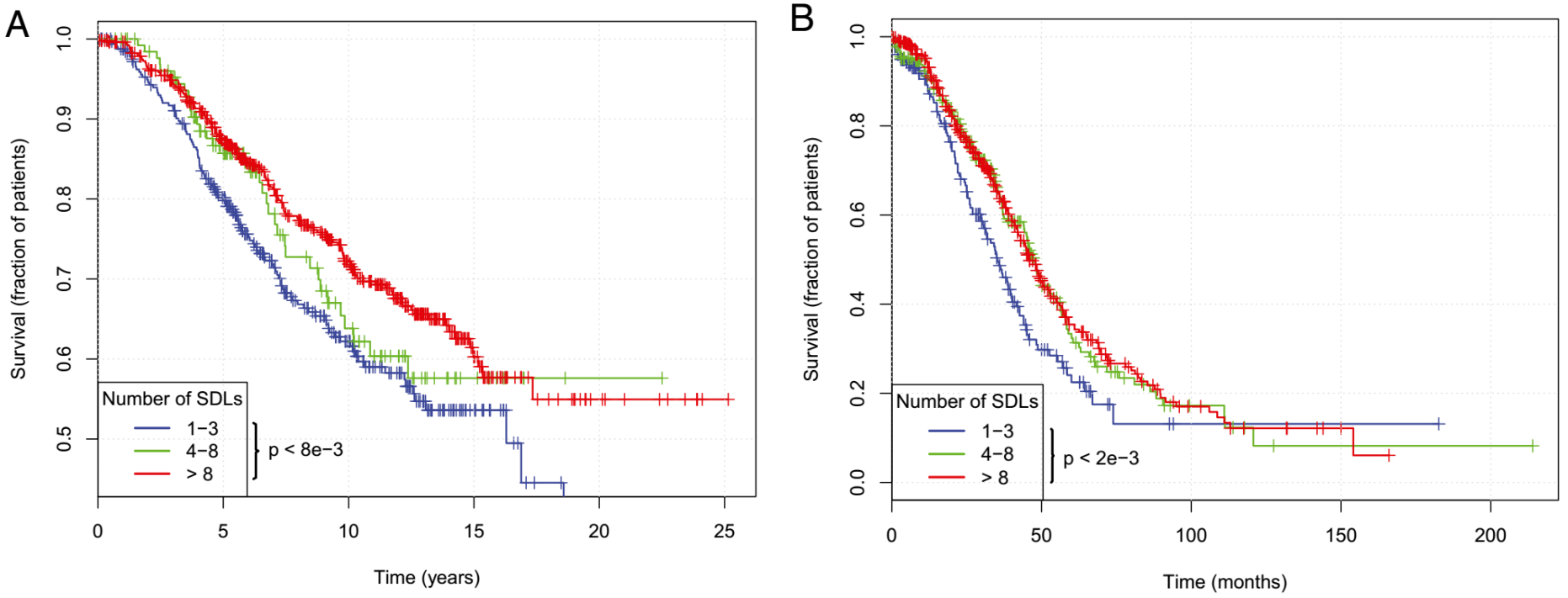


Fig. 5. Kaplan–Meier survival curves for patient groups that have one to three, four to eight, or more than eight active SDLs. (*A*) Survival times for the patients with ER^+ BC. (*B*) Survival times for patients with serous epithelial OC.

SDL的类型

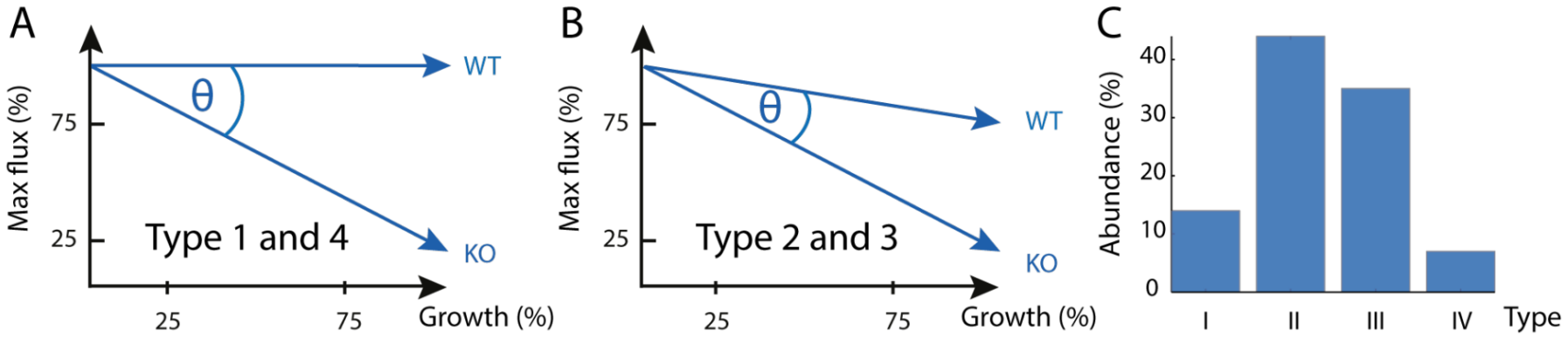


Figure S7: Reaction pairs can be separated into four types. We select SDLs when cell growth is more affected by a flux increase in the KO model. **a)** Type I SDL do not affect the reference cell at all, but are detrimental to cell growth in the KO. **b)** Type II pairs affect both the reference and KO cell, but the detrimental effect is larger in the KO. Type III and IV instead affect the reference growth more and should not be considered SDLs. **c)** Type I and II SDLs together constitute the largest group.

结论

- 1，SDL在肿瘤细胞中的出现频率较低
- 2，具有SDL的肿瘤细胞有更小的体积
- 3，SDL能提高癌症患者的存活时间
- 4，SDL具有累积效应

评价

- 创新点

  1，在合成致死的基础上，考虑基因表达量的影响，即合成剂量致死。

  2，发明了一种识别合成剂量致死基因对的方法。

- 不足

  1，主要证明了SDL对肿瘤细胞及癌症患者的影响，并没有详细说明治疗癌症患者的方法。

- 启发

  1，创新不仅体现在发明和发现上，还有对已知事物的发展和方法上的创新

谢 谢