Lecture III

Applications of Our Model

Our model considerably lowers the threshold for cancer research

Table of Content

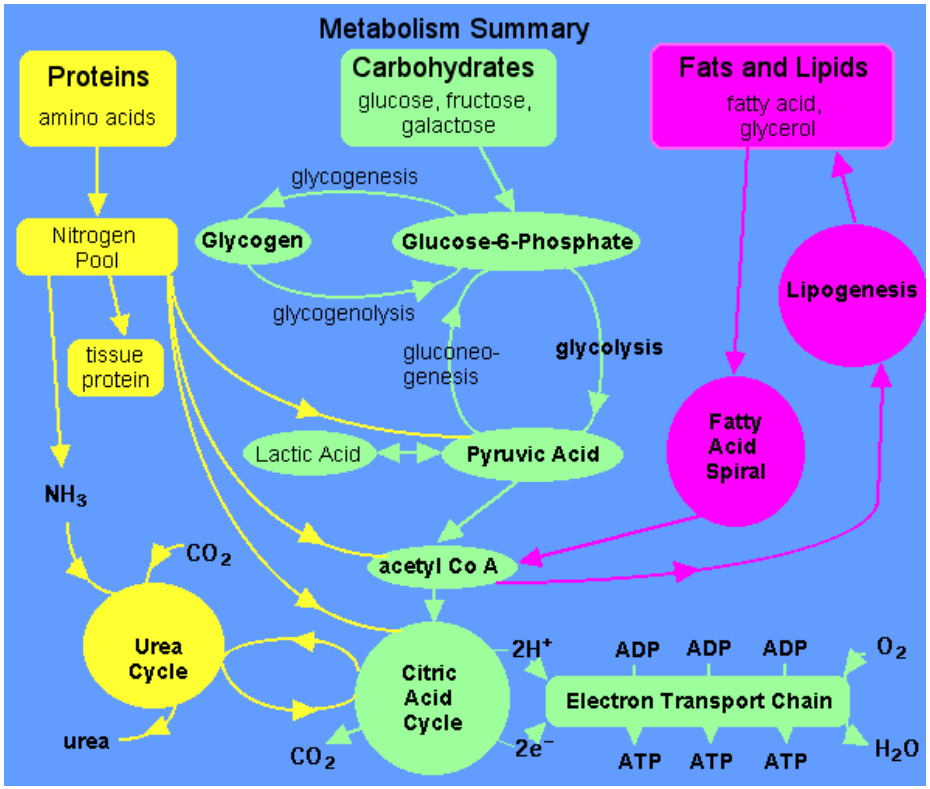
- Stress response during cancer development： epigenomic regulation
- Ten examples of solving cancer problems using our model：
  - Establish an evolutionary model for a specific cancer type from end-to-end
  - Endogenous and exogenous causes of cancer development
  - Diffused vs. solid cancer types
  - Drivers of cancer metastasis and metastasis targets
  - Reasons for drug resistance at the chemistry level
  - …
- Unique biology of metastasize cancers
- Summary and perspective

肿瘤演化理论的应用

- 大幅降低肿瘤研究的门槛值
  - 本科生可以做非常优秀的肿瘤研究，如2-3年级的学生发表一作的文章
  - 二年级学生可以回答有一定难度的肿瘤生物学问题
- 肿瘤发病率与年龄的关系
- 肿瘤耐药解析
- 胆管癌特别恶性的原因解析
- 肿瘤血液标识物预测

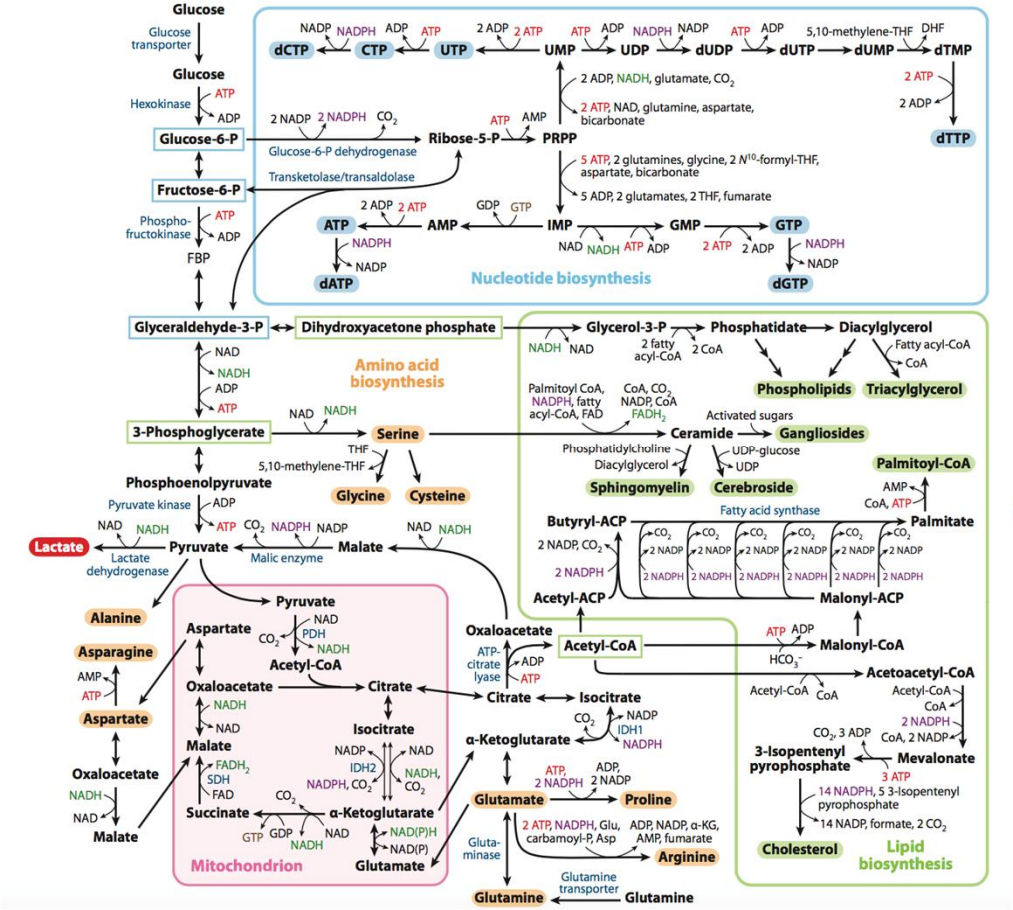
Central Metabolism

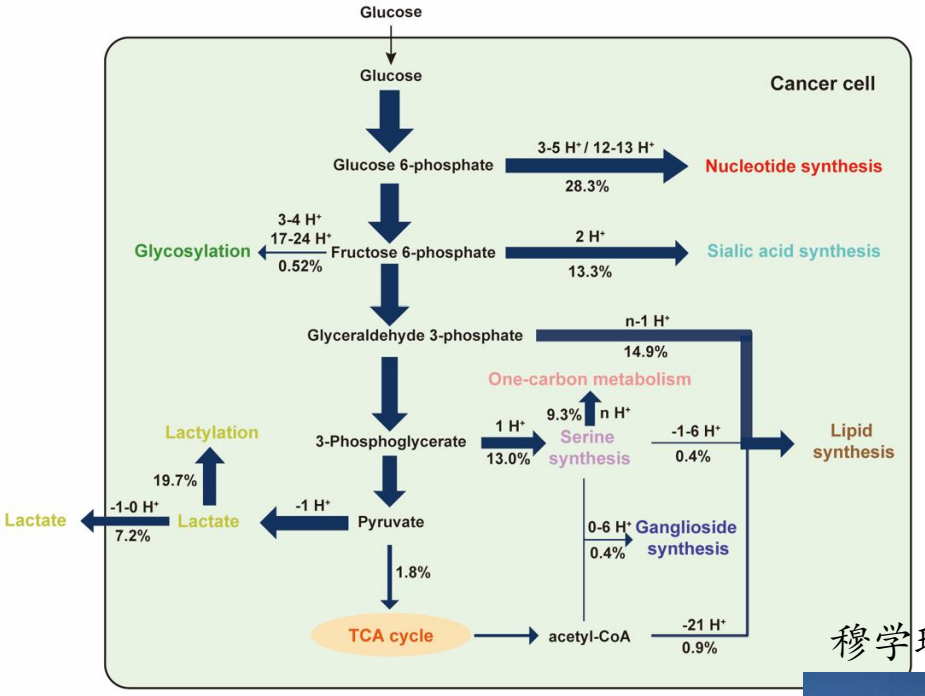
- Our cells need amino acids, carbohydrates, and fatty acids as the basic nutrients to provide energy, basic units for synthesizing biomolecules



Glucose Metabolism

- Glucose metabolism is in the central part of cancer metabolism





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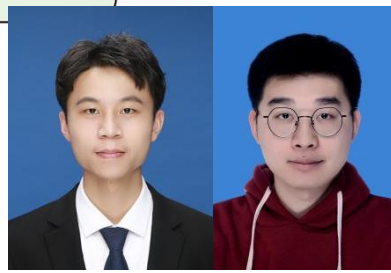
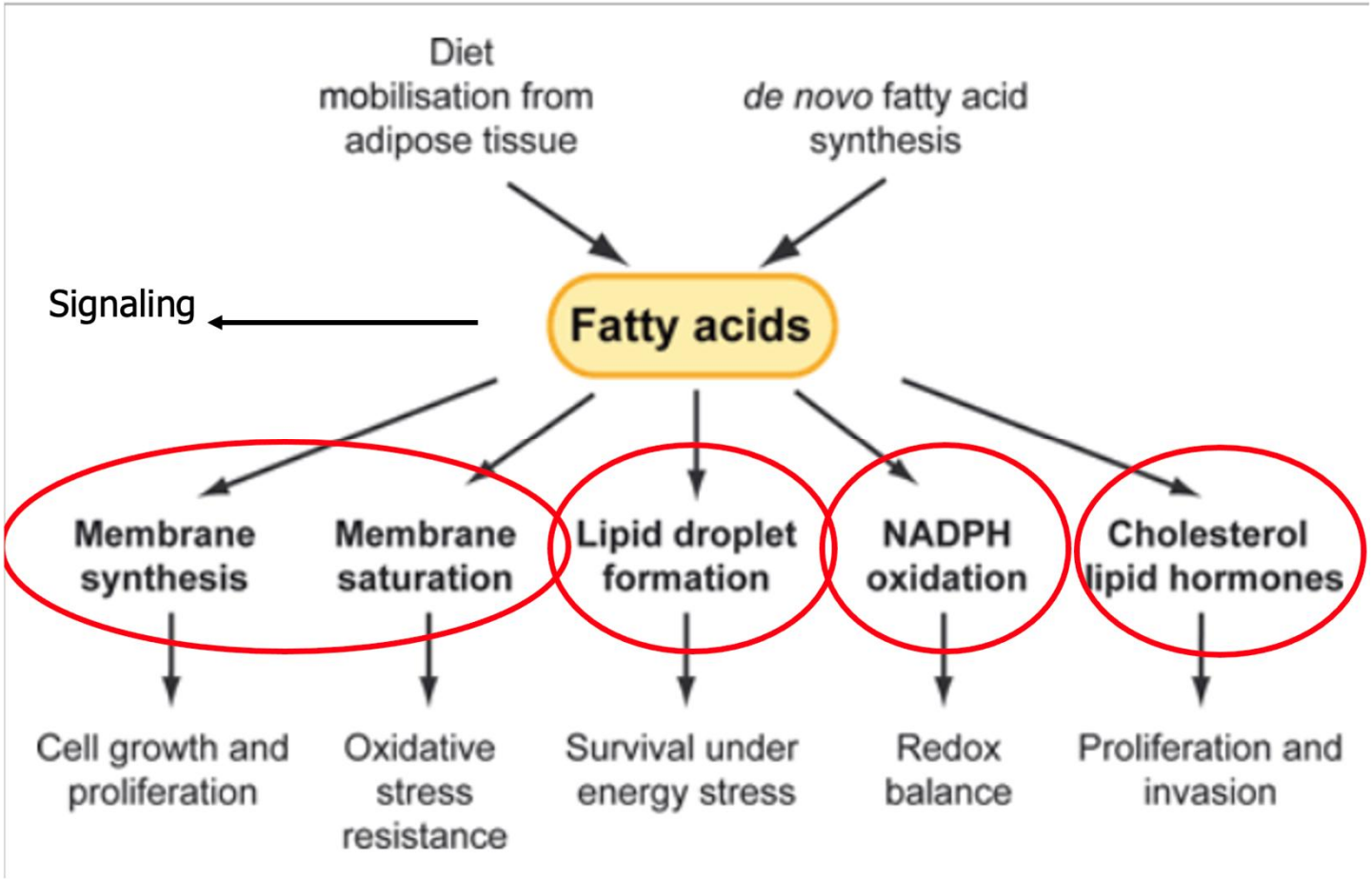


Fatty Acid Metabolism

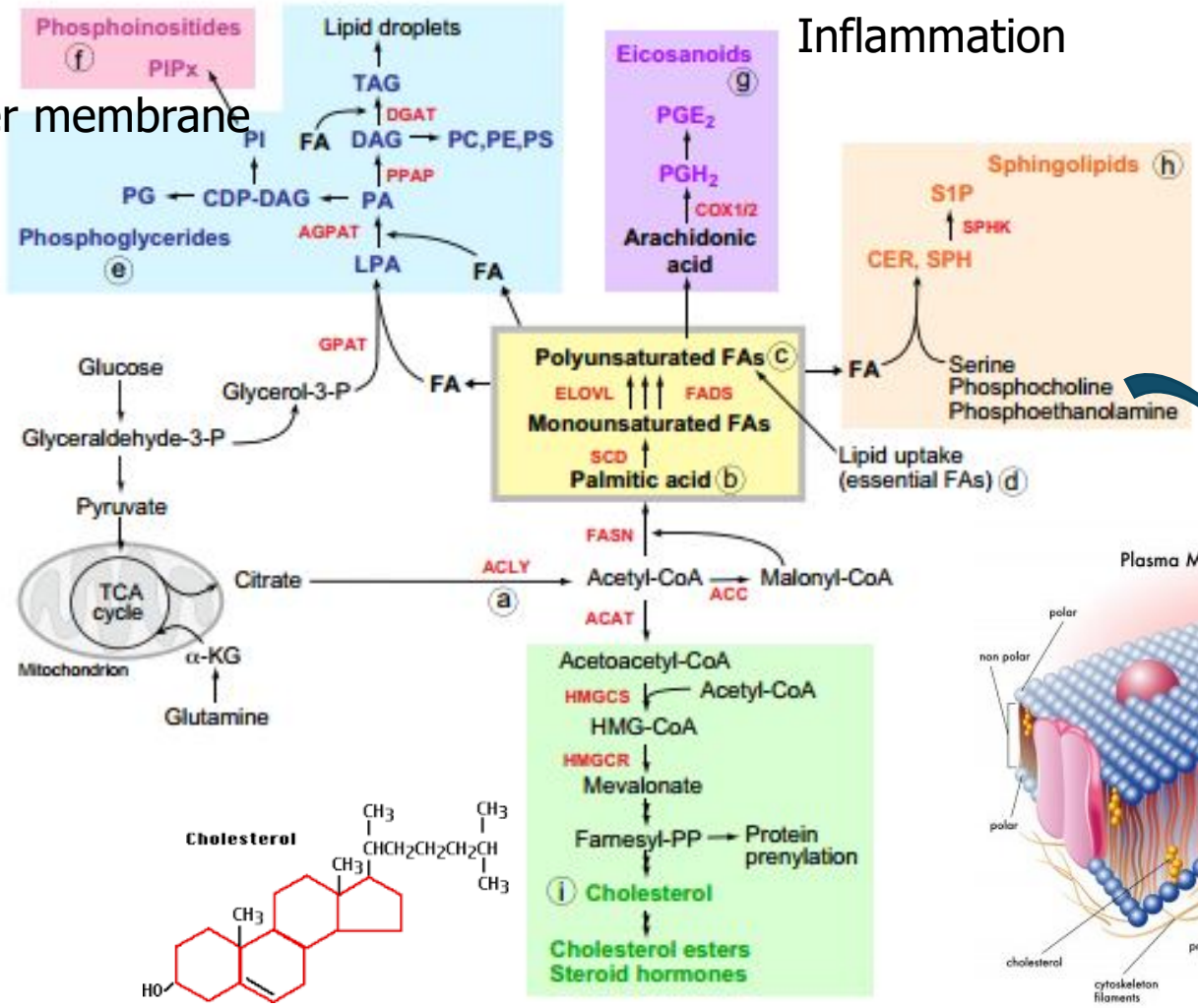


Lipid Synthesis

Inner membrane

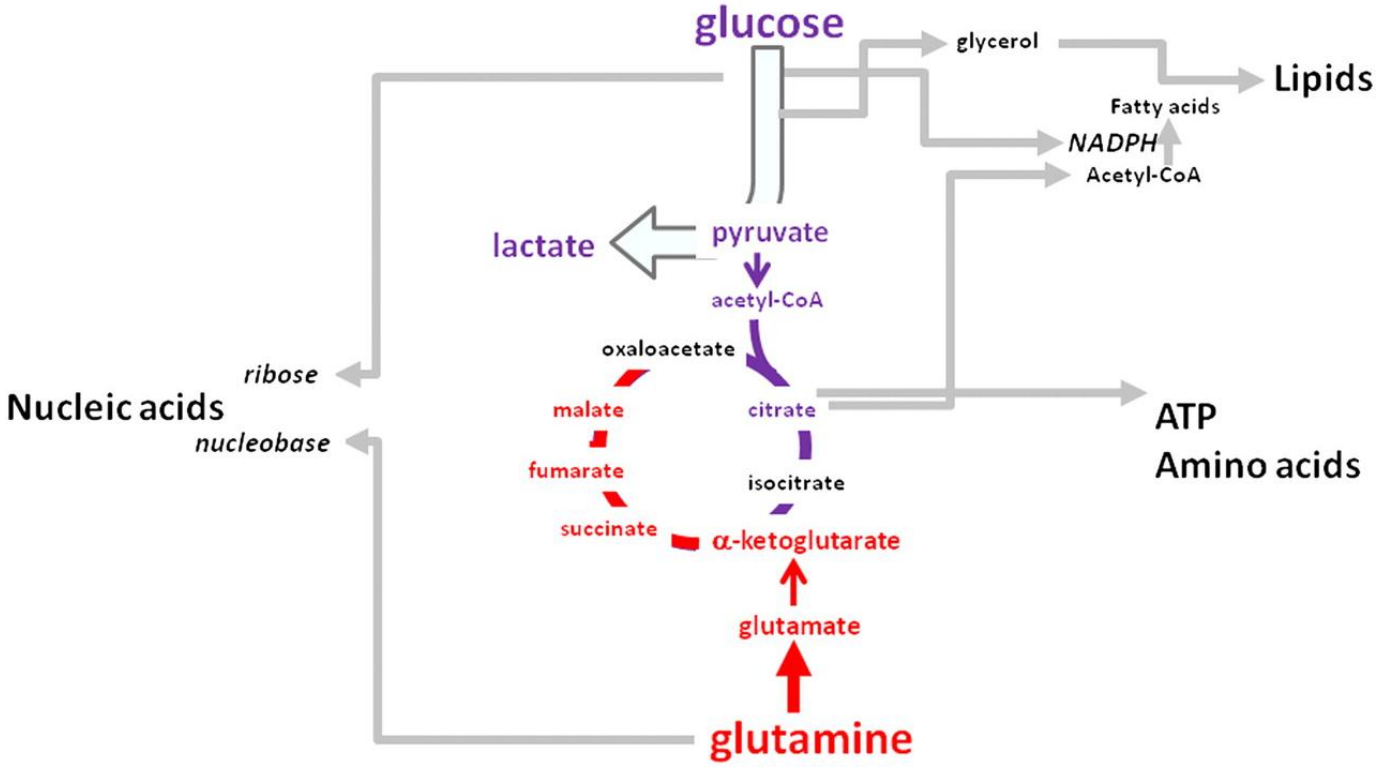
Inflammation

In cancer lipid metabolism is predominantly used for antioxidation and energy production

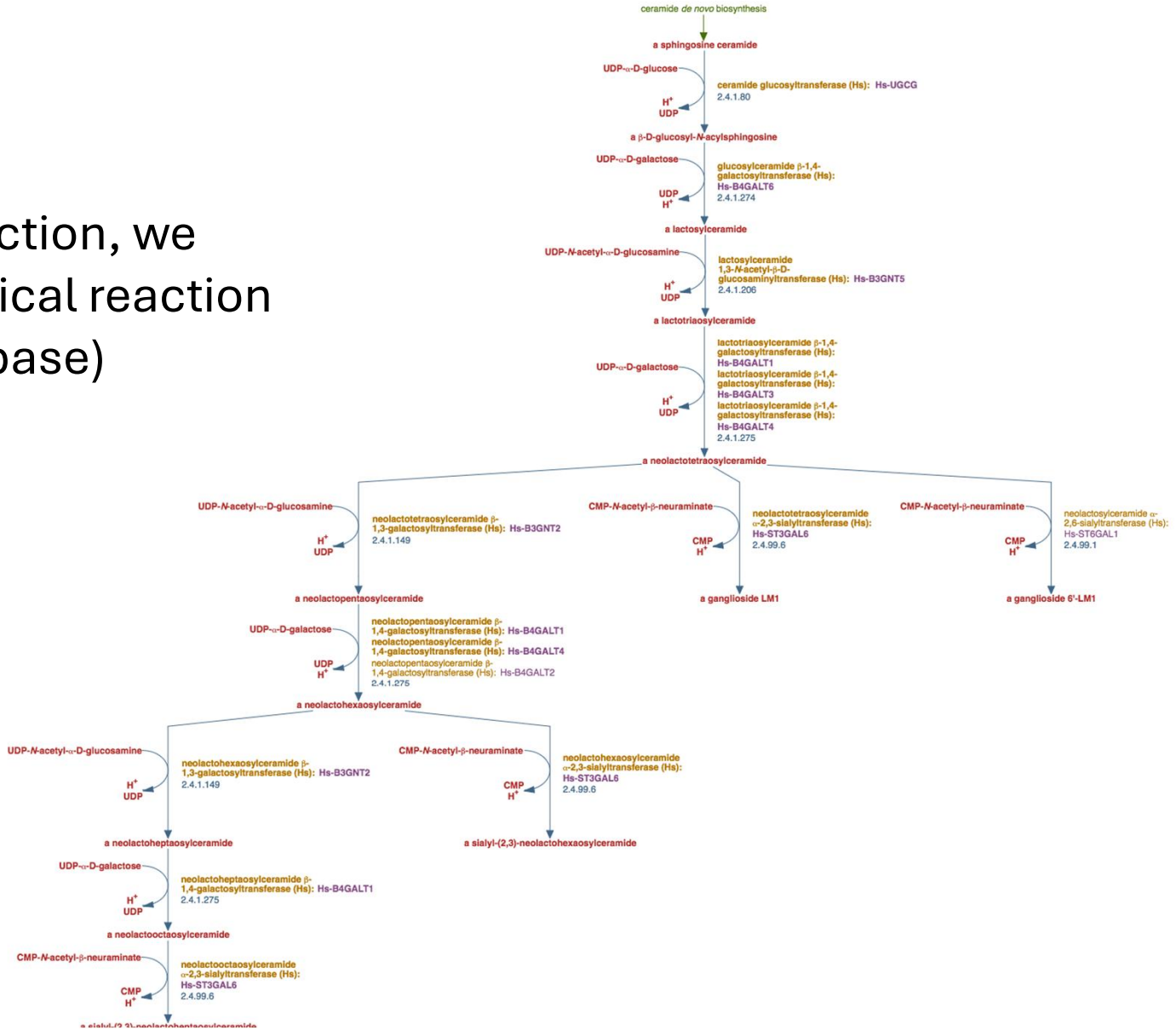


Amino Acid Metabolism

- In cancer, glutamine is predominantly used for production of nucleotides, energy and other amino acids



For each enzymatic reaction, we need to know the chemical reaction equation (BioCyC database)



Stressors and Metabolic Reprogramming

- 细胞浆的碱性化是驱动肿瘤的主要压力
  - 细胞增殖是细胞在持续碱性压力下逃生的出口，停止增殖细胞将死亡
  - 细胞转移是细胞在持续碱性压力下逃生的另一个出口，抑制细胞转移将加速细胞增殖
- 其他的代谢重编程 及组织的化学物理环境决定了肿瘤的其他行为
- 肿瘤细胞还受到其它的压力
  - 胞外的酸性压力、缺氧压力、氧化压力、营养竞争 。。。

Physicochemical Conditions in Normal vs. Cancer Tissues

Healthy epithelial cells

- Intracellular pH : 6.8-7.0
- Extracellular pH: 7.3 – 7.5
- Intracellular vs. extracellular electrolyte concentration:
  - Sodium: 10 ： 140
  - Potassium: 145 ： 4
- Plasma membrane potential: 70 mV
- Mitochondrial membrane potential: 140 mV

Cancer cells

- **Intracellular** pH : **7.2 – 7.5**
- **Extracellular** pH: **6.4 – 6.6**
- Intracellular vs. extracellular electrolyte concentration:
  - **Sodium (Na^+)**: 60 ： 140
  - Potassium **(K^+)**: 145 ： 5
- **Plasma membrane potential**: **27** mV
- **Mitochondrial membrane potential**: **210 - 280** mV

底层化学物理条件改变的影响

- **例1**：肿瘤细胞浆的pH比正常细胞的要高。一个流行的观点是肿瘤细胞使用Na^+/H^+交换器NHE1持续将H^+泵出细胞，导致胞内碱性化。
- 对正常细胞，从反应热力学的角度，这有可能

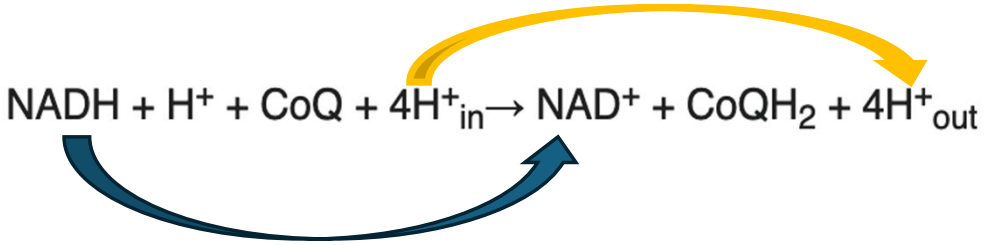
$$\Delta G_{Na^+} + \Delta G_{H^+} = 8.31 \times 310 \times (\ln(\frac{12}{140}) + \ln(\frac{10^{-6.6}}{10^{-7.4}})) = 8.31 \times 310 \times (-0.615) = -1583J$$

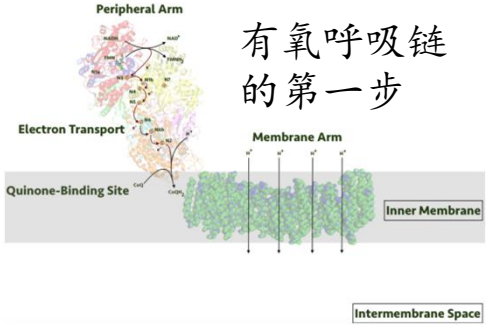
- 但在肿瘤中，这不大可能，因为肿瘤细胞内Na^+的浓度远高于正常细胞，从**10:140 mmol/L** 增加到 **60:140 mmol/L**

$$\Delta G_{Na^+} + \Delta G_{H^+} \geq 8.31 \times 310 \times (\ln(\frac{59}{140}) + \ln(\frac{10^{-6.6}}{10^{-7.4}})) = 8.31 \times 310 \times 0.978 = 2519J$$

底层化学物理条件改变的影响

- **例2**：肿瘤的线粒体内膜电势比正常细胞的高50–100%，





有氧呼吸链的第一步

- 这导致电子传递链将氢离子，从线粒体基质推到线粒体内膜之外的难度增加、因此效率下降到正常的 < 10%
- 进而导致线粒体内膜两侧的氢离子浓度差下降，使得产生ATP的效率下降

- Cancer enabler: epigenomic regulation

Stress-Induced Metabolic Reprogramming

- We have learned that under chronic inflammation and persistent iron overload, human cells will become increasingly more alkaline in their intracellular pH
- pH is a fundamental property that must remain stable as changes will alter biomolecular structures, functions, interactions and reaction rates
- Considerable metabolic reprogramming takes place in such cells, to produce more protons to keep the pH stable, which substantially change the behaviors and the nature of the cells
- We have studied ~50 reprogrammed metabolisms, each giving rise to new phenotypes of the affected cells

Stress & Epigenomic Regulation

- Cancer biology is stress biology throughout the entire development of a cancer

- Majority of the metabolic reprogramming is selected through epigenomic regulation and life/death

Epigenome

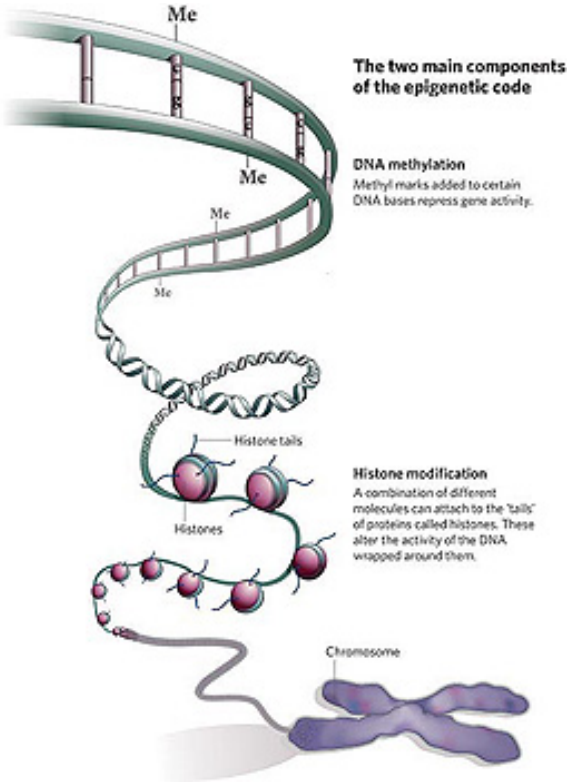
- Epigenome is about DNA re/folding, and differently folded structures expose different parts of DNA transcriptionally accessible

- The folding is determined by electrostatic interactions, predominantly between histones and DNA plus DNA methylations

- Epigenomic level changes can enable transcription of specific genes largely independent of transcription factors, hence often used to deal with stress

Epigenomics in Human

- DNA can have chemical modifications, such as methylation and histone modification, which can affect transcription of the relevant genes.
- These modifications are collectively defined as the epigenome of a cell.
- Unlike genomes, epigenomes can be modified by environmental conditions
- Like genomes, some epigenomic modifications can be inherited by future off-springs but for a limited number of generations.



A Model Potentially Useful

- A group of researchers in Israel has conducted an interesting study aiming to elucidate the mechanism of (a) how epigenomic level activities may be regulated and (b) what type of epigenomic information may be passed on to the future generations
- They prepared a toxin G418, which can kill the cells of fruit-fly larva if injected and not pumped out
- They also developed a genetic system to insert a gene into larva cells, which encodes a transporter and can pump out the toxin if activated, plus a random promoter associated with development

A Model Potentially Useful

- They prepared two sets of cultures, one being generally engineered and one being wild type; for the genetically engineered one, they tried 8 different and randomly selected promoters
- Then they injected the toxin into each cultured larva
- All the ones without the inserted gene are killed
- 7 out of the 8 groups of larvae with the inserted gene and promoter pumped out the toxin and developed into the adulthood fruit-flies but with a long delay.
- The off-springs of the survived larvae all pumped out the toxin after insertion and develop into adulthood without any delays, but only for four generations.

A Model Potentially Useful

- Speculations and proposal by the authors:
- Larva has an encoded mechanism to allow the cells to “broaden” the application of development-associated “IF-THEN” response systems, in a systematic manner, through epigenomic level changes
- This system is probably activated under persistent and unfamiliar stresses
- The authors even suggest that Polycomb is the master regulator of this general stress-response system at the epigenomic level

Genome Instability

- Genome instabilities are common in cancer cells, and they are considered a "trademark" for these cells.
- It is widely believed that sporadic tumors (non-familial ones) are originated due to the accumulation of several genetic errors (mainstream thinking but it may not be correct)
- Studies of cancer genomes, to learn about “driver mutations” have been popular but also disappointing as not many new insights have been gained about cancer initiation and development

Mutations in Other Diseases

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PMCID: PMC3909954
NIHMSID: NIHMS546313

Somatic Mutation, Genomic Variation, and Neurological Disease

Annapurna Poduri,[1,2] Gilad D. Evrony,[3,4] Xuyu Cai,[3,4] and Christopher A. Walsh[2,3,4,*]

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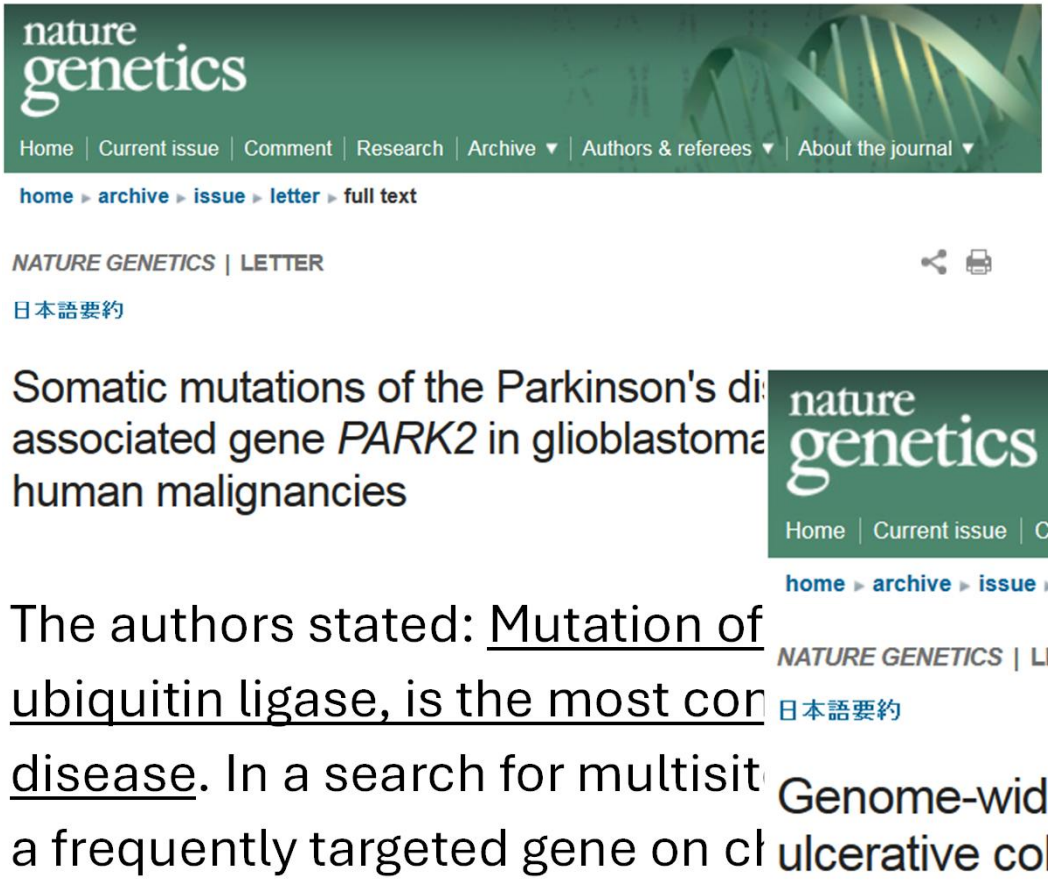
- … Increasingly, somatic mutations are being identified in diseases other than cancer, including neurodevelopmental diseases. Somatic mutations can arise during the course of prenatal brain development and cause neurological disease, resulting in brain malformations associated with epilepsy and intellectual disability.

Mutations in Other Diseases



- The authors stated: Mutation of
  ubiquitin ligase, is the most con
  disease. In a search for multisit
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Mutations in Other Diseases

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Mitochondrial DNA Aberrations and Pathophysiological Implications in Hematopoietic Diseases, Chronic Inflammatory Diseases, and Cancers

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#1: Derivation of Cancer Evolutionary Model

- Step 1: collect transcriptomic data of cancer-prone inflammatory tissues, cancer tissues, and normal tissues
  - E.g., colorectal adenoma vs. colorectal adenocarcinoma, cirrhosis vs. liver cancer
- Step 2: develop biomarkers for each stressor, reprogrammed metabolism, and cellular behavior
  - E.g., cytosolic alkaline stress, extracellular acidity stress, hypoxia, oxidative stress; nucleotide de novo synthesis, sialic acid synthesis, lipid synthesis; persistent cell division, cell migration, drug-resistance

#1: Derivation of Cancer Evolutionary Model

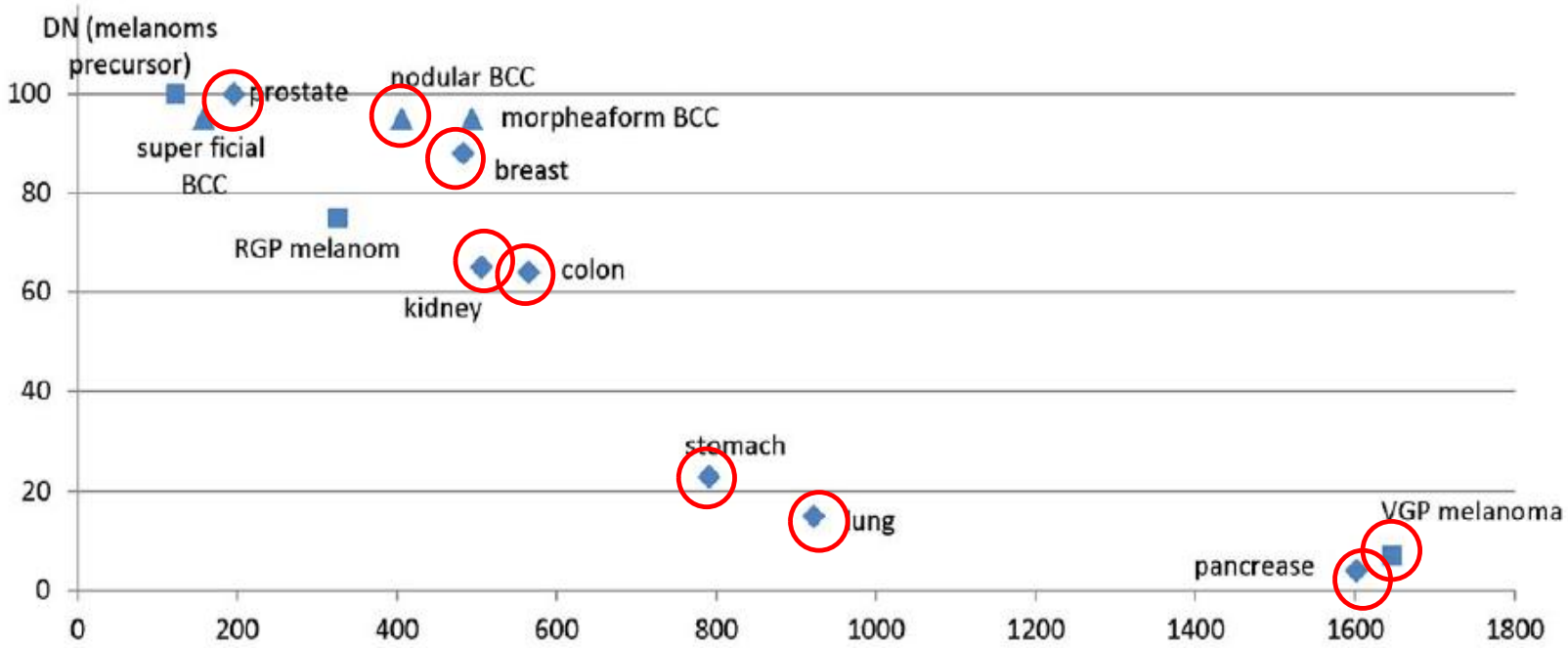
- Step 3: quantify and validate the validity of each biomarker
- Step 4: establish correlations between stress biomarkers and reprogrammed metabolisms; and between reprogrammed metabolisms and cellular behaviors
  - Cytosolic alkaline stressor vs. {nucleotide synthesis, sialic acid synthesis}; sialic sialic deployment vs. cell migration
- Steps 5: establish possible causal relationships among the detected correlated relationships via structural equation modeling

#1: Derivation of Cancer Evolutionary Model

- Steps 5: Build causal network from stressors to cellular behaviors, e.g., cell migration, drug resistance
- Step 6: Apply your knowledge and information from the literature to interpret each causal relationship in the model
- Step 7: Experimentally validate key steps in the model

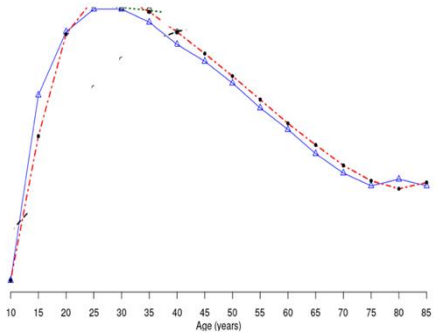
#2: Determinants of Survival Time

- By comparing the average number of differentially expressed genes for each cancer type and its five-year survival rate, one can get the following



#3: 为什么年龄大了反而不容易得肿瘤

- 绝大部分的肿瘤发病率曲线（vs. 年龄）是单峰分布

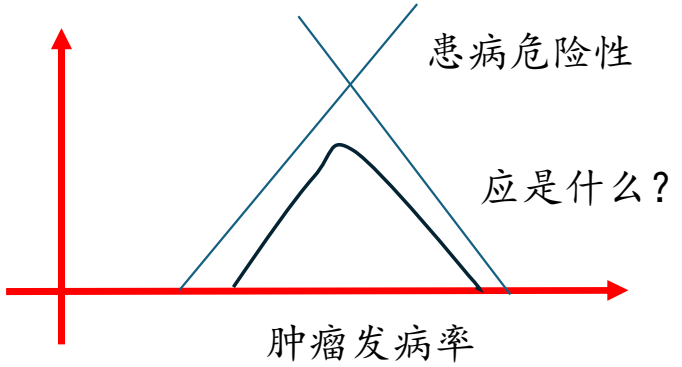


睾丸癌发病率

- 为什么肿瘤发生的概率（在过了峰值后）会随着年龄增长而降低
- 一个自然的假设：有两个因素决定睾丸癌的发病率：一个随年龄上升而上升，一个随年龄上升而下降

为什么年龄大了反而不容易得肿瘤

- 已有的理论认为：一个器官患肿瘤的危险性与这一器官从出生到目前为止细胞分裂总次数成正相关;另一个因素是什么？

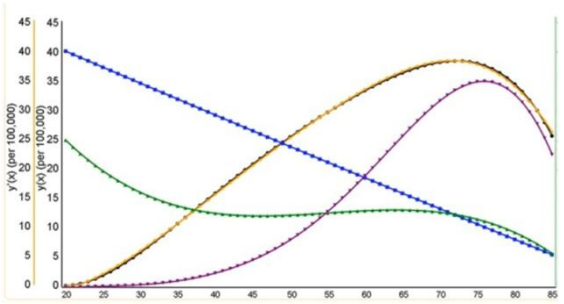


- 我们的分析发现：每种肿瘤都需要特有的、血液中的某些生长因子，如雌性、雄性激素，或其它生长因子，都随年龄的上升而下降。
- 这表明：肿瘤有可能通过在血液中消除这些生长因子来治疗

为什么年龄大了反而不容易得肿瘤

- 我们分析了三种肿瘤的发病曲线，都符合我们的假设，且预测的生长因子都有文献支持

- 肿瘤的发生需要两条件：内因（发炎、铁积累），及外因：血液中有足够的、相关生长因子



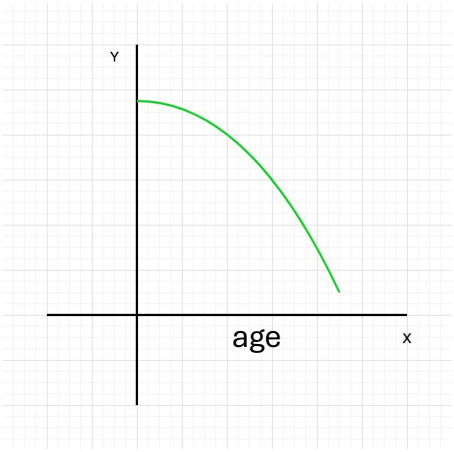
- 这表明：肿瘤有可能通过在血液中消除这些生长因子，来治疗

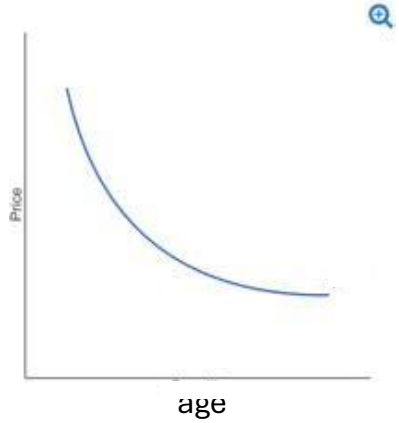
每种肿瘤所需的生长因子

- 其生长因子受体的表达Ri应与细胞周期C成强相关,且

$$C = \sum Ri + \varepsilon$$

- 确定每一生长因子产生的器官及随年龄增长的变化趋势

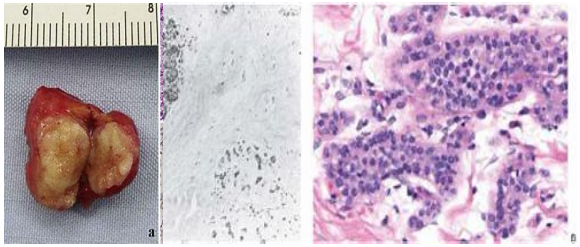




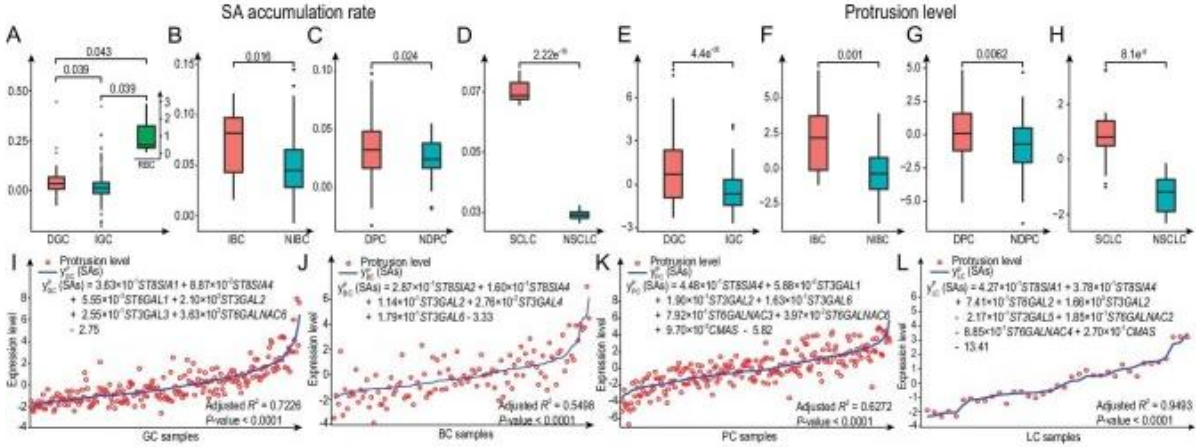
肖隽

#4: Solid vs. Diffused Cancer Types

- 导致弥散性肿瘤的原因是什么？
- 为什么弥散性肿瘤患者相对年轻？
- 为什么弥散性肿瘤更恶性？



- 差异性表达分析：确定哪些基因在弥散性肿瘤比相应的实体瘤一致性的上调



Key Detern ncer Types

- 弥散性肿瘤的细
- 带负电的唾液酸
- 胃癌弥散性肿瘤
- 弥散性胃癌细胞 形变将激活上皮细胞– 间充质转
- Specifically neede at diffuse subtypes tend to occur on

Diffuse tumors: Molecular determinants shared by different cancer types

Xuan Li [a b], Dingyun Liu [a], Zhipeng Wu [a], Ying Xu [b]

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Highlights

- A key molecular determinant of diffuse cancers that are generally more aggressive than non-diffuse cancers and morphologically different from each other is sialic acids deployed on the surface of cancer cells.
- Poly-sialic acid synthesized by *ST8SIA4* confer differential immunoactivities between diffuse and non-diffuse cancers.
- Combining the Michaelis-Menten kinetic model with sialic acid synthase, sialyltransferase, and sialidase-related genes, the rates of sialic acid transfer, degradation, and accumulation are evaluated.
- Specifically needed circulating growth factors determine that diffuse subtypes tend to occur on average in younger patients.

李轩

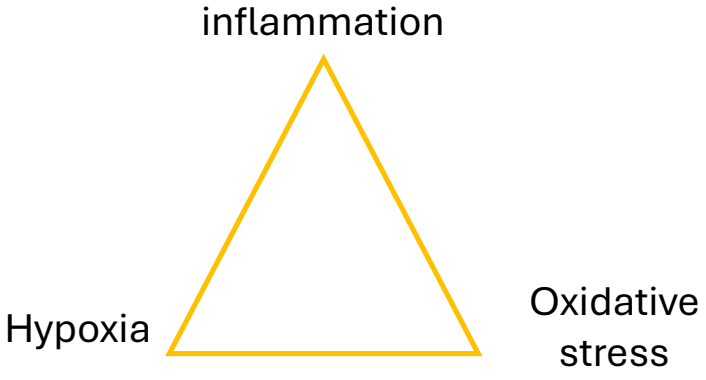
印戒细胞癌 (signet ring cancer)

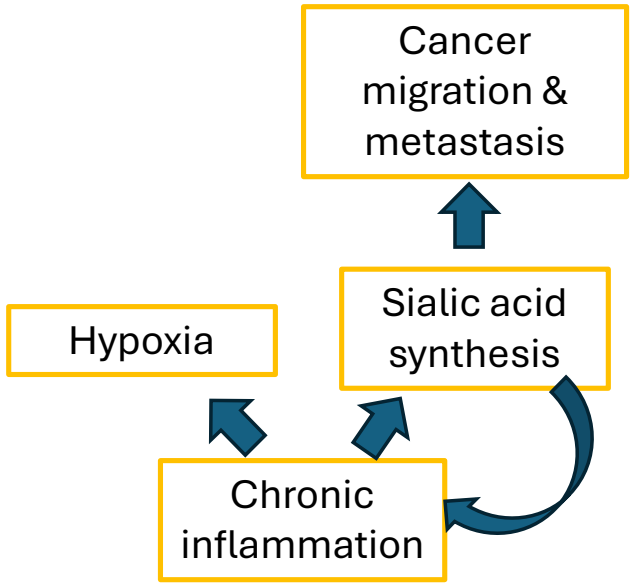
Cancer types	Information of diffuse-like tumors
GC	**Diffuse gastric cancer (DGC)** is characterized by the presence of multiple small, separate tumors that infiltrate the tissue stroma. DGC cells are poorly or un- differentiated and lack cell-to-cell adhesion. Glandular structures are rarely seen in DGC. Some of DGC tissues contain more than 50% signet-ring cells, referred to as signet-ring cell carcinoma. DGCs account for 32% of all GCs [3], and their average 5-year survival rate is lower than the other GCs, 45.6% vs. 57.7% [8].
BC	There are two types of diffuse-like BCs, accounting for < 3% of all BCs with significantly lower 5-year survival rates than other BCs, 40.5% vs. 63.2% for IBC and 65.1% vs. 90.0% for SRCC [2,9]. **Inflammatory breast cancer (IBC)** is the most aggressive BC subtype. Compared to other BCs, IBC is associated with acute inflammation and generally poorly differentiated with diffuse brawny infiltration, showing no underlying mass structure [1,9,25]. **Signet-ring cell carcinoma (SRCC)** is defined, according to the WHO's classification, as a poorly cohesive carcinoma in which more than 50% of tumor cells are with prominent cytoplasmic mucin and a crescent-shaped nucleus eccentrically placed. They are poorly or un- differentiated and each tumor appears as individual cells or in loose cell-clusters [2,26].
PC	There are two types of diffuse-like PCs, accounting for < 6% of all PCs with significantly lower 5-year survival rates than other PCs, < 65% vs. > 90% for those with high GG and 83.6% vs. 93.4% for SRCC [2,10]. PCs with **Gleason grade** (GG, from 1 to 5)≥4 are defined as poorly or un-differentiated tumors growing in diffuse patterns. Tumors with GG 4 have poorly formed glandular lumina, while those in GG 5 are without glandular differentiation. Therefore, a tumor with Gleason score (GS, sum of the primary and secondary GG, range from 2 to 10)≥8 with GGs ≥ 4 is considered as a diffuse-like tumor [6,10]. SRCC cancer tissues are derived from prostate epithelial cells [2,26].
LC	There are two types of diffuse-like LCs, accounting for < 15% of all LCs with significantly lower 5-year survival rates than other LCs, 7% vs. 18% for SCLC and 9.7% vs. 26.1% for SRCC [2,11,12]. **Small-cell lung carcinoma (SCLC)** is defined as tumors with cells having a relatively small size, a round-to-fusiform shape, scant cytoplasm, and absent or inconspicuous nucleoli. The tumors are mostly poorly or un- differentiated, fall short of glandular differentiation, and grow as diffuse sheets [5,27]. **SRCC** cancer tissues are derived from lung epithelial cells [2,26].
HC	**Diffuse hepatocellular carcinoma (DHCC)** also known as cirrhotomimetic HCC or cirrhosis-like HCC, is a subtype of HC. Different from massive HCC, DHCC shows cirrhosis-like diffuse growth. Cancer tissues exhibit pseudo-glandular and trabecular patterns and may lack well-demarcated boundaries [4,28,29]. DHCC generally blend into the background of the cirrhotic liver. It accounts for < 20% of all HCC [28,29] with significantly lower 5-year survival rates than other HCCs, 13.6% vs. 46.0% [13].
TC	**Diffuse sclerosing variant papillary thyroid carcinoma (DSVPTC)** is characterized by histologic features of numerous psammoma bodies, extensive lymphocytic infiltration, squamous metaplasia, diffuse fibrosis, calcification, and absence of string colloids together. DSVPTC, with highly diffuse appearance, can involve the thyroid gland extensively without forming a dominant mass [7,30]. This subtype accounts for < 7% of all TCs [7] with significantly lower 5-year survival rates than the classic papillary thyroid carcinoma, 74.4% vs. 89.4% [14].

#5: Hypoxia & Malignancy Level

- While persistent intracellular alkalization drives the development of cancer, the hypoxia level is the key factor that determines the grade (分化度 of a cancer

- The kay idea:





应用#6: 为什么胆管癌特别恶性

应用以下发现:

$$R(OH^-, FR) \approx R(H^+, NT) + R(H^+, SA) + \varepsilon$$

前者驱动细胞增殖，后者驱动细胞转移

Computational analyses to reveal the key determinants of the high malignancy level of cholangiocarcinoma

January 2025 · Journal of Translational Internal Medicine 12(6):602-617
DOI: 10.1515/jtim-2024-0033

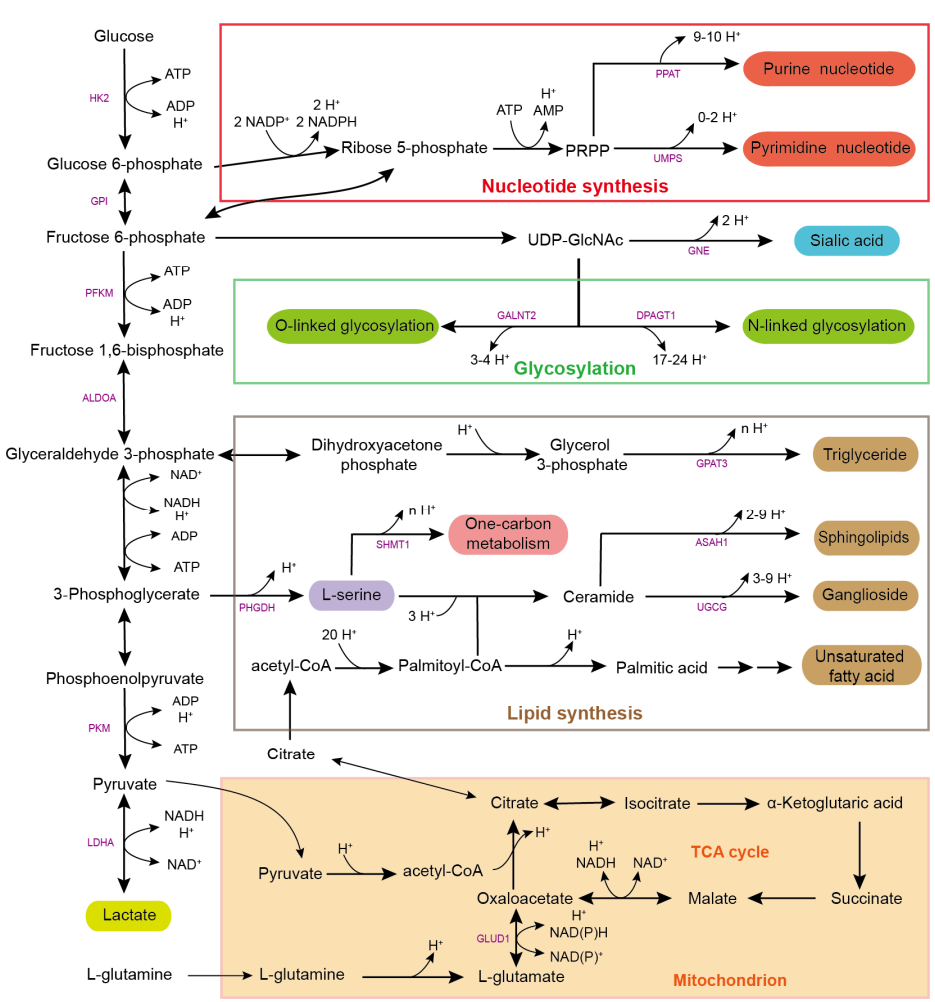
Xuan Li · Aoran Liu · Xuechen Mu · Show all 9 authors · Ying Xu

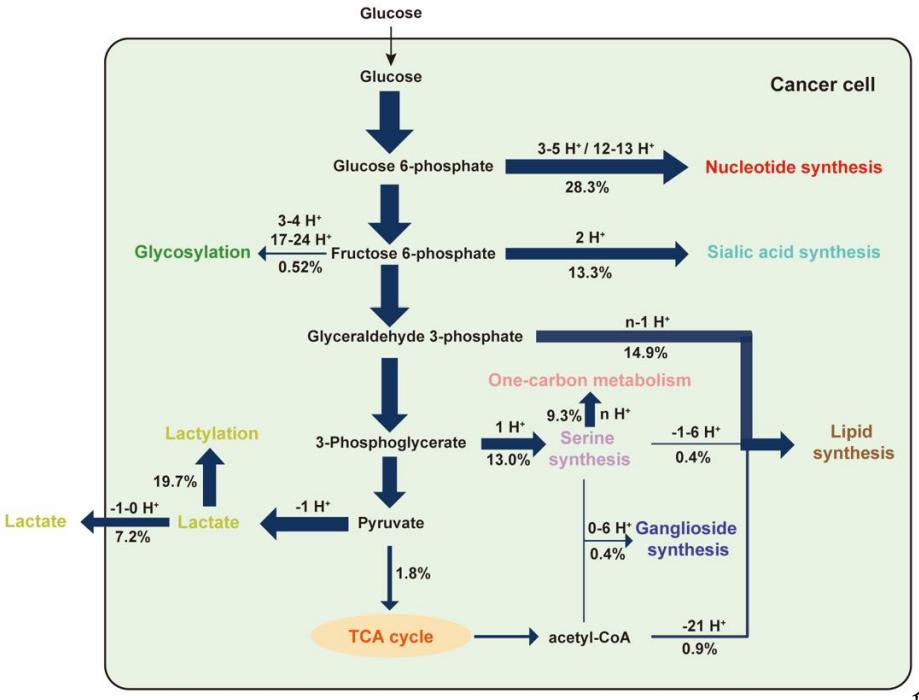
胆汁酸抑制细胞周期，因此抑制核苷酸合成，这迫使细胞加大**唾液酸合成**来维持pH稳定，而唾液酸浓度的增加驱动肿瘤细胞迁徙

- 肿瘤患者93%以上死于肿瘤转移

李轩

应用#7:解析肿瘤需要大量糖的原因





穆学琛　　黄振羽

Quantitative Biology
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On why cancer cells require a great amount of glucose

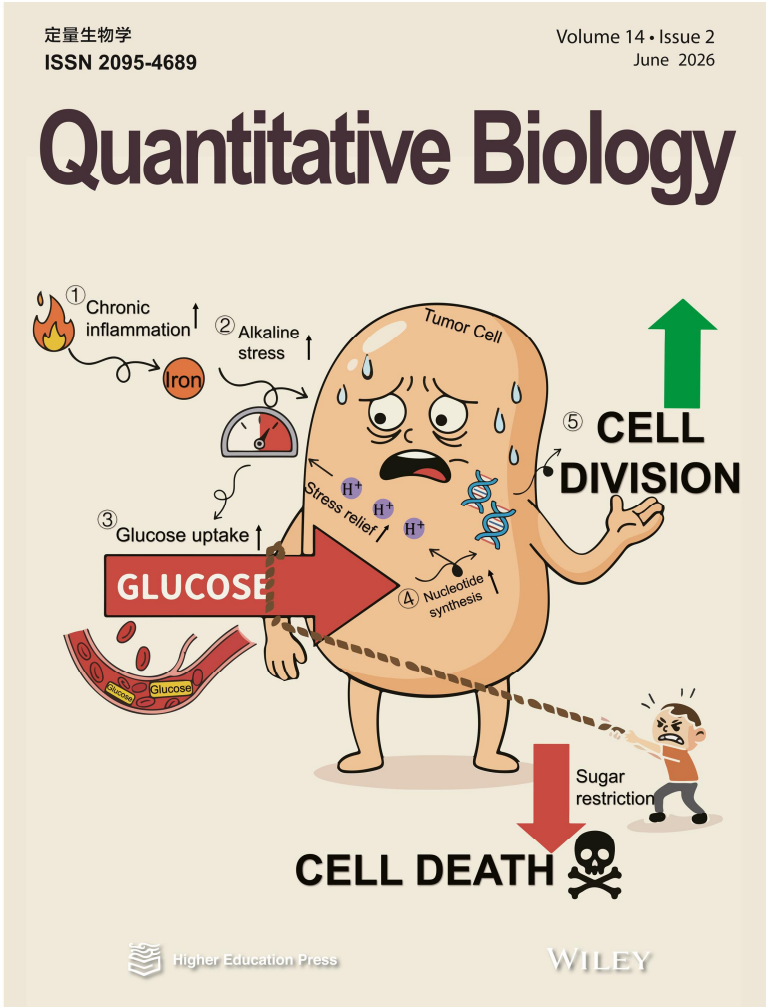
Xuechen Mu, Aoran Liu, Rui Shi, Long Xu, Zhenyu Huang, Ye Zhang, Ying Xu

First published: 05 December 2025 | https://doi.org/10.1002/qub2.70025 | VIEW METRICS

Xuechen Mu and Aoran Liu contributed equally to this work.

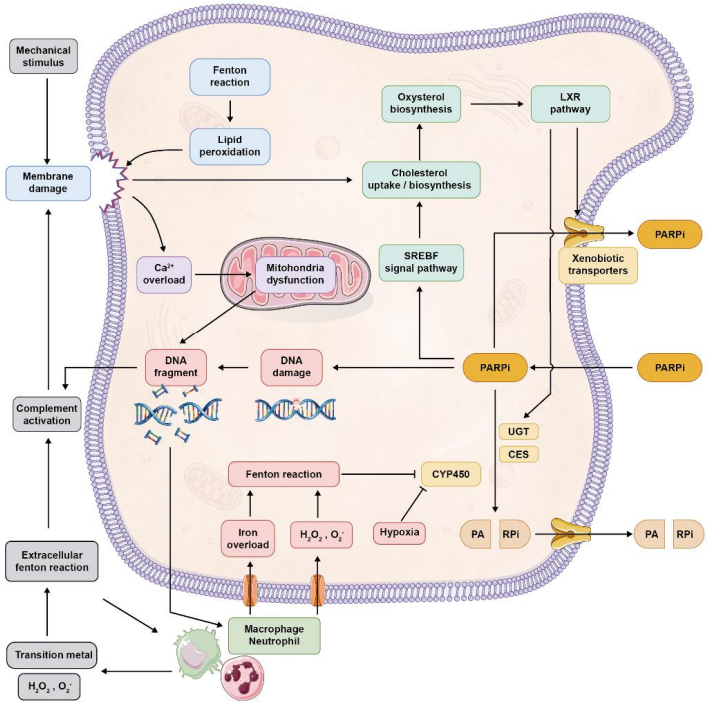
Abstract

The traditional thinking has been that cancer cells require a great amount of glucose to support their rapid growth, but the reality may be different. We have previously demonstrated that all cancer cells in The Cancer Genome Atlas harbor persistent Fenton reactions in their cytosol, which generate OH^- and ultimately kill the cells by alkalosis if not neutralized timely. Here, we present data to show that (1) cancer cells uptake large amounts of glucose to produce sufficient levels of H^+ions to keep the cytosolic pH stable, hence keeping the cells viable; (2) *de novo* nucleotide biosynthesis represents the predominant acidifying pathway and gets on average the largest allocation of glucose metabolic flux among the 19 cancer types investigated; and (3) although the H^+ions produced by nucleotide biosynthesis and other acidifiers keep the cells alive, the synthesized nucleotides drive cancerous cell proliferation. Taken together, it is not that cancerous cell division requires high levels of glucose imports, instead it is the life-saving nucleotide syntheses that drive cell division. Understanding this causal relationship correctly is significant since it explains why cancers depend so heavily on glucose but not on other nutrients. More importantly, this realization may lead to fundamentally novel and more effective ways to treat cancer.



应用#8：肿瘤耐药机理解析

- 通过对比分析对PARP抑制剂耐药的卵巢癌及没有使用这一药物的卵巢癌组织转录数据分析，我们建立了以下具有广泛意义的肿瘤耐药机制



芬顿反应 → 细胞膜受损 → 胆固醇合成 & 摄入上升 → 胆固醇被氧化成羟基胆固醇 → LXR上升 → 异物代谢上升→氧化药物 & 释放药物 → 耐药

许龙

#9: Determinants of Metastasized Targets

- 是什么导致肿瘤转移到大脑？
- 比较分析TCGA中转移到脑及转移到其它器官的各种原发癌的转录数据
- 回答以下两个问题：
- Question #1: what characteristics do brain-metastasizing cancers have to go through brain-blood barrier (BBB)?
- Question #2: what characteristics do brain-metastasizing cancers have for it to survive in brain?

Determinants of Metastasized Targets

- Published studies have shown that it is relatively easy for lipophilic molecules with low molecular weights and overall positive charges to cross the BBB, which can be captured by the following quantities

$$EP(i) = N_R(i) + N_H(i) + N_K(i) \quad (1)$$

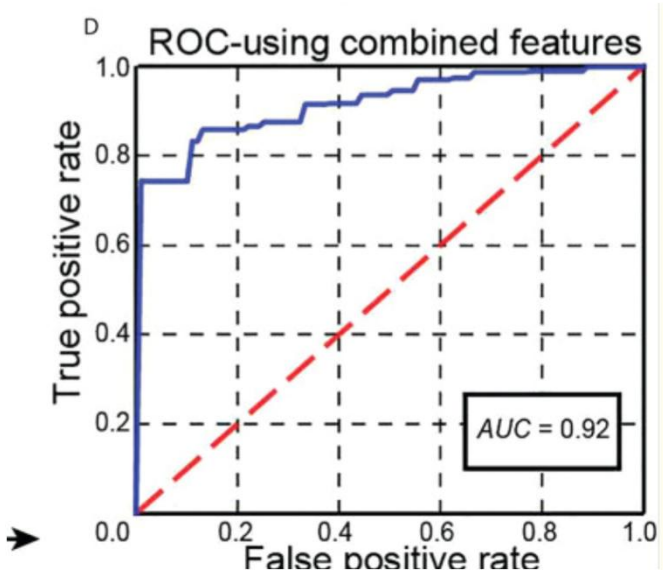
$$EN(i) = N_D(i) + N_E(i) \quad (2)$$

$$EC(i) = EP(i) - EN(i) \quad (3)$$

$$EW(i) = W \cdot N(i) \quad (4)$$

$$EH(i) = H \cdot N(i) \quad (5)$$

刘丁赟



Determinants of Metastasized Targets

- In addition, cancer cells metastasized to brain tend to express more proteins involved survival under stressors typically found in neuronal tissues

Front Oncol. 2022 Sep 28;12:1003715. doi: 10.3389/fonc.2022.1003715

Brain metastases: It takes two factors for a primary cancer to metastasize to brain

Dingyun Liu [1,2], Jun Bai [1,3], Qian Chen [1,2], Renbo Tan [1,2], Zheng An [1,4], Jun Xiao [1,2], Yingwei Qu [1,2], Ying Xu [1,4,*]

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PMCID: PMC9554149 PMID: 36248975

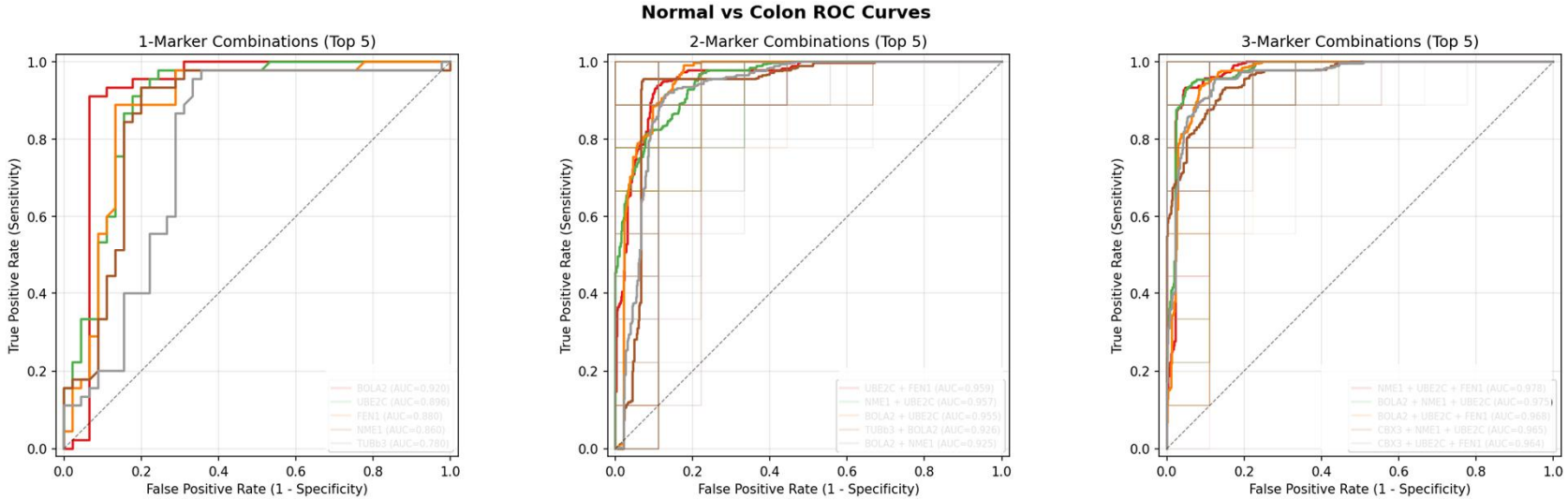
应用#10：肿瘤血液标识物预测

我们研发了一套预测**泛肿瘤**血液标识物（17种肿瘤）的计算方法：

- 膀胱癌(BLCA)，乳腺癌(BRCA)，宫颈癌(CESC)，胆管癌(CHOL)，结直肠癌(COAD，READ)，食管癌(ESCA)，肝细胞癌(LIHC)，肺癌(LUAD，LUSC)，卵巢癌(OV)，胰腺癌(PAAD)，前列腺癌(PRAD)，胃癌(STAD)，睾丸癌(TGCT)，甲状腺癌(THCA)，和子宫内膜癌(UCEC)

- #1:找到在17种肿瘤中比相应对照器官/组织普遍上调的基因
- #2:去除在公共数据库中任何非肿瘤疾病中上调的基因 -- 几个百个基因
- #3:预测其蛋白能分泌入血的基因 -- ～100 基因
- #4：根据我们对肿瘤发生、发展的理解， 共选出最好的九个基因（已申请专利）

- 已在四种肿瘤（BRCA、COAD、LIHC、LUAD）各45个患者血液vs 非肿瘤（对应性别、年龄的）人群做了验证：**1-组合：AUC 92%； 2-组合：AUC 95.9%；3-组合：AUC 97.8%（BRCA）**



- **近期目标：**验证在17种肿瘤（每种50-100个血液样本，尽量早期的）我们血液标识物的预测水平

许龙　穆学琛　石博城　张晔

- Metastasized cancers

Why Metastatic Cancer So Malignant

- For reasons that are not understood, once a cancer is metastasized to a new location, it becomes substantially more aggressive and more difficult to control; over 93% of cancer death is related to metastasized cancers
- Drugs designed for primary cancers generally lose their effectiveness on metastatic cancers, and currently no drugs specifically designed for metastatic cancers
- Question: why cancer becomes so deadly once it is metastasized to new locations

How to Address this Issue?

- We have collected all the gene-expression data of metastatic cancer tissue samples with matching primary cancer tissues from public database on the Internet
- Resulting in 16 sets of genome-scale transcriptomic data, covering 11 types of primary-to-metastatic cancers and 858 tissue sample
  - prostate-to-bone metastases;
  - breast-to-brain metastases;
  - breast-to-liver, colon-to-liver, pancreas-to-liver and prostate-to-liver metastases;
  - bone-to-lung, breast-to-lung, colon-to-lung, kidney-to-lung and pancreas-to-lung metastases

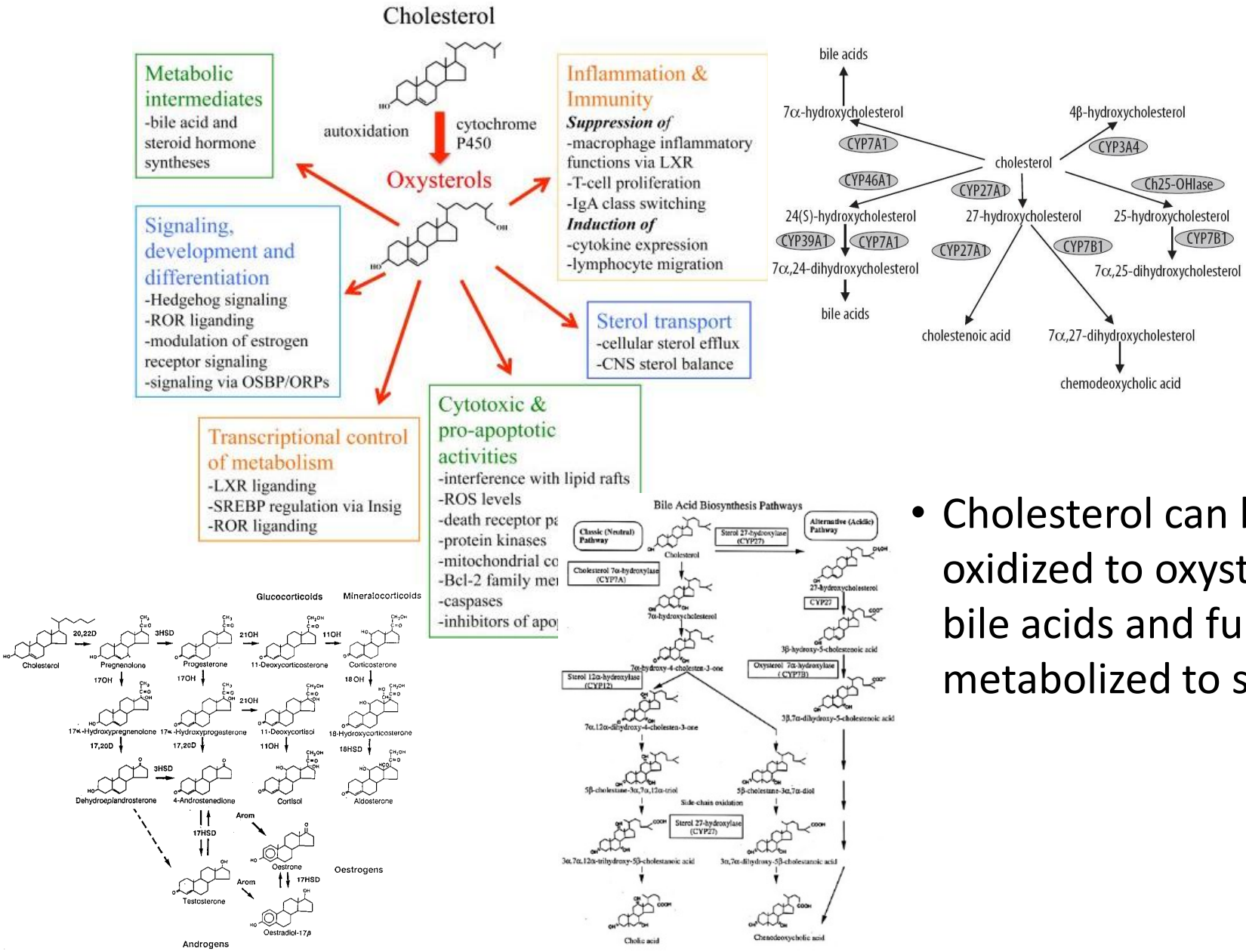
Questions to Ask

- Question #1: are there genes (pathways) consistently up-regulated across all the metastatic cancer samples in comparison with the matching primary cancer tissues
- The answer is yes, there are a few dozen such genes?

- Question #2: what are the functions of these genes?
- Answer: A substantial fraction of these genes are involved cholesterol influx and metabolism

More Questions to Ask

- Question #3: what do cholesterols do in metastatic cancers?
- Question #4: why do metastatic cancers need cholesterol?
- Both questions can be answered through mining omic data!

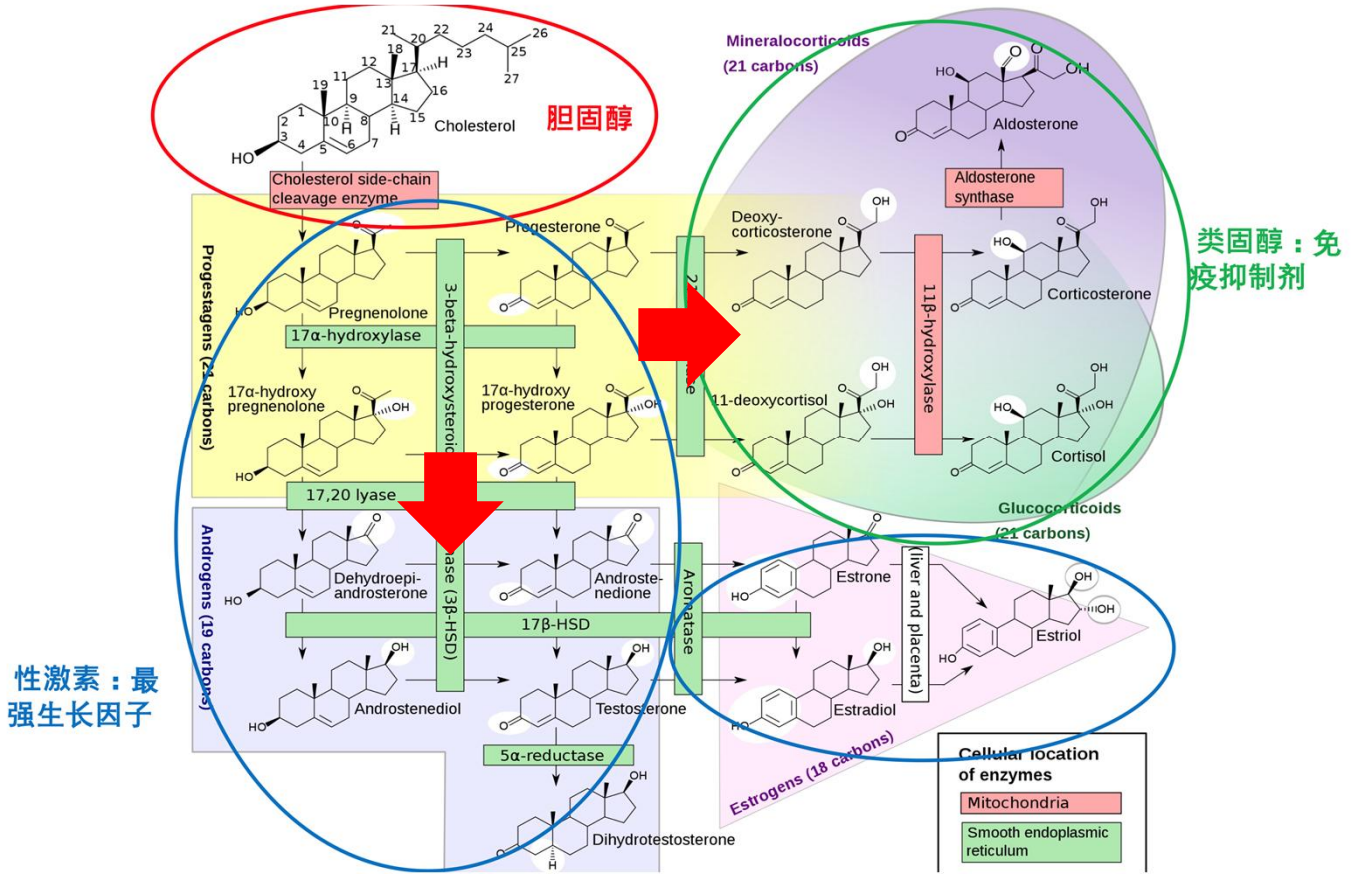


- Cholesterol can be oxidized to oxysterols, bile acids and further metabolized to steroids

Key Observations

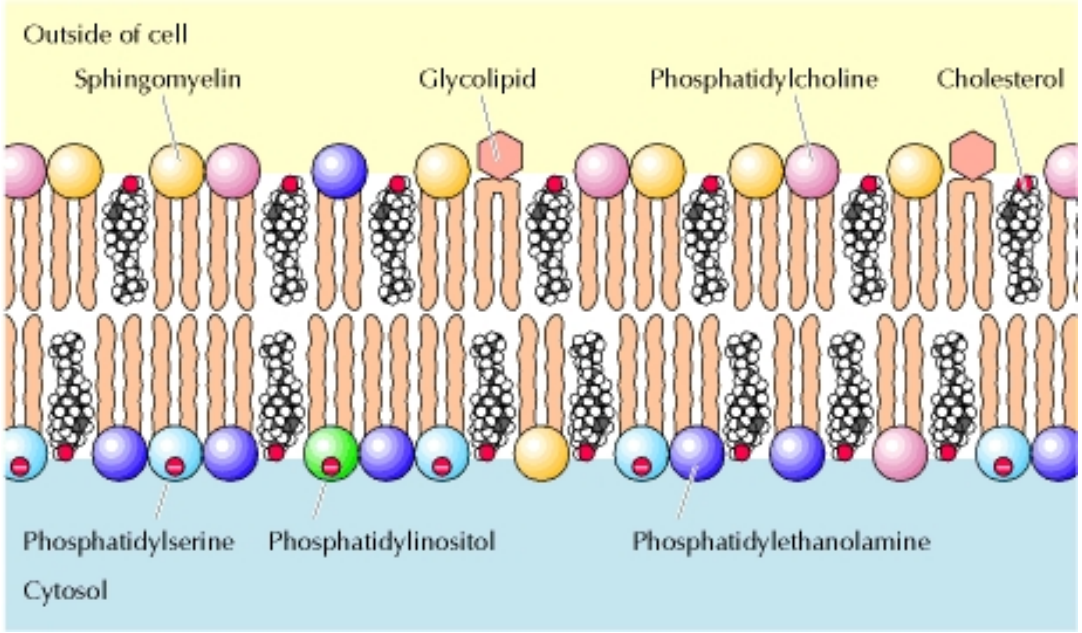
- Cells obtain cholesterol through either biosynthesis (HMG-CoA) or uptake from circulation of cholesterol-carrying lipoprotein particles: high, low and very low-density lipoproteins (HDL, LDL and VLDL) and chylomicrons.
- The average percentages of cholesterol (or cholesterol ester) in these particles are: 5% in chylomicron, 25% in VLDL, 47% in HDL and 61% in LDL
- By checking these genes' expression levels, one can infer if cholesterol uptake or biosynthesis is up-regulated

Cholesterol Metabolism



Why Cholesterol?

- Among the many functions of cholesterols, a key function is that they are a key ingredient of cell membrane
- It is known that cholesterol concentration affects O2 permeability: the higher the cholesterol concentration, the lower the permeability



Cholesterol as a Barrier of O2

- Published studies have shown red blood cells tend to have lower cholesterol concentration in their plasma membrane in more hypoxic environment
- Primary cancer cells generally have lower level of cholesterol in their plasma membrane
- The complement system keeps attacking the plasma membrane of metastasized cancers, leading to their damaged membrane
- All these lead to our main hypothesis: cancer cells need to increase their membrane cholesterol when they move from hypoxic environment to O2-rich environment

O2-Rich *versus* Cholesterol

- Metastatic cancers tend to have higher O2 level and oxidative stress compared to their primary counterparts, revealed by expression levels of HIF, SOD and other oxidative stress response genes

- Multiple evidences show that membranes of metastatic cancer cells tend to be damaged by increased oxidative stress
  - genes in response to membrane damages are up-regulated
  - the catabolism of the oxidized products of phospholipids, a key component of cell membrane, is up-regulated
  - indication of lipid peroxidation

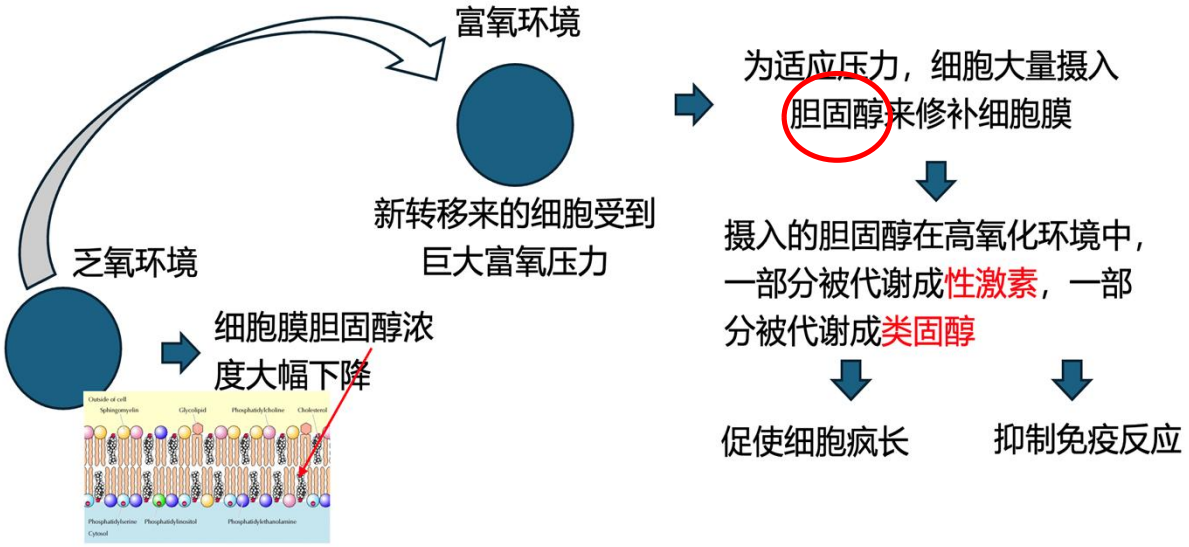
O2-Rich *versus* Cholesterol

- These lead to the (continuous) loss of membrane cholesterol, hence creating a need for (continuous) influx of cholesterol

- Published studies have established that (1) SREBP is the main regulator for cholesterol influx; (2) O2 can regulate SREBP, and PDZK1 is another regulator

- Strong positive correlations are observed in all datasets between the responses to membrane damages and SREBP or PDZK1

一旦肿瘤转移了


富氧环境
新转移来的细胞受到
巨大富氧压力
乏氧环境
细胞膜胆固醇浓
度大幅下降
为适应压力，细胞大量摄入
胆固醇来修补细胞膜
摄入的胆固醇在高氧化环境中，
一部分被代谢成性激素，一部
分被代谢成类固醇
促使细胞疯长
抑制免疫反应

What is Cancer

- Cancer is a disease in which intracellular pH is continuously elevated, and cell proliferation is an essential part of the survival process under persistent intracellular alkalizing stress.
- It generally takes two types of factors for a cancer to take place, namely endogenous driving forces for cell proliferation and exogenous growth factors specific to individual cancer types
- If this is experimentally validated, cancer could be potentially treated through stopping the availability of growth factors needed by individual cancers.

Becoming A Cancer Systems Biologist:

the basic requirements

- Become knowledgeable in molecular/cell biology, evolutionary biology, human metabolism, biochemistry
- Become proficient in one programming language, able to use machine/deep learning methods, capable of doing simple statistical analyses
- Familiar with various relevant databases such as TCGA, GO, GTEx, BioCyc,
- Able to conduct the basic statistical analyses of omic data

Becoming A Cancer Systems Biologist:

the more the better

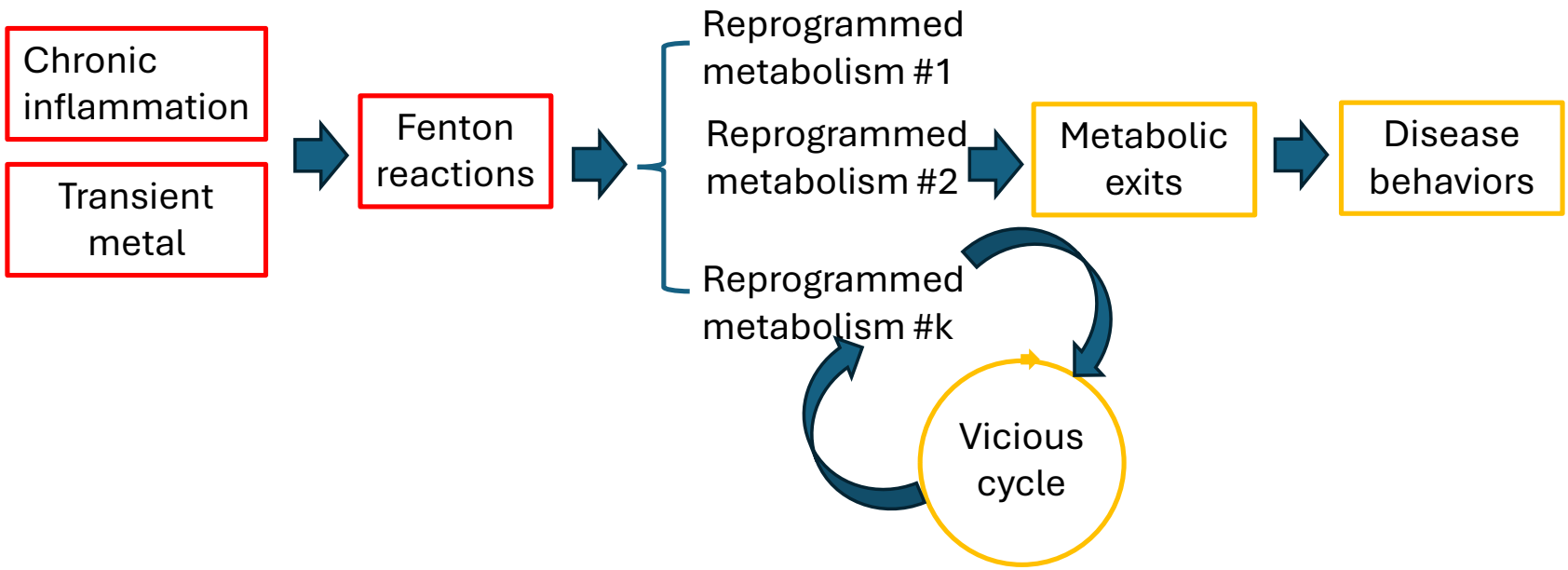
- Able to interpret hundreds of biological pathways enriched by differentially expressed genes in cancer vs. controls
- Capable of building qualitative disease evolution model based on statistical analyses such as Bayesian networks
- Able to build quantitative dynamic models for cancer evolution using existing mathematical frameworks
- Capable of developing quantitative models based on chemical reaction kinetic and thermodynamic theories

Perspectives

- Personally, I believe that we are getting close to getting full understanding of cancer biology
- Highly reliable blood-borne biomarkers for earlier detection of cancer will emerge very soon
- Highly effective treatment strategies will become available through 老药新用

Perspectives

- Similar research strategies should be applicable to other diseases such as Alzheimer's disease, diabetes, Parkinson disease …..



Summary: A New Way to Study Complex Diseases

- Research on the drivers and mechanisms of disease onset and progression: through **multi-omics data** analysis, AI-based **causal inference**, and **computational chemistry** analysis, identify disrupted chemical homeostasis—the **major driving stressors** at the chemical level
- Discover and establish which RMs are utilized to maintain chemical homeostasis—**the evolutionary pathways**
- Epigenetic regulation, genetic mutations, and dedifferentiation are utilized to help cells initiate RMs and adapt to the stressors —**stress response biology**
- A systematic approach is needed to integrate data and chemical/physical theories to constrain the solution space, so that the evolutionary models solved are biologically meaningful—**systems biology**
- By doing so, we can identify the **root causes** and **core mechanisms** of cancers, AD, and other diseases

Acknowledgements

- All members in the Systems Biology Lab for Metabolic Reprogramming, School of Medicine, **Southern University of Science and Technology**

- Past members of the Computational Systems Biology Lab, the **University of Georgia**
- Funding support from Chinese National Natural Science Foundation