ICSB2025 (December 6-7, 2025)

- The 14th International Workshop on Cancer Systems Biology
- https://sysbio.med.sustech.edu.cn/

12月6日（上午）

Session	时间	内容	主讲人
开幕式	8:30–8:50	开幕式	孙之荣（清华大学） 徐鹰（南方科技大学）
	8:50–9:00	合影	
Session1	9:00–9:50	主题报告：Metabolic Regulation of Cancer and Immunity	吕志民（浙江大学）
	9:50–10:40	主题报告：Genetic Dissection of Chromatin Regulatory Network	Chao Lu（哥伦比亚大学）（线上）
Session2	10:50–11:40	主题报告：Mesenchymal Stem Cells and Inflammatory Tumor Environment	时玉舫（苏州大学）（线上）
	11:40–12:30	主题报告：Quantifying the immune temperature of cancer cells with spatial omics	Jiguang Wang（香港科技大学）

12月6日（下午）

Session	时间	内容	主讲人
Session1	14:00–14:50	主题报告：Dynamical Systems Biology with AI	陈洛南（上海交通大学）
	14:50–15:40	主题报告：铁死亡、铁科学与重大疾病诊治	王福俤（浙江大学）
	15:40–16:30	主题报告：从化学稳态失衡/再平衡的角度解析阿兹海默症（关联脑血管疾病）的发生、发展	徐鹰（南方科技大学）
Session2	16:45–17:35	主题报告：3-D chromatin structure, methylation and gene expression correlation in cancer cells	高毅勤（北京大学）
	17:35–18:25	主题报告：To Be or Not to Be —— The Existentialism of PIK3CA Mutation in Lung Cancer	季红斌（西湖大学）

12月7日（上午）

Session	时间	内容	主讲人
Session1	8:00–8:50	主题报告：Gut Microbiome/Metabolites in MASLD and HCC via Gut–Liver Axis	Jun Yu（香港中文大学）
	8:50–9:40	主题报告：Exploring the pathogenesis and translational applications of common mental disorders based on multi-omics data	岳伟华（北京大学）
	9:40–10:30	主题报告：AI × Cancer Biology：Harnessing Big Data to Decode 3D Genome Architecture and Therapeutic Vulnerabilities	Melissa J. Fullwood（南洋理工大学）
Session2	10:40–11:30	主题报告：Systems biology approaches to deciphering prostate cancer regulation	Jindan Yu（埃默里大学）
	11:30–12:20	主题报告：Advancing computational tools and resources to study metabolic reprogramming in cancer	Chi Zhang（俄勒冈健康与科学大学）

12月7日（下午）

Session	时间	内容	主讲人
Session1	13:50–14:40	主题报告：Mesoscale intravital fluorescence microscopy	吴嘉敏（清华大学）
	14:40–15:30	主题报告：Adeno-to-squamous transition drives resistance to KRAS inhibition in LKB1 mutant lung cancer	Micheal Zhang（德克萨斯大学达拉斯分校）（线上）
	15:30–16:20	主题报告：Revolutionizing Target Discovery for Complex Diseases: A Deep Learning-Driven Approach	谢正伟（北京大学）
Session2	16:35–17:25	主题报告：Cross-kingdom regulation of host metabolic homeostasis by gut microbial enzymes and metabolites	姜长涛（北京大学）（线上）
	17:25–18:15	主题报告：Percolation and its function in biological systems	Zeyu Shen（香港科技大学）

肿瘤信息学

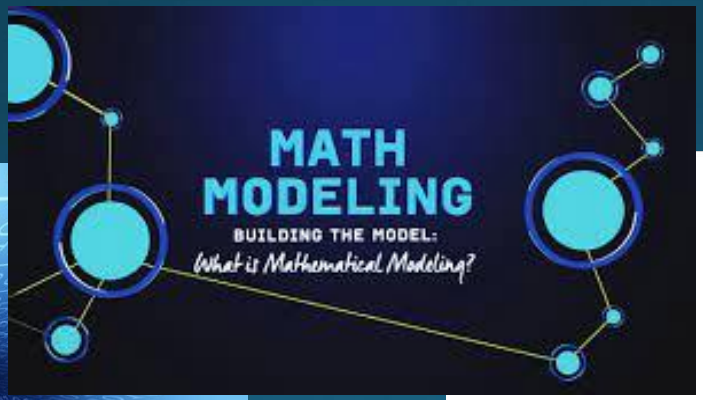
Cancer Biology: an informatics perspective

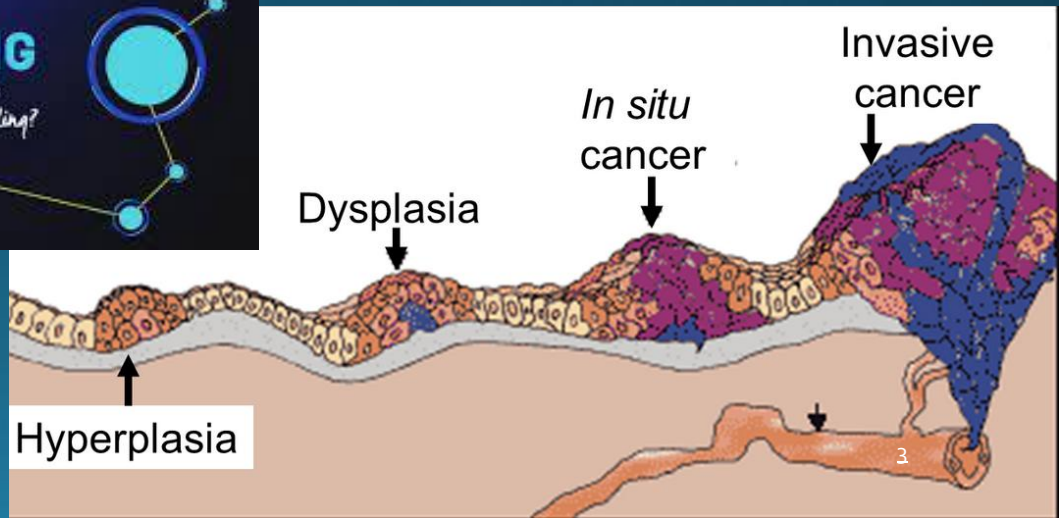
徐鹰

南方科技大学医学院

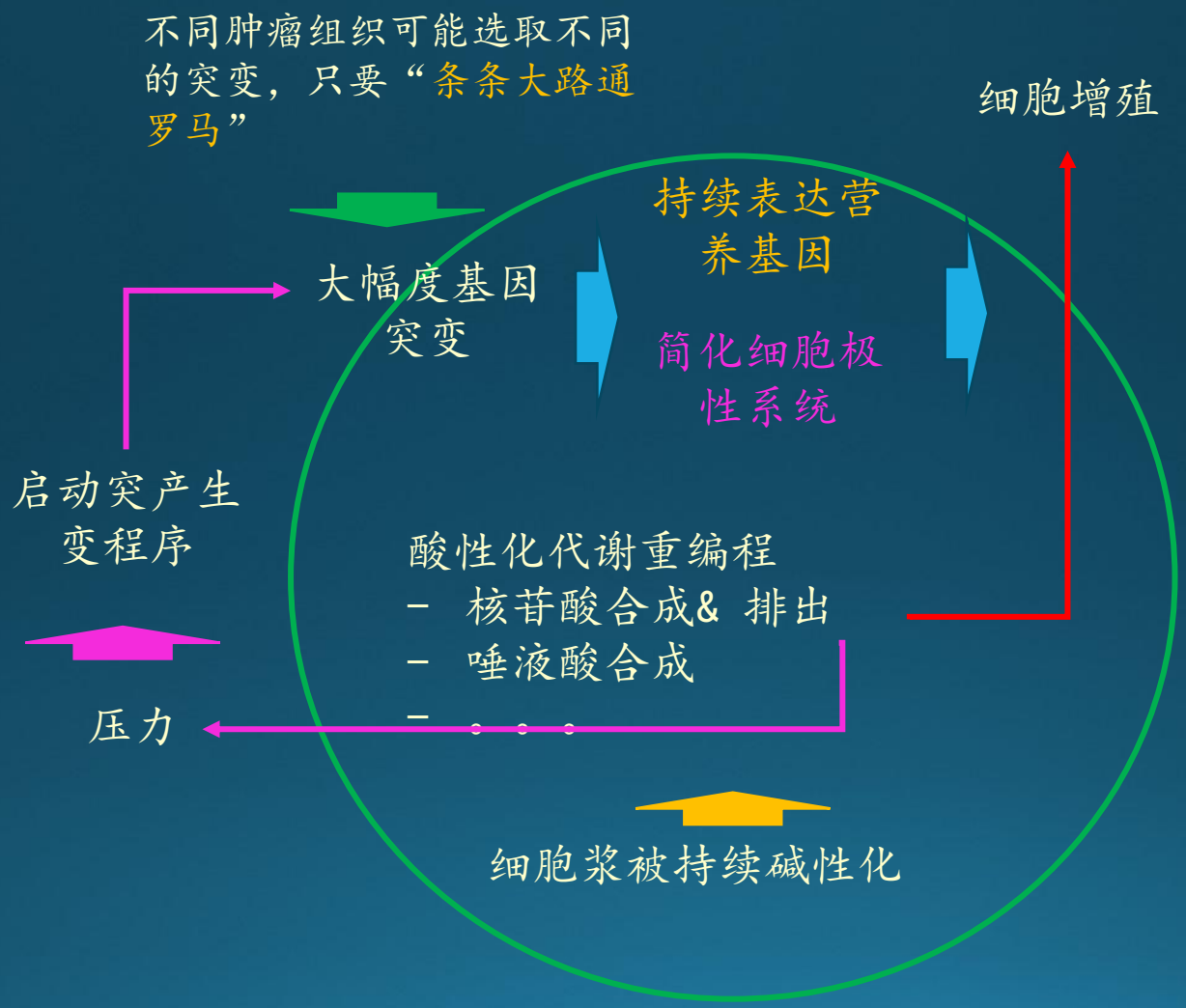
Lecture III

Various characteristics of cancer, enablers for cancer occurrence, epigenomics vs. stressors, become a cancer systems biologist





初始模型

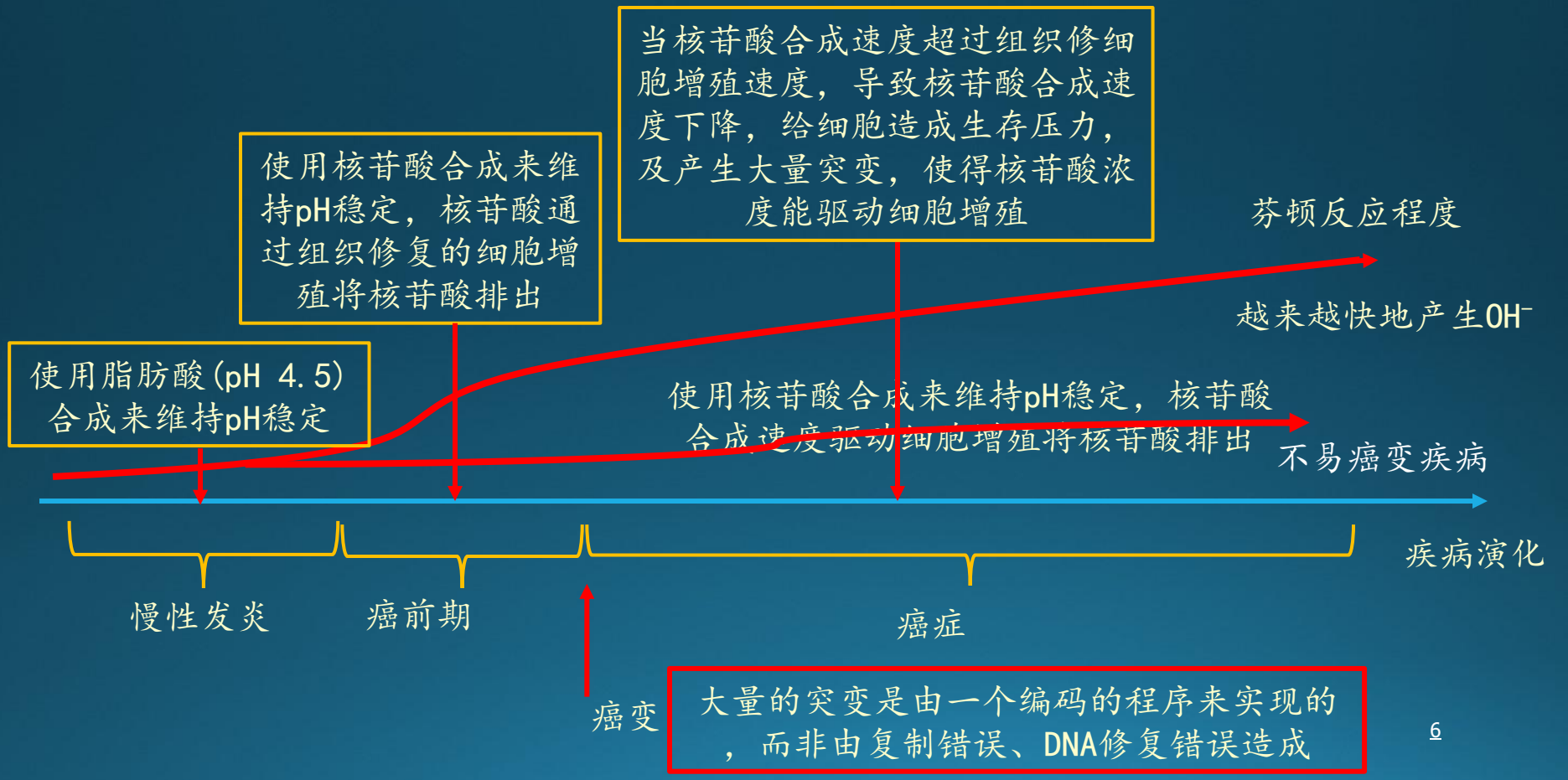

不同肿瘤组织可能选取不同的突变，只要“条条大路通罗马”
细胞增殖
持续表达营养基因
大幅度基因突变
简化细胞极性系统
启动突产生变程序
酸性化代谢重编程
– 核苷酸合成& 排出
– 唾液酸合成
– 。。。
压力
细胞浆被持续碱性化

- 如果这是疾病的“稳态”，它是如何演化到这一步的

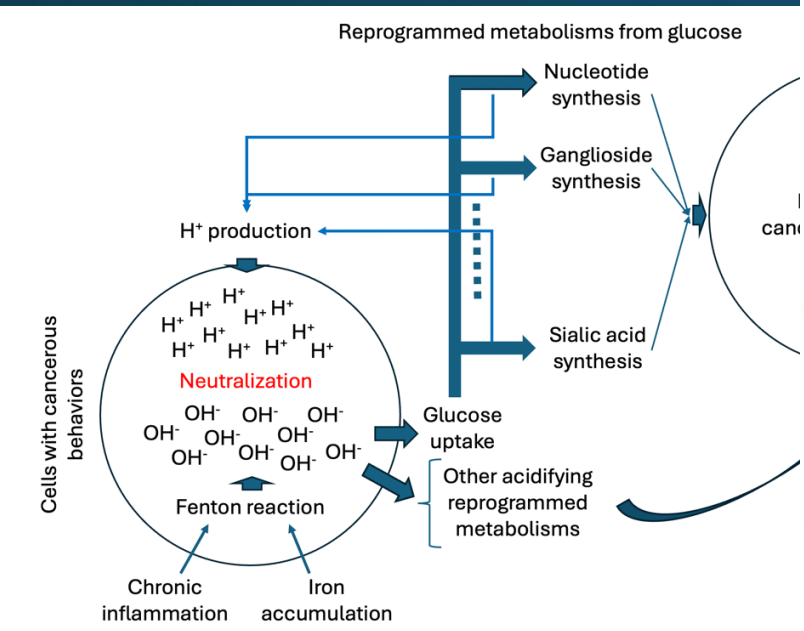
- Cancer evolution

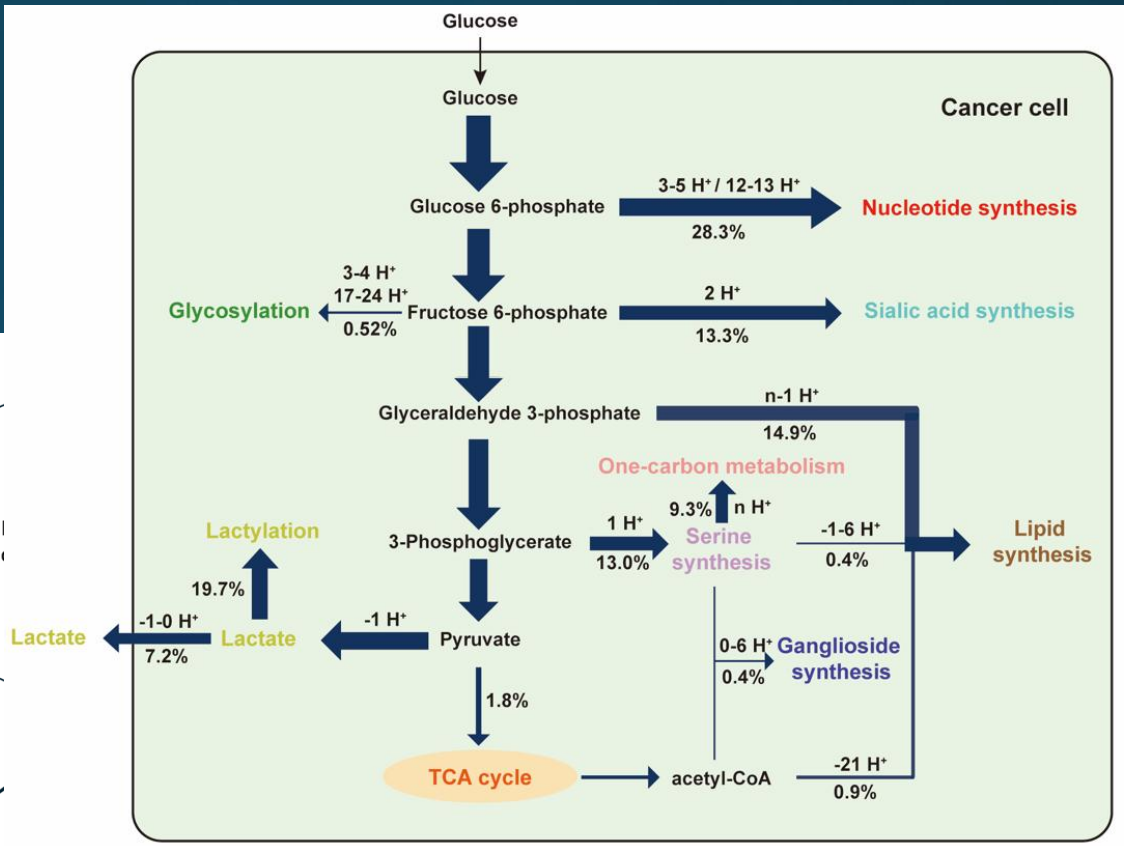
从慢性发炎到癌变

- 从慢性发炎到癌变的演化过程中，芬顿反应持续增强，细胞内的酸性化代谢重编程经过三个重要阶段

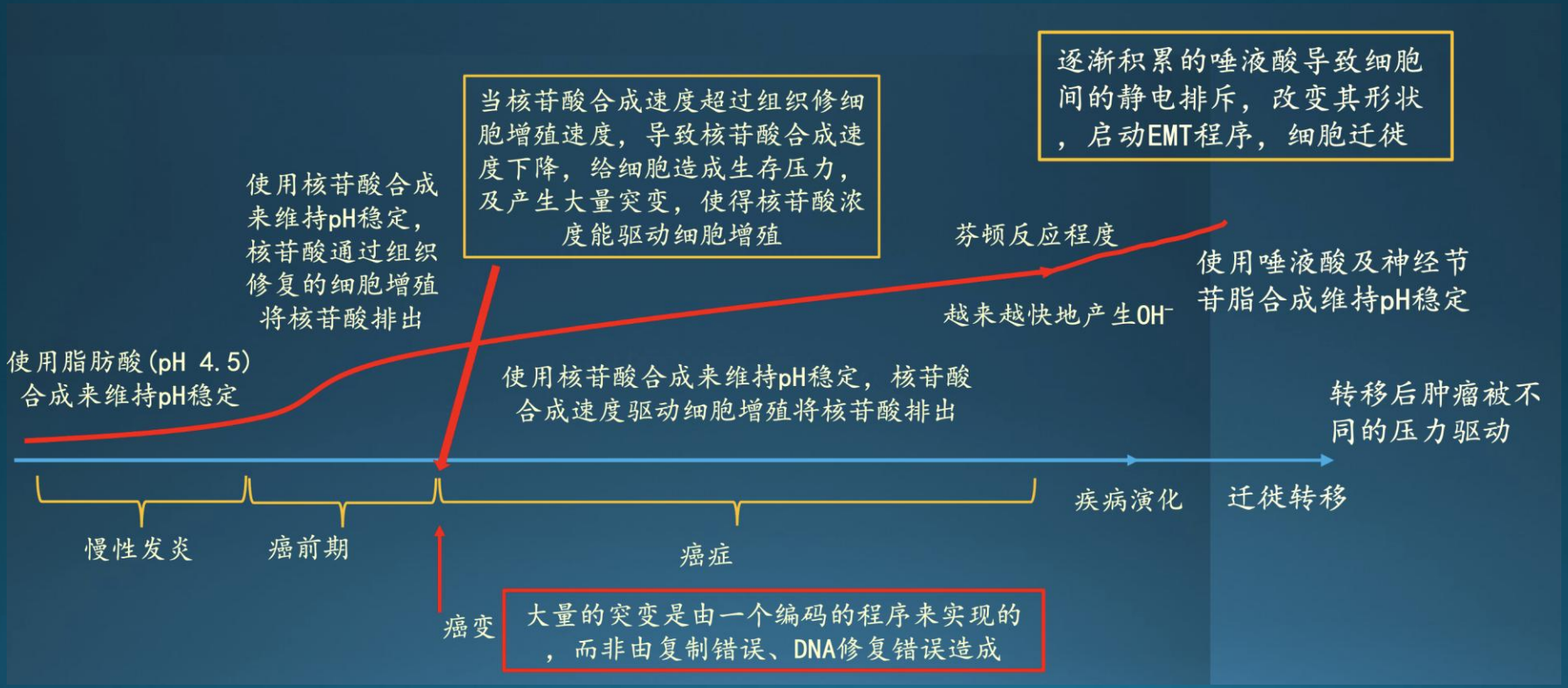


Glucose Metabolism in Cancer





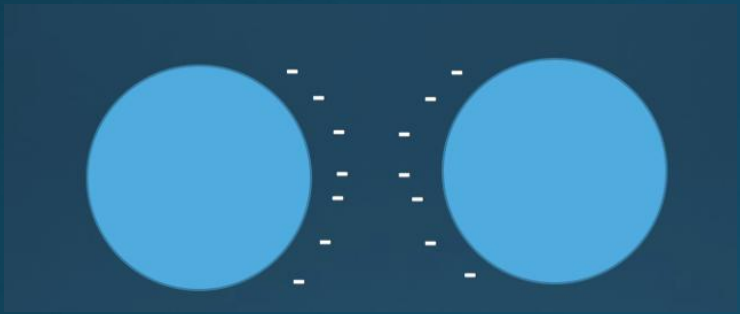
Core Model for Cancer Evolution

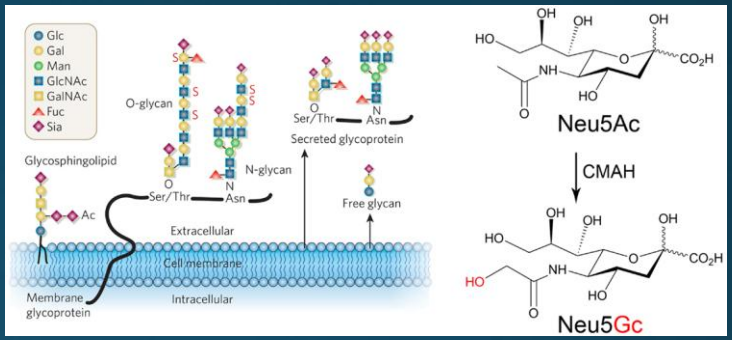


Where do the other characteristics of a cancer fit in this model?

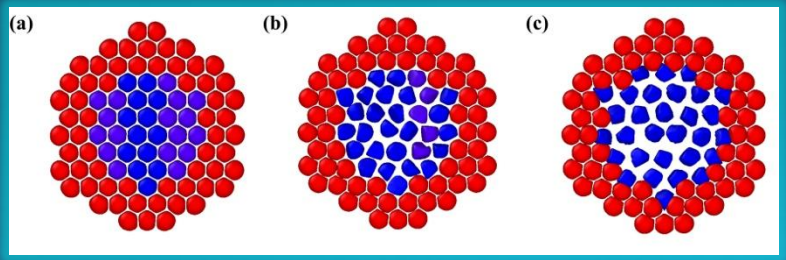
Sialic acid synthesis -> cell migration

- Majority of the cancers overproduce sialic acids and put them on cell surface
- Each sialic acid carries a negative charge





- Continuous accumulation of negative charge on cell surface will create increasingly stronger repulsion among adjacent cells



Sialic acid synthesis -> cell migration

- Published studies have established that persistent physical compression will lead to considerable deformation of cell shape and activate the epithelial-to-mesenchymal transition (EMT), which drives cell migration and metastasis

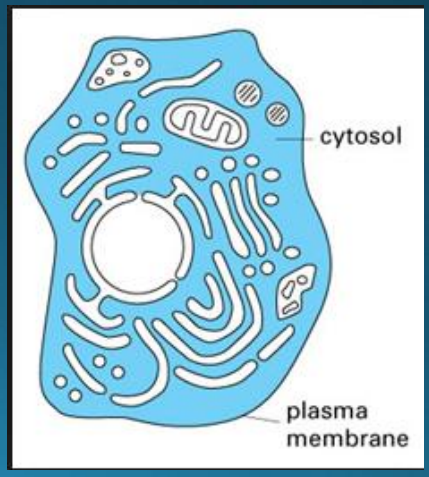
- Expression based analyses indeed reveal that key sialic acid genes show strong correlation with cell migration and reduced survival time

- We predict that gradual deployment of sialic acids on cancer cell surface plays a driving role in cancer metastasis.

Fenton Reaction and Acidifying Metabolic Reprogramming

- We have predicted that all acidifying metabolic reprogramming in each cancer tissue are induced to keep the intracellular pH stable for cells affected by Fenton reactions
- All cancer samples in TCGA use nucleotide de novo synthesis and sialic acid synthesis as the major acidifiers
  - The former drive persistent cell division and the latter drive cell migration

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



Zhou, et al. GPB, 2022.

Implications

- Guided by this "equality", we developed a model to explain why bile-duct cancer is most malignant

- A receptor of bile acids represses cell cycle progression, hence limiting the rate of nucleotide biosynthesis.
- By the above equation, syntheses of ganglioside + sialic acid must be high enough to keep the intracellular pH stable
- This drives cancer migration and metastasis, hence the high malignancy level

Implications

- By a similar analysis, we have explained why pancreatic cancer is highly malignant since some pancreatic enzymes repress cell-cycle progression

- Prediction: using the same idea, one should be able to explain why some cancers rarely metastasize.

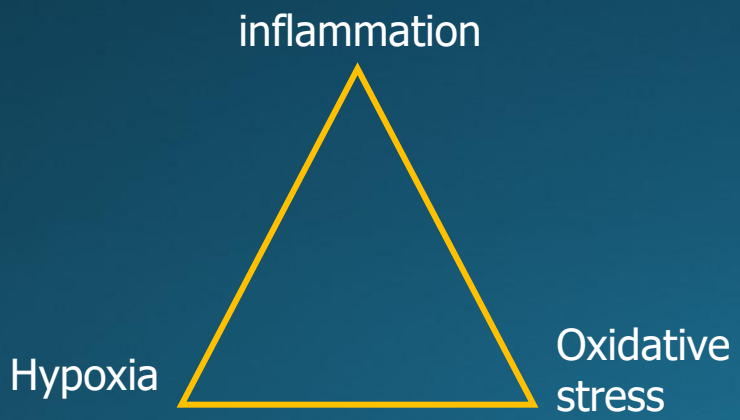
Cancer Characteristics and Causes

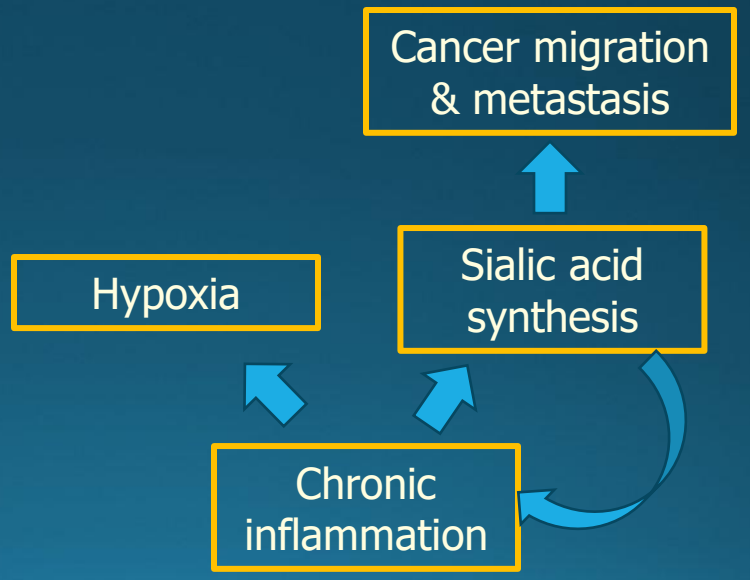
- Persistent cell division
- Cell migration
- Diffuse vs. solid tumor cancer
- Hypoxia vs. malignancy level
- Organ-specific cancer behaviors
- Drug resistance
- T cells performance in cancer tissues
- Age-dependent cancer occurrence rates
- The distinct biology of metastasized cancers

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

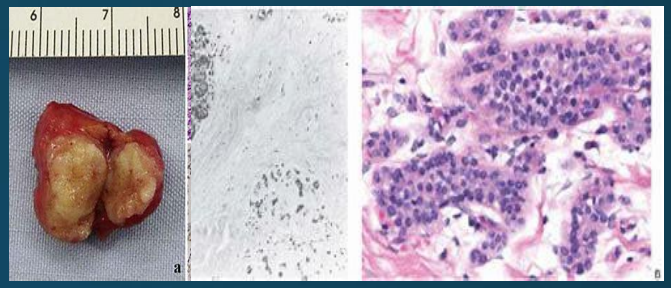
- The kay idea:



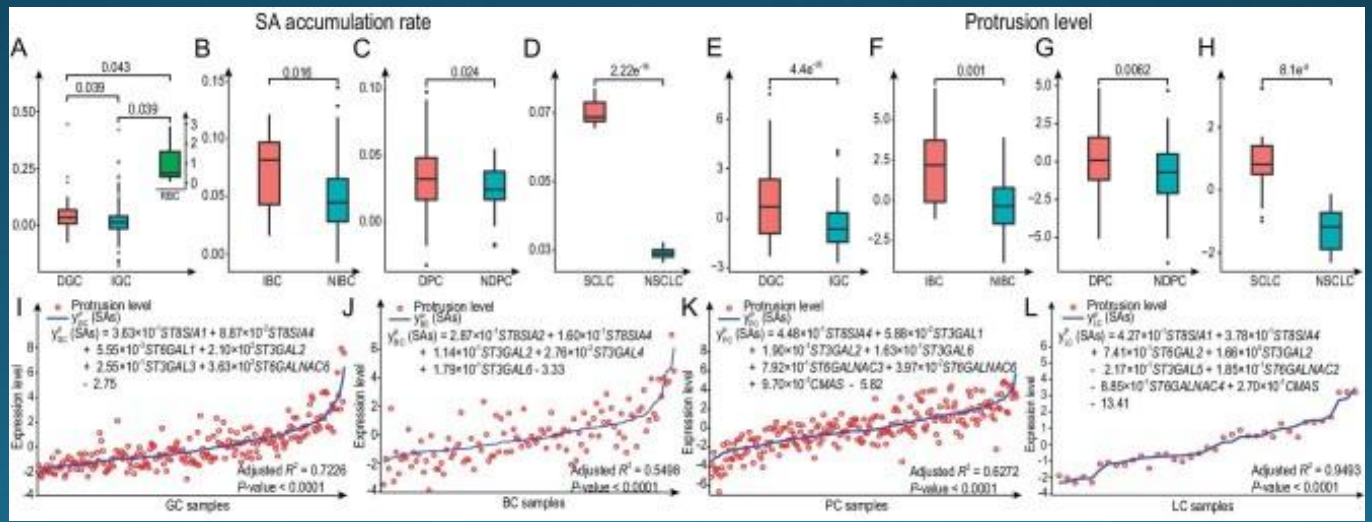


Solid vs. Diffused Cancer Types

- 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?

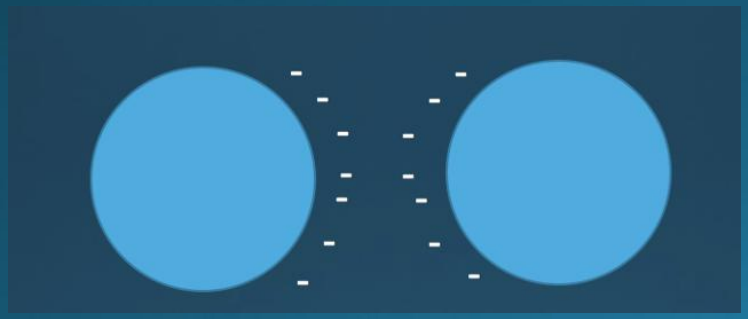


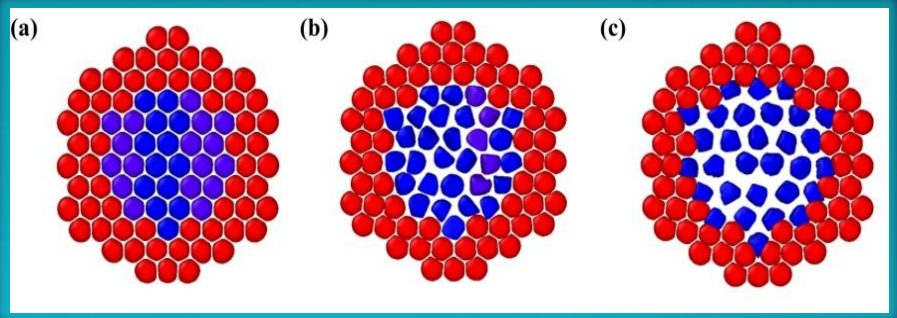
- 差异性表达分析：确定哪些基因在弥散性肿瘤比相应的实体瘤一致性的上调



弥散性的主要原因

- 弥散性肿瘤的细胞表面积累了更多的唾液酸
- 带负电的唾液酸导致细胞间的相互排斥
- 胃癌弥散性肿瘤细胞间的排斥力是实体瘤的4倍
- 弥散性胃癌细胞间的排斥力可导致细胞形变，而细胞的形变将激活上皮细胞– 间充质转化程序，驱动细胞移动





为什么有些肿瘤用唾液酸

- 芬顿反应更高 -》唾液酸更高
- 环境因素抑制细胞增殖 -》唾液酸更高
  - 直接抑制细胞增殖：胆管癌、胰腺癌
  - 唾液酸抑制发炎，导致炎症越厉害，唾液酸越多？？

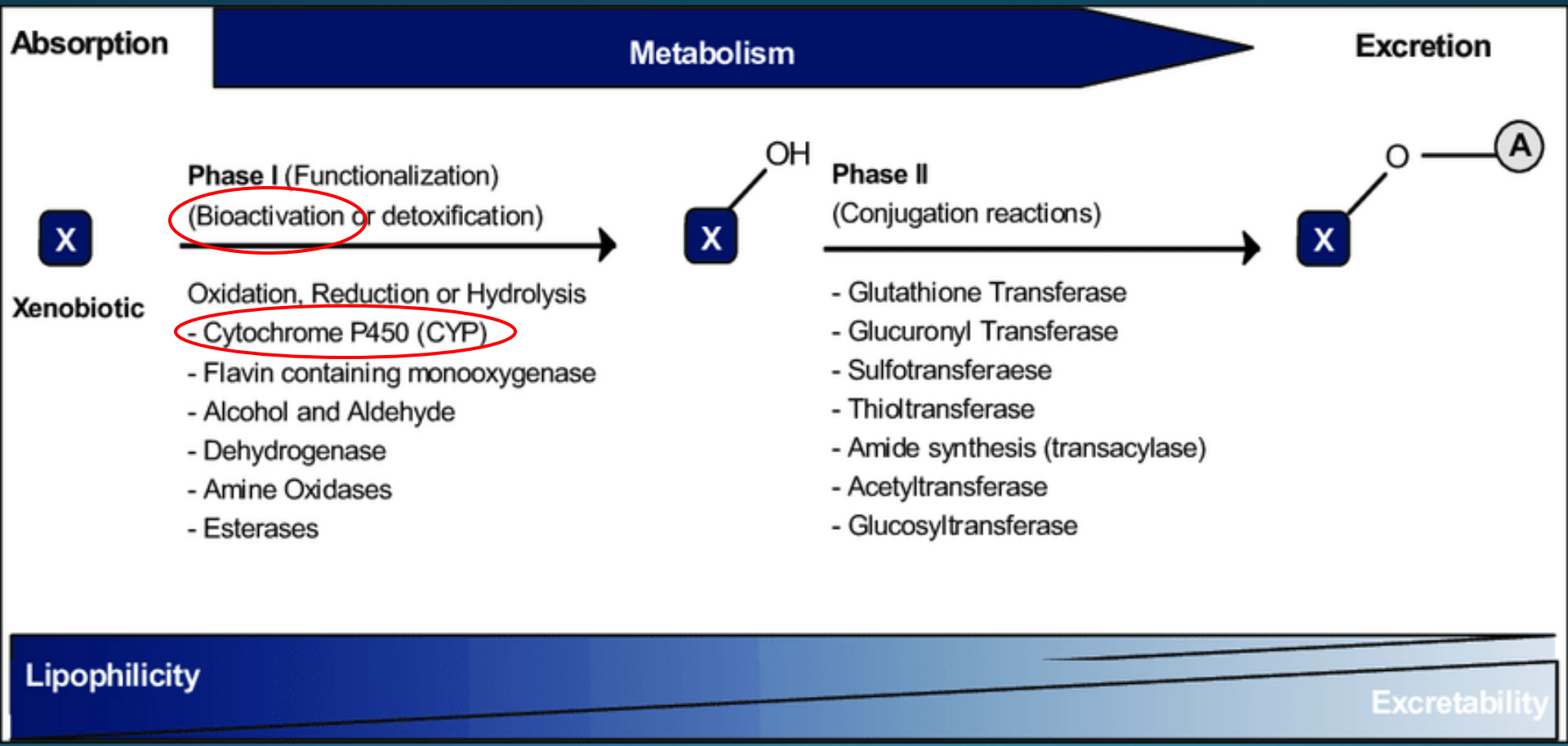
$$R(FR, OH^-) \approx \sum_i R(Mi, H^+)$$

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].

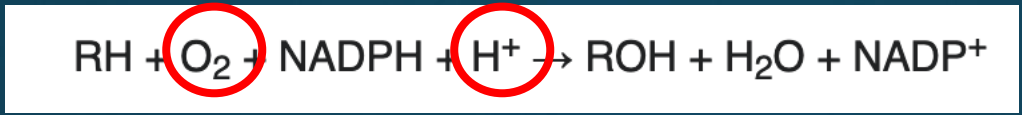
Drug Resistance

- Cellular drug metabolism



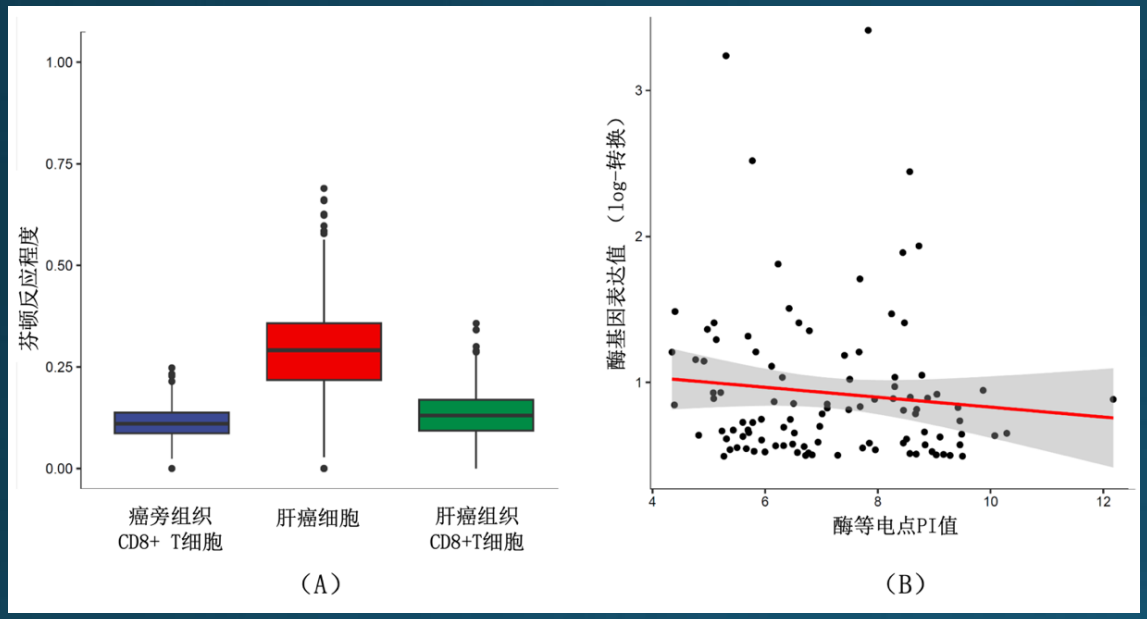
Drug Resistance

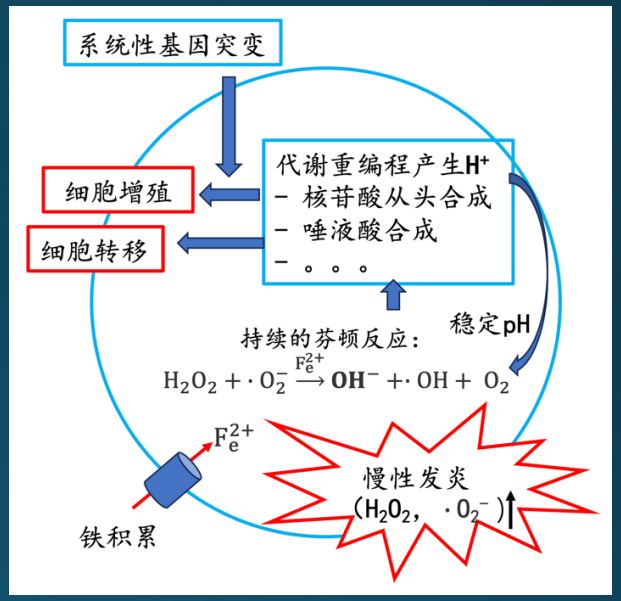
- The general form of P450 enzymes



- Cancer tissue cells progressively become more hypoxic and alkaline, namely lower O2 and H^+
- The effectiveness of the enzymes decreases gradually

T cells in Cancer

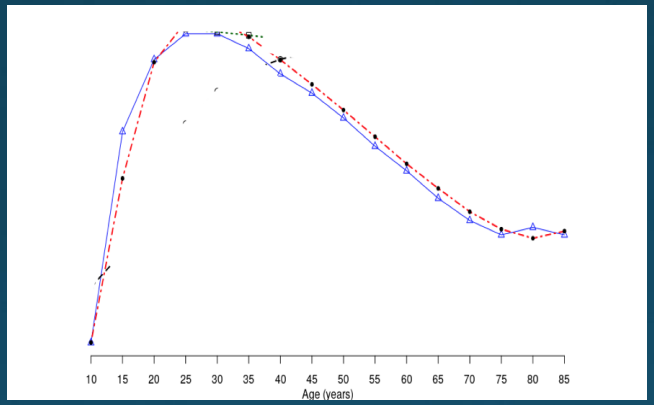




In human cancer， it is combination of extracellular acidity, intracellular Fenton reaction and nutrient deprivation that leads to the under/no performance of cytotoxic T cells

与年龄相关的肿瘤发病率

- 绝大部分的肿瘤发病率曲线（vs. 年龄）是单峰分布

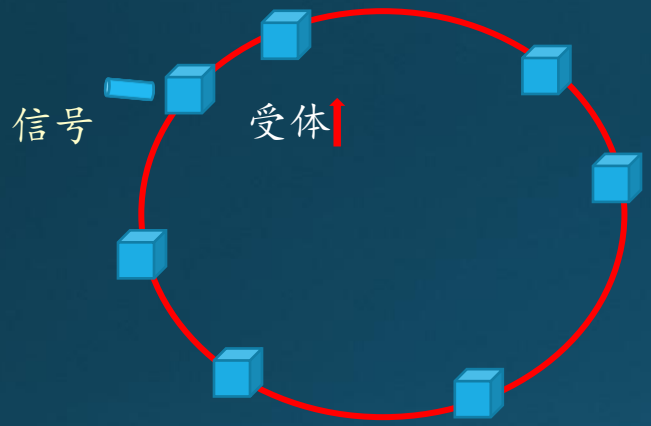


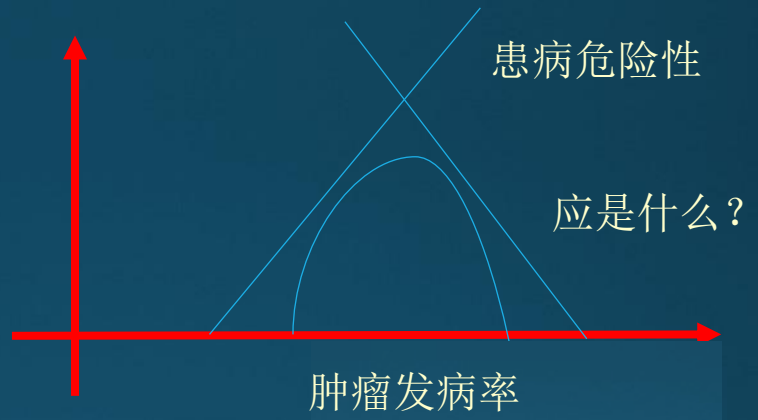
三阴性乳腺癌发病率

- 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：有两个因素决定三阴性乳腺癌的发病率：一个随年龄上升而上升，一个随年龄上升而下降

与年龄相关的肿瘤发病率

- 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





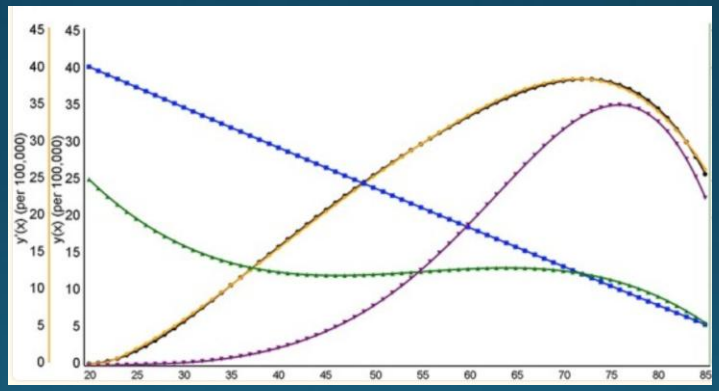
- 科学假设：每种肿瘤需要特有的、血液中的某些生长因子，如雌性、雄性激素

- 计算验证：寻找血液中的生长因子，（1）其细胞表面受体在肿瘤中上调上调，（2）与细胞周期强相关，且（3）其在血液中的浓度随年龄增长而下将，并且可以解释肿瘤基于年龄的发病率曲线

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



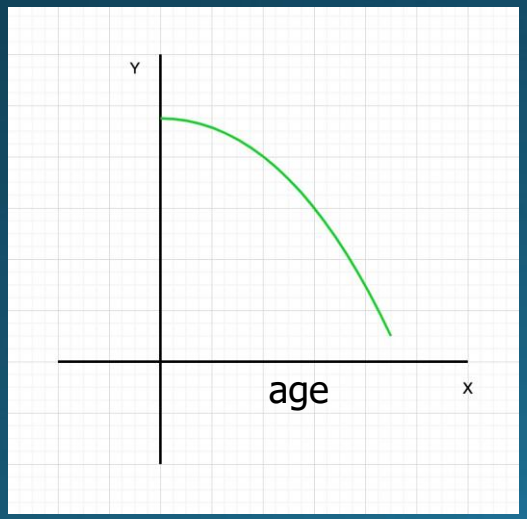
- 这表明：肿瘤有可能通过在血液中消除这些生长因子，来治疗

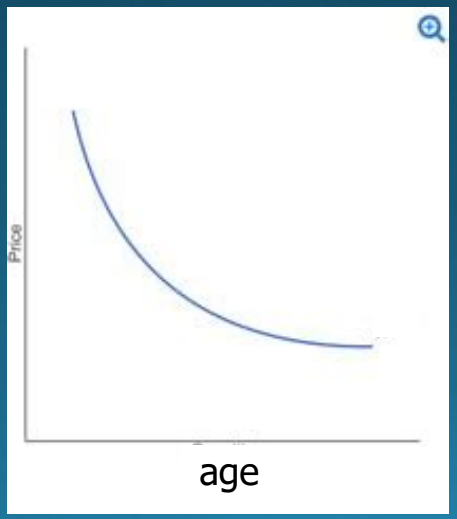
每种肿瘤所需的生长因子

- 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





Hereditary Cancers

- One type of breast cancer is induced by BRCA gene mutations
- There are various other genomic mutations induced cancers
  - kidney cancer due to mutations in fumarate hydratase (FH)
  - colon cancer due to APC mutations
  - retinoblastoma due to Rb-1 mutations
  - Li-Fraumeni syndrome due to p53 mutations
  - Cowden syndrome due to PTEN mutations
  - Von Hippel-Landau syndrome due to VHL mutations
  - .....
- Why do these mutations lead to cancer (in specific organ(s))?

Hereditary Cancers

- What do these mutated genes have in common?
- The mutations all lead to the accumulation of reactive oxygen species (ROS)
- E.g., one of the functions of BRCA is to neutralize hydrogen peroxide; hence its mutation leads to increased accumulation of ROS
- Mutations in p53 can interfere with the normal response to oxidative stress through attenuating the activation and function of Nf-E2-related factor 2. This effect is manifested by decreased expressions of phase 2 detoxifying enzymes NQO-1 and HO-1 and increased ROS level.

Other Cancer-inducing Mutations

- kidney cancer resulting from mutations in fumarate hydratase
- *APC* mutation-induced colon cancer
- retinoblastoma induced by *RB1* mutations
- Li-Fraumeni syndrome due to *P53* mutations
- Cowden syndrome caused by *PTEN* mutations
- Von Hippel-Lindau syndrome because of *VHL* mutations
- ….

- All lead to accumulation of ROS

Other Cancer-inducing Reasons

- Microbe-induced cancers: mostly related to chronicle inflammation and associated hypoxia
- Industrial carcinogens induced cancers: probably related to either ROS accumulation and/or inflammation
- Radiation-induced cancer: mostly related ROS production

- 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

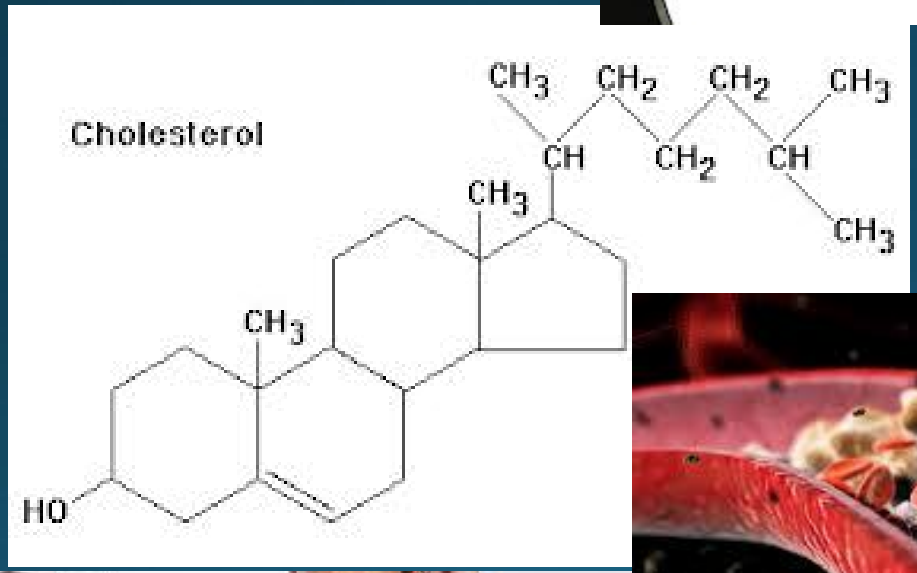
- Resulting in 16 sets of genome-scale transcriptomic data, covering 11 types of primary-to-metastatic cancers and 858 tissue sample
  - prostate-to-bone metastases;
  - breast-to-brain metastases;
  - breast-to-liver, colon-to-liver, pancreas-to-liver and prostate-to-liver metastases;
  - bone-to-lung, 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?

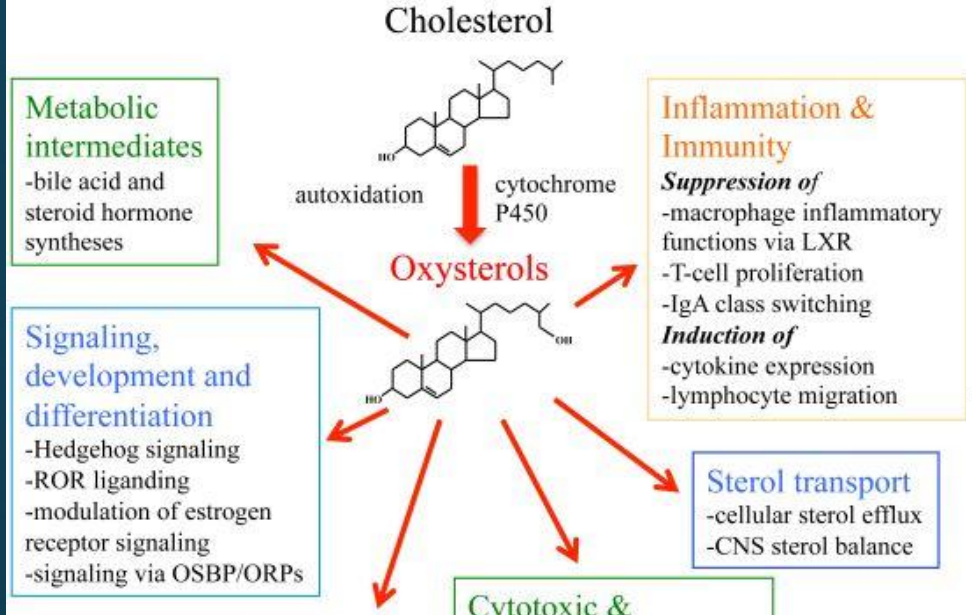
- Question #2: what are the functions of these genes?
- Answer: A substantial fraction of these genes are involved cholesterol influx and metabolism

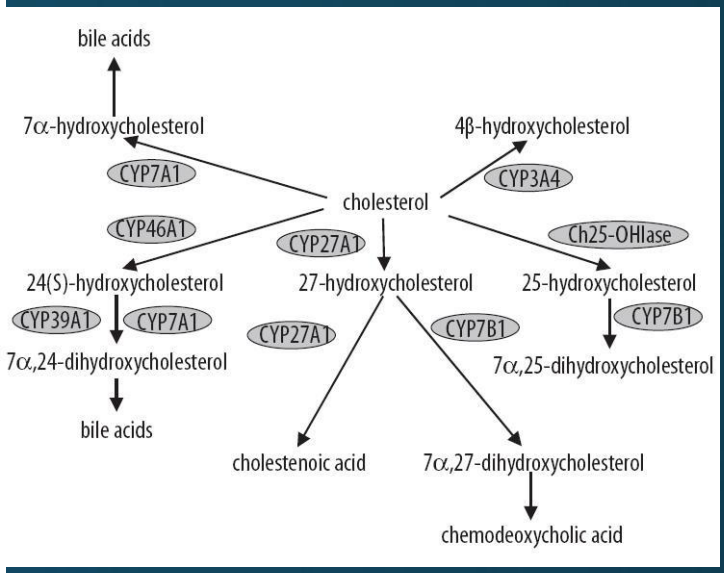
Cholesterol?

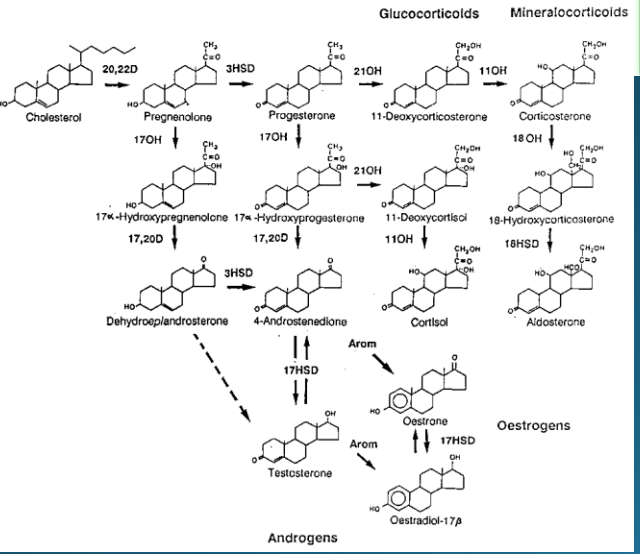


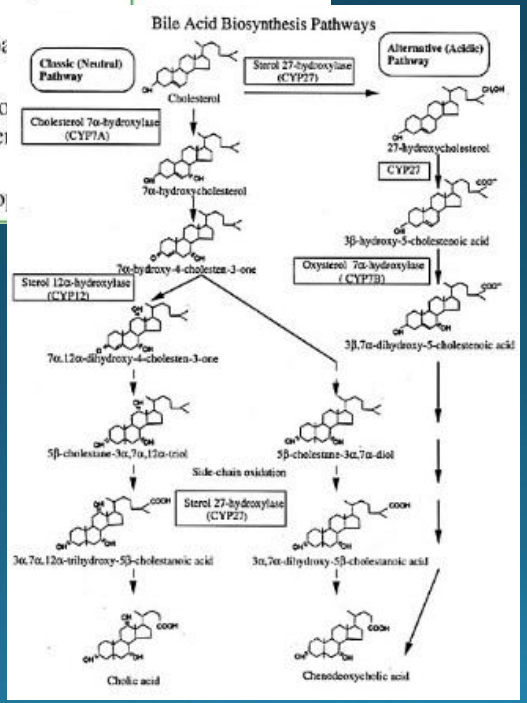
More Questions to Ask

- 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

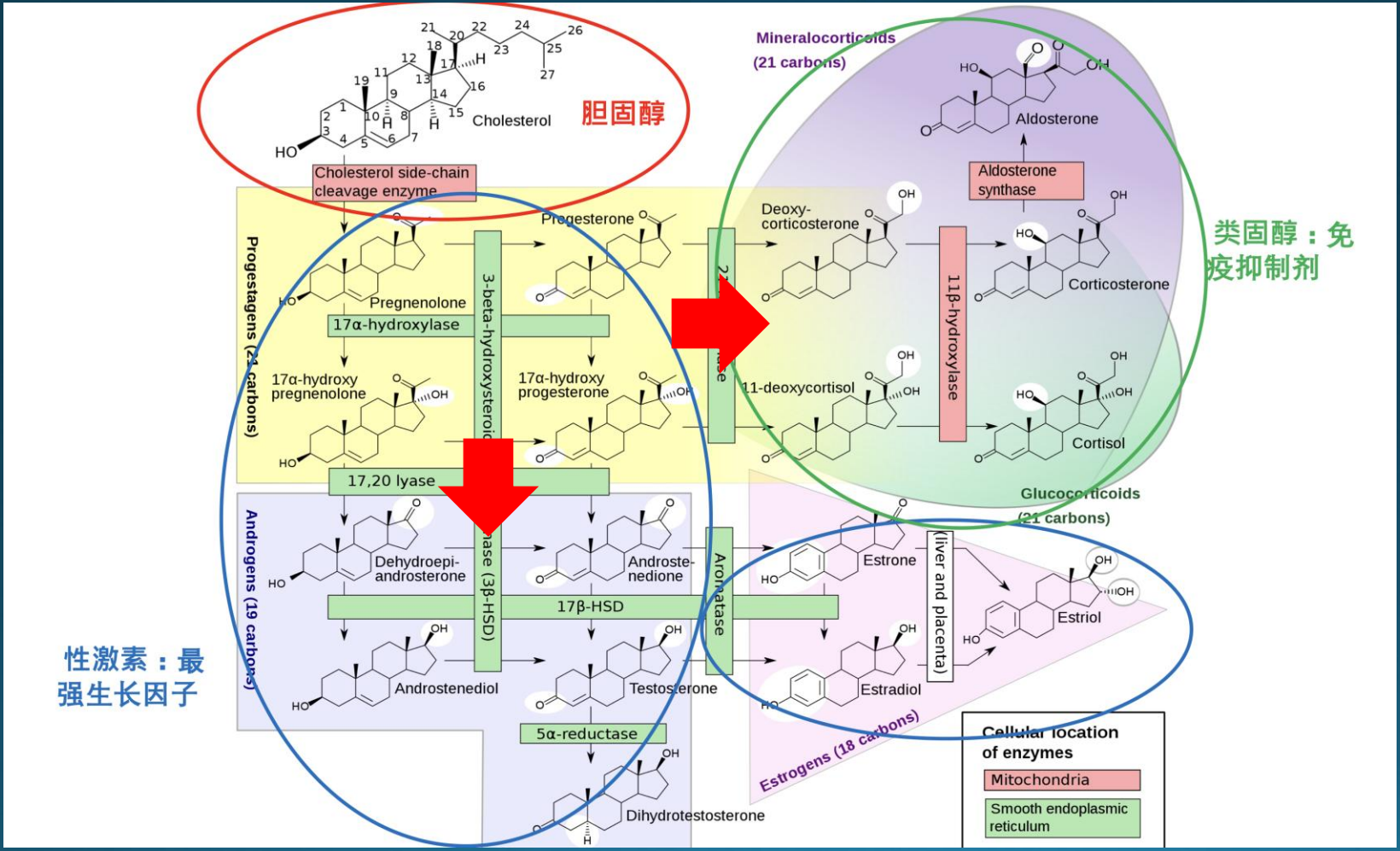
Key Observations

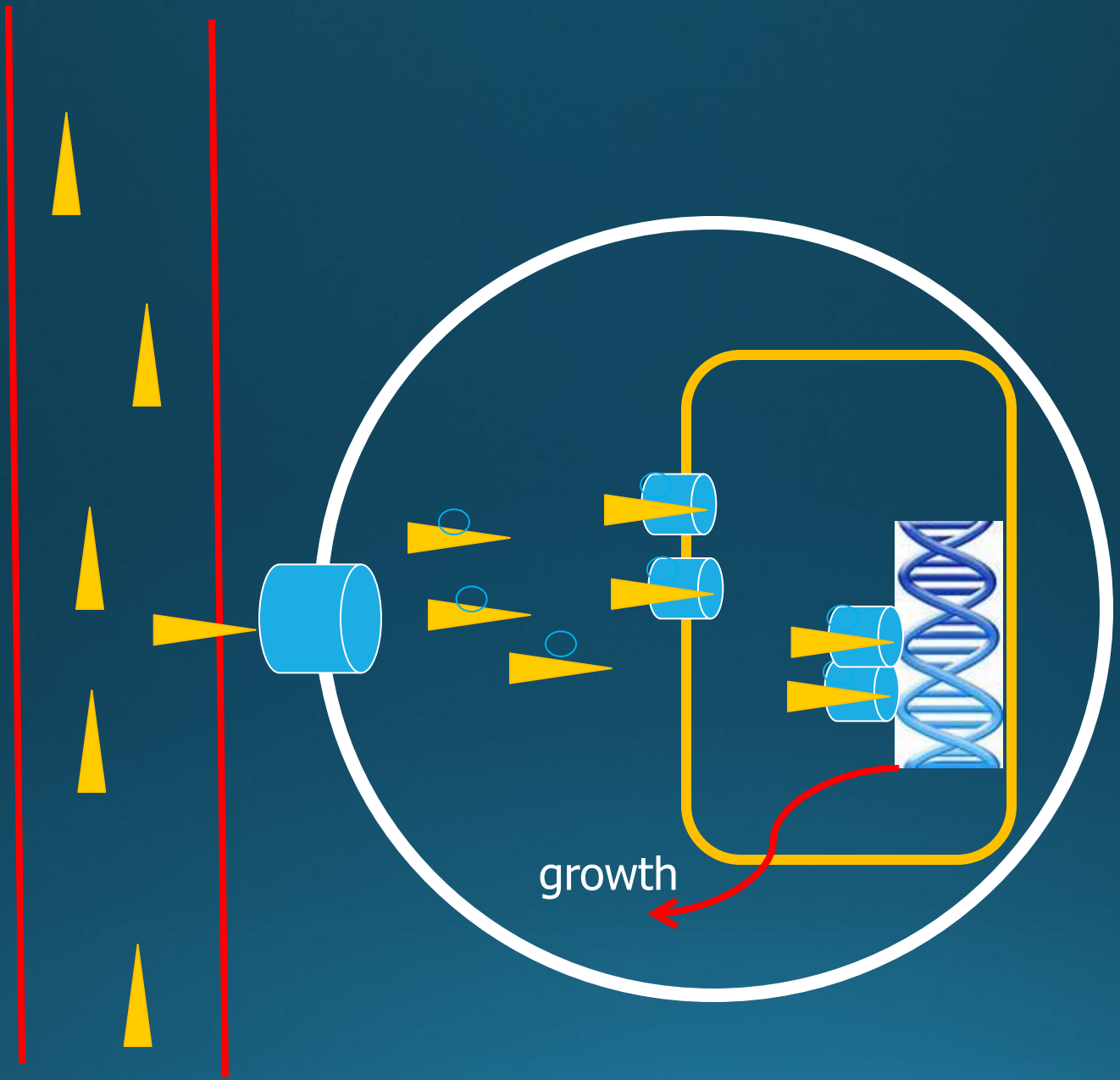
- 14 out of 16 datasets show upregulation in SRB1, LDLR, or LRP5, one show up-regulation in cholesterol biosynthesis and the other shows over-expression of CD36, indicating that all metastatic cancers have increased cholesterol influx

- Interestingly, all 16 datasets show upregulation in cholesterol efflux or esterification genes

- Question 5: what do cholesterols do when going through the cells?

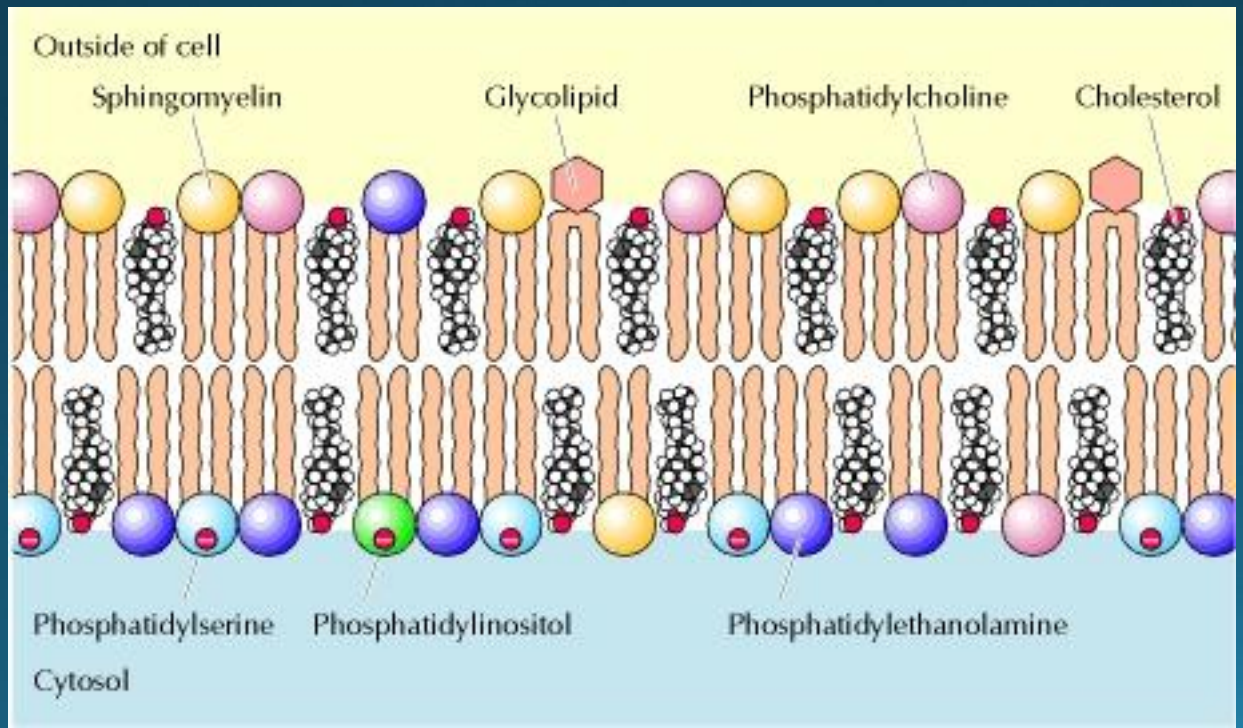
Cholesterol Metabolism




growth

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 O_2

- 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 O_2-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

Any Supporting Evidence?

- Several cancer-epidemiology studies have found that taking cholesterol-lowering drugs, such as Statins, can prolong the survival time of cancer patients, hence providing indirect but strong evidence that cholesterol has an important role in cancer-related death in general.

Implications

- If the model is correct, cholesterol, in any form (HDL, LDL or VLDL) is BAD for cancer patients

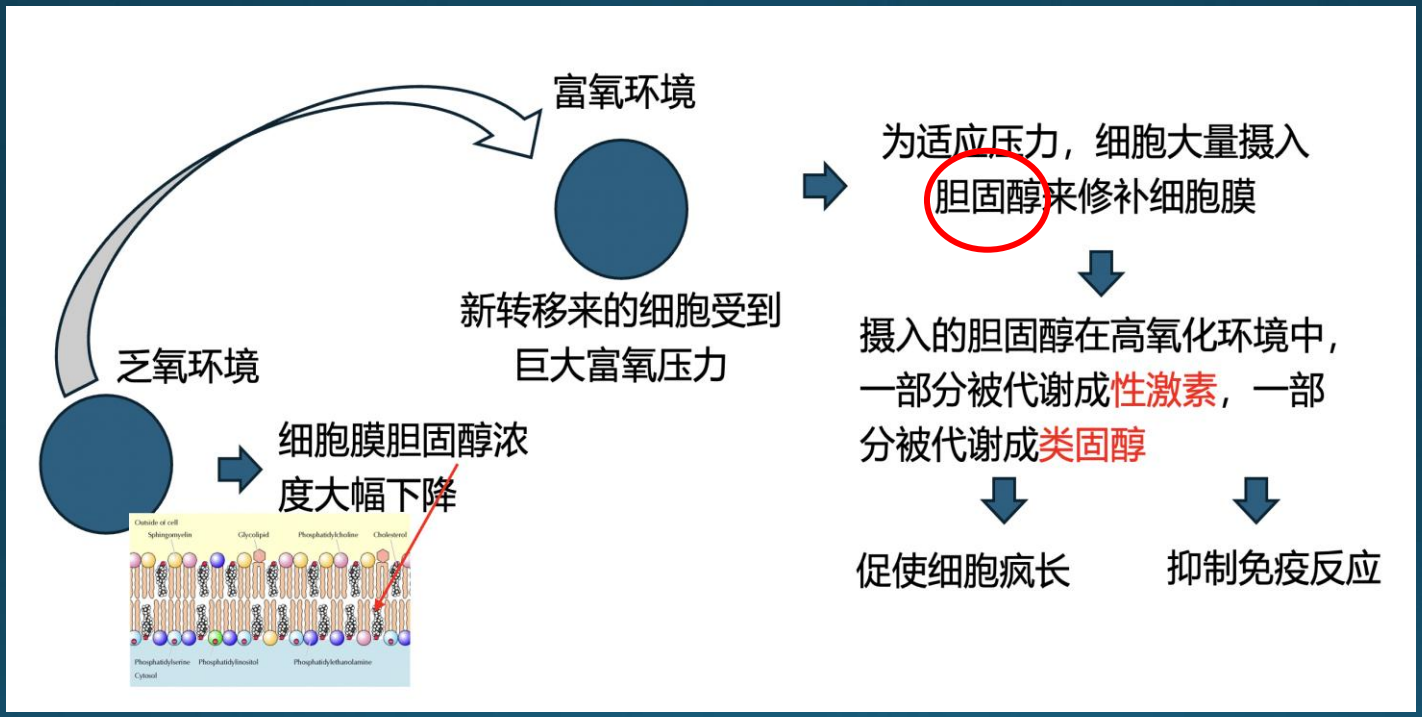
- Some "incurable" primary cancers may be the result of utilization of cholesterol in their cells as we have observed although the reason for using cholesterol may be different from here

- While both primary and metastatic cancers proliferate, the dominating reasons for their cell proliferation are fundamentally different from each other

Implications

- Proliferation for primary cancers is a way to survival; hence inhibition of proliferation by drugs will increase cellular stress and cell death
- Proliferation for metastatic cancers is a side product of other processes so inhibition of cell proliferation will generally not increase the stress level of the cancer cells
- This realization suggests that we have been using the wrong way to treat metastatic cancers
- Potentially the conclusion of metastatic cancer being terminal illness may not be well justified

一旦肿瘤转移了



- 不吃富含胆固醇的食物
- 将血液总胆固醇降到正常范围的下界

Destination of a Metastasizing Cancer

- Cancer tend to metastasize to four locations: liver, lung, brain, bone
  - Why those four?

- What molecular factors may dictate if a primary cancer can metastasize to brain and thrive as a secondary tumor?

Strategy

- How should we proceed when tackling this problem?
- 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?

According to the Literature

- Published studies have shown that it is relatively easy for lipophilic molecules with low molecular weights and overall positive charges to cross the BBB

- Specifically, BBB endothelial cells membrane is lipophilic and negatively charged; and the tight junctions connecting such cells permit only small molecules

Find the Differentially Expressed Proteins on Cell Surface

- Examined all the differentially expressed genes between BMP (brain-metastasizing primary cancers) and NBMP samples

- Examined the top 100 most differentially expressed transmembrane proteins, consisting of 97 downregulated and three upregulated in BMP vs. NBMP

Computing Potentially Relevant Features

- Have calculated the following features of each such protein: the number of charges, the total molecular weight, and the hydropathy index

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

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

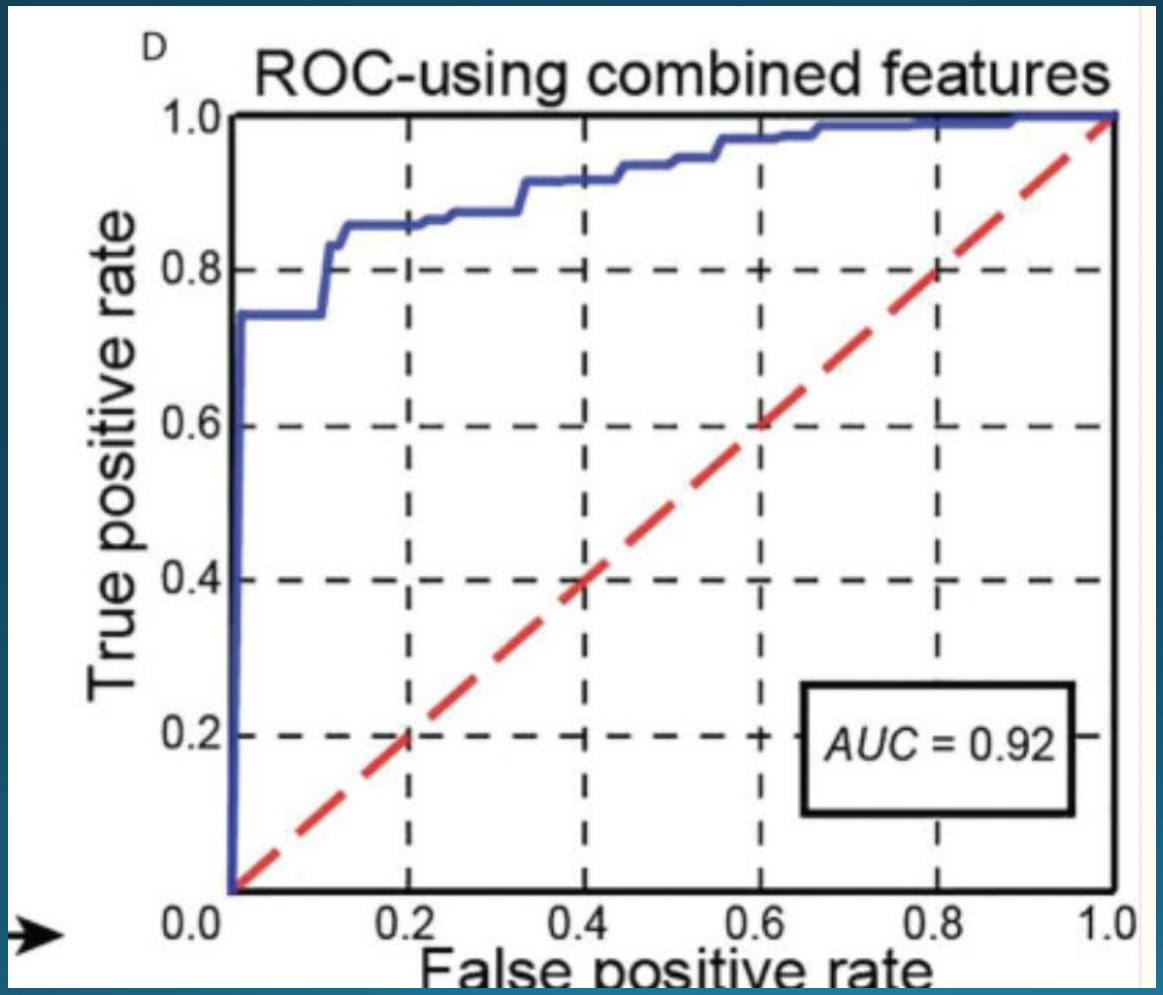
$$EC(i) = EP(i) - EN(i) \quad (3)$$

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

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

- N_R (i), N_H (i) and N_K (i): the numbers of the amino acids arginine, histidine, and lysine in the extracellular parts of the protein
- N_D (i) and N_E (i) are for the numbers of aspartate and glutamate
- ***W*** representing the molecular weight for each of the 20 amino acids; ***H*** being the hydropathy index

Classification between BMP vs. NBMP



Functional Differences between BMPs vs. NBMPs

- BMPs have a considerably higher average level of FRs than that in NBMPs, suggesting that BMPs are facing stronger alkalosis, hence stronger neutralizing RMs

Enzymes	MedianTPM-BMPs	MedianTPM-NBMPs	H^+ -producing reactions
ARSA	34.61	30.21	H2O + N-acyl-1-β-D-(3-O-sulfo)-galactosyl-sphing-4-enine → a β-D-galactosyl-(1↔1')-N-acylsphing-4-enine + H^+ + sulfate
CANT1	41.95	37.17	a ribonucleoside 5'-diphosphate + H2O → a ribonucleoside 5'-phosphate + H^+ + phosphate
CASK	12.34	8.89	ATP + L-seryl-[protein] → ADP + H^+ + O-phospho-L-seryl-[protein]
CERK	25.48	19.19	an N-acylsphing-4-enine + ATP → ADP + an N-acylsphing-4-enine 1-phosphate + H^+
EPHA4	3.89	1.74	ATP + L-tyrosyl-[protein] → ADP + H^+ + O-phospho-L-tyrosyl-[protein]
EZH2	14.61	8.53	L-lysyl27-[histone H3] + 3 S-adenosyl-L-methionine → 3 H^+ + N6,N6,N6-trimethyl-L-lysyl27-[histone H3] + 3 S-adenosyl-L-homocysteine
FYN	11.32	9.37	ATP + L-tyrosyl-[protein] → ADP + H^+ + O-phospho-L-tyrosyl-[protein]
GLYATL2	0.15	0.06	an acyl-CoA + glycine → an N-acylglycine + CoA + H^+
MYO3A	0.10	0.04	ATP + L-seryl-[protein] → ADP + H^+ + O-phospho-L-seryl-[protein]
NMNAT2	1.62	0.97	diphosphate + NAD+ → H^+ + ATP + β-nicotinamide D-ribonucleotide
PDE11A	0.17	0.13	3',5'-cyclic GMP + H2O → GMP + H^+
PDE3A	4.35	1.94	a nucleoside 3',5'-cyclic phosphate + H2O → a nucleoside 5'-phosphate + H^+
PGLS	40.61	36.71	6-phospho-D-glucono-1,5-lactone + H2O → 6-phospho-D-gluconate + H^+
ULK1	19.70	17.45	ATP + L-seryl-[protein] → ADP + H^+ + O-phospho-L-seryl-[protein]
XDH	0.79	0.58	H2O + NAD+ + xanthine → H^+ + NADH + urate
YARS1	29.19	23.15	ATP + L-tyrosine + tRNATyr → AMP + diphosphate + H^+ + L-tyrosyl-tRNATyr

Functional Difference between BMPs vs. NBMPs

- *ARSA*, a regulator of neuron myelination, can boost the neuronal survival and differentiation.
- *CASK* regulates the development of brain neurons, hence providing a range of capabilities for cell survival.
- *CERK* is highly expressed in cerebellar Purkinje cells and converts ceramide to a sphingolipid, which is known to play powerful roles in dealing with oxidative stress.
- *EPHA4* meditates motor neuron death and regulates axon guidance and proliferation of neural stem cells , hence having the capabilities for overcoming stresses.
- *EPHX2* alters neuronal susceptibility to ischemic cell death, another survival related gene.
- *EZH2* is important for neuronal survival and regulates the self-renewal and differentiation of cells in the cerebral cortex.

Functional Difference between BMPs vs. NBMPs

- *FYN* tempers excitatory and inhibitory synaptic transmission stimuli of neurons and is a key responder to oxidative stress.
- *NMNAT2* acts as an essential axon maintenance factor of neurons and its overexpression can ameliorate oxidative stress .
- *PDE11A* is highly expressed in hippocampus and plays key roles in inflammation modulation.
- *ULK1* works in brain iron accumulation and regulates the autophagy-mediated cell survival of brain-metastasized tumor cells.
- *XDH* is needed for neuronal survival *via* maintenance of cold tolerance.
- *PGLS* is a marker gene for brain-derived cells, associated with cell redox homeostasis, and regulates the viability of breast tumor cells in the brain microenvironment .

- 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

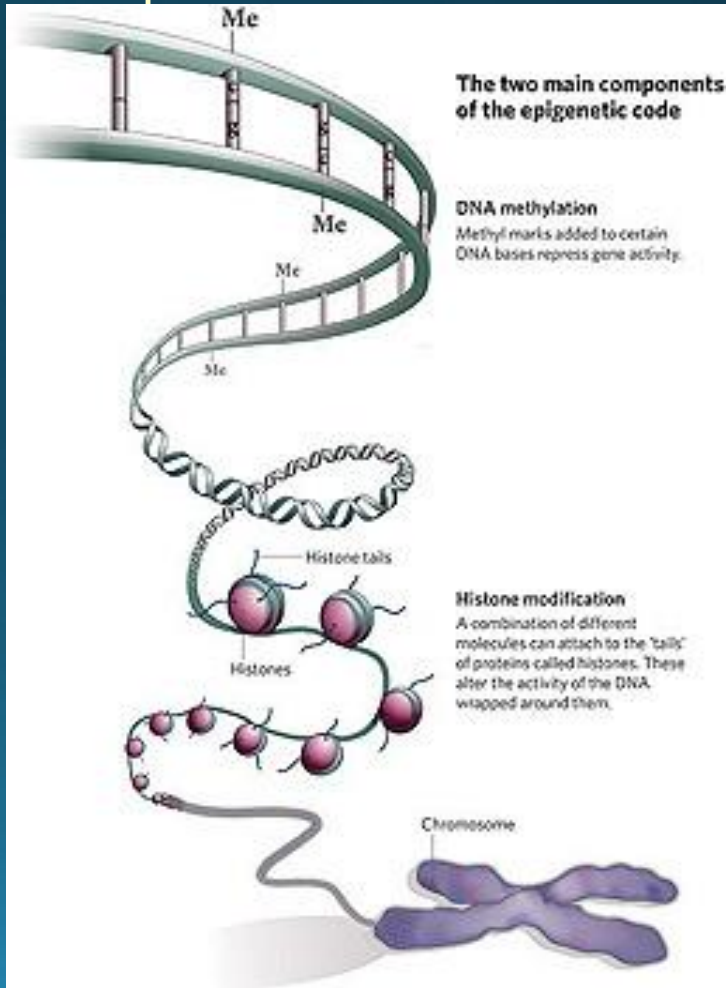
- Majority of the metabolic reprogramming is selected through epigenomic regulation and life/death

Epigenome

- Epigenome is about DNA 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.



Stresses Encountered by Cancer

- As the disease evolves, cancer (or cancer forming) cells have to overcome tremendous stresses encountered

- The defining stresses of a cancer are probably those induced by Fenton reactions
  - overcoming increased pH
  - coping with continuous damages to cellular components, including DNA
  - riding of continuously synthesized nucleotides
  - coordinating different aspects of cell division, which is not driven by top-down signals
  - ROS associated stresses

Responses to Stresses

- Some of these stresses are responded through regulatory mechanisms such as
  - activation of glycolytic ATP synthesis and nucleotide synthesis to produce protons for neutralizing continuous OH- production
  - utilization of more powerful mitogenic factors, such as cholesterol and steroidal derivatives, to accelerate cell division to keep pace with nucleotide synthesis

- Some of these stresses are responded through selection of mutations such as
  - P53 to avoid immune attacks as well as cell-cell competition
  - MYC to accelerate cell cycle progression to meet the need to rid of synthesized nucleotides at a rate comparable to that of their synthesis

Responses to the Stresses

- Some stresses are adapted through changes at the epigenomic level
- Compared to regulatory responses, changes at the epigenomic levels are kept and can be applied to future similar stresses for a few generations
- Compared to genomic changes (mutations), epigenomic changes are not permanent and can be refined.

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

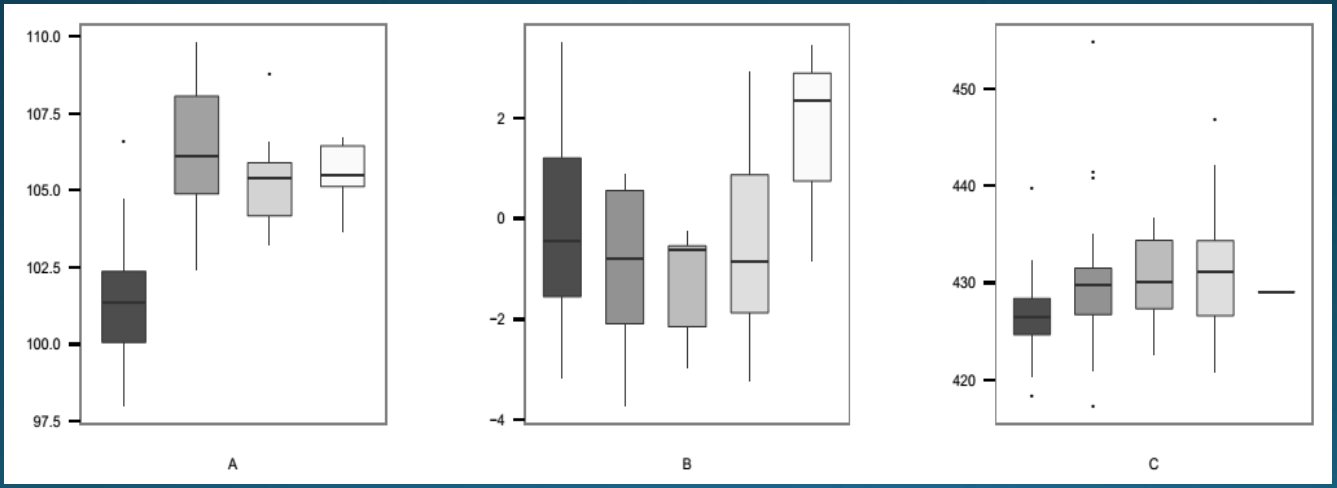
- They prepared two sets of cultures, one being generally engineered and one being wild type; for the genetically engineered one, they tried 8 different and randomly selected promoters
- Then they injected the toxin into each cultured larva
- All the ones without the inserted gene are killed
- 7 out 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

Possible Relevance to Human Cancer

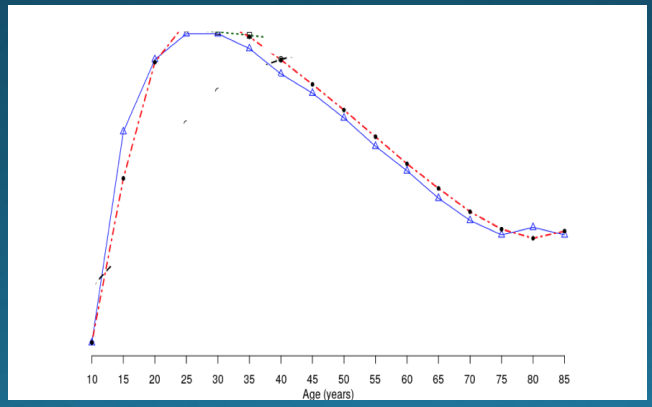
- Polycomb seems to be behave in a similar fashion to those of the epigenomic associated enzymes, suggesting the possibility that Polycomb may have similar roles to those in fruit fly larva



Gastric cancer melanoma Lung cancer

The Predictive Power of the Model

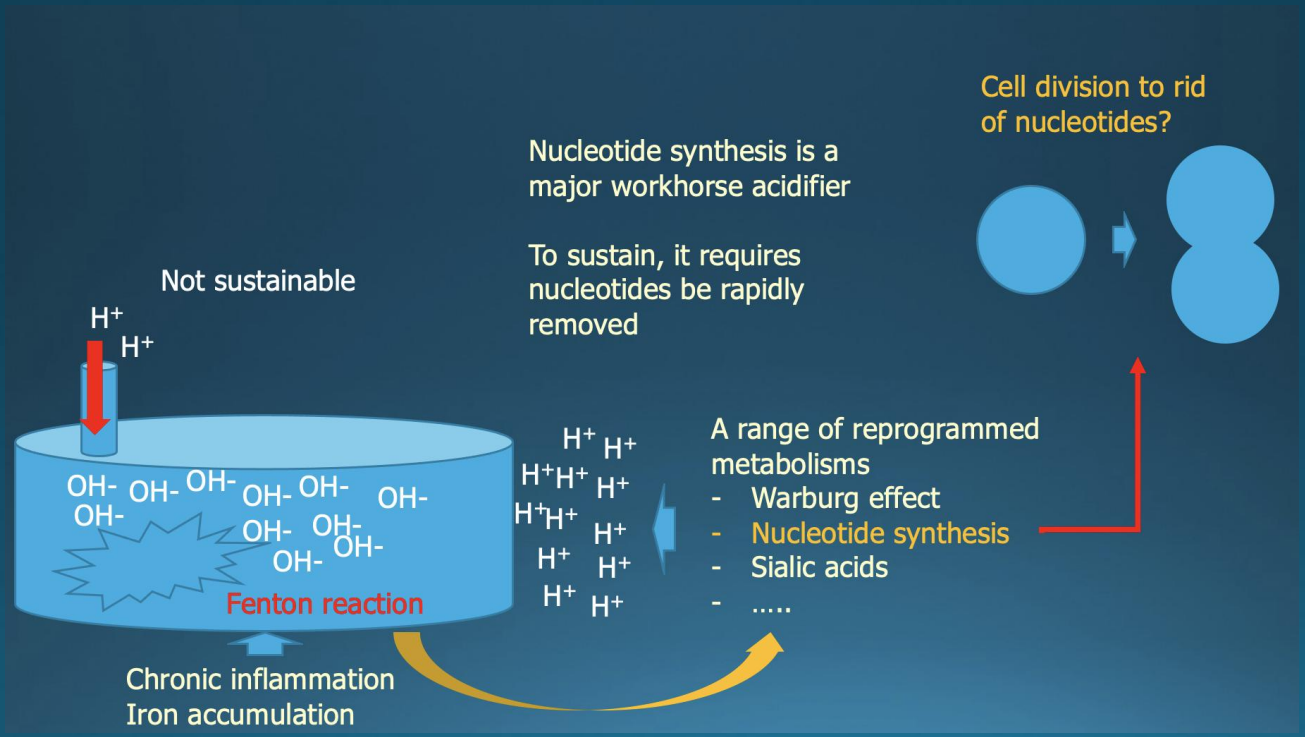
- We anticipate that any of the following questions is answerable through cancer omic data analyses and modeling
- What are the general characteristics of the most and the least deadly cancers?
- What determine the rate of cancer occurrence in an organ?
- Why the age-dependent cancer occurrence rate generally follows a unimodal distribution?



三阴性乳腺癌发病率

The Predictive Power of the Model

- What determines the rate of cell division of a cancer?
  - It is the level of cytosolic Fenton reaction

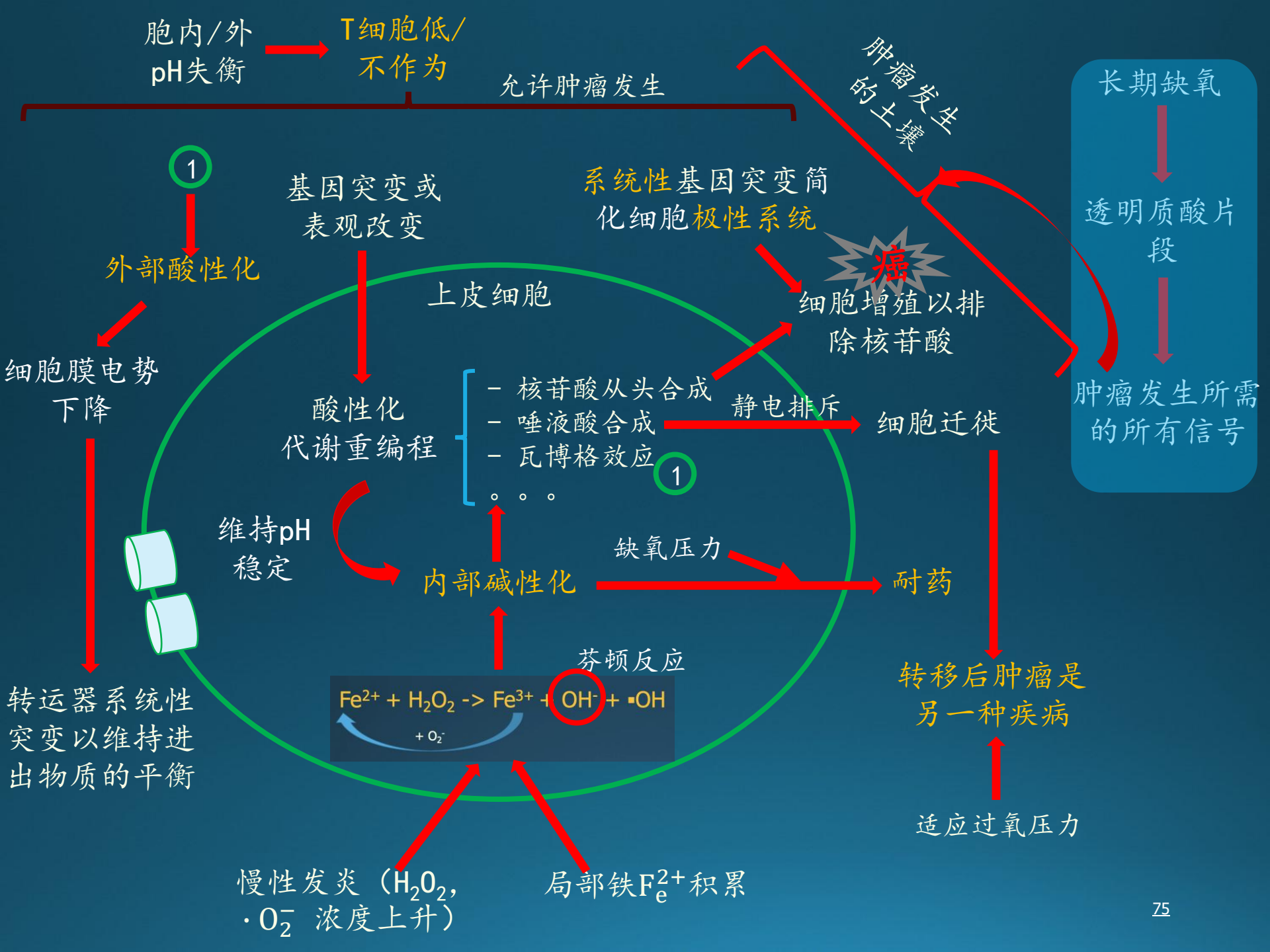


Predictive Power of the Model

- What determines the malignancy level of a cancer?
  - It is the hypoxia level – which is widely known but not well understood.
- What dictates the level of drug resistance?
  - It is the combined level of hypoxia and alkalinity.
- What are the core reasons for the activation of vast majority of reprogrammed metabolisms, such as Warburg effect and de novo synthesis of nucleotides?
  - It is to keep the intracellular pH stable

The Predictive Power of the Model

- What drives a cancer to metastasize?
  - It is the synthesis and accumulation of sialic acids on cell surface.
- Why metastasized cancers tend to be un-treatable using drugs designed for primary cancers
  - It is a disease driven by hyperoxia, fundamentally different from primary cancers
- Any many others ….


胞内/外
pH失衡
T细胞低/
不作为
允许肿瘤发生
肿瘤发生
的土壤
长期缺氧
透明质酸片
段
肿瘤发生所需
的所有信号
1
基因突变或
表观改变
系统性基因突变简
化细胞极性系统
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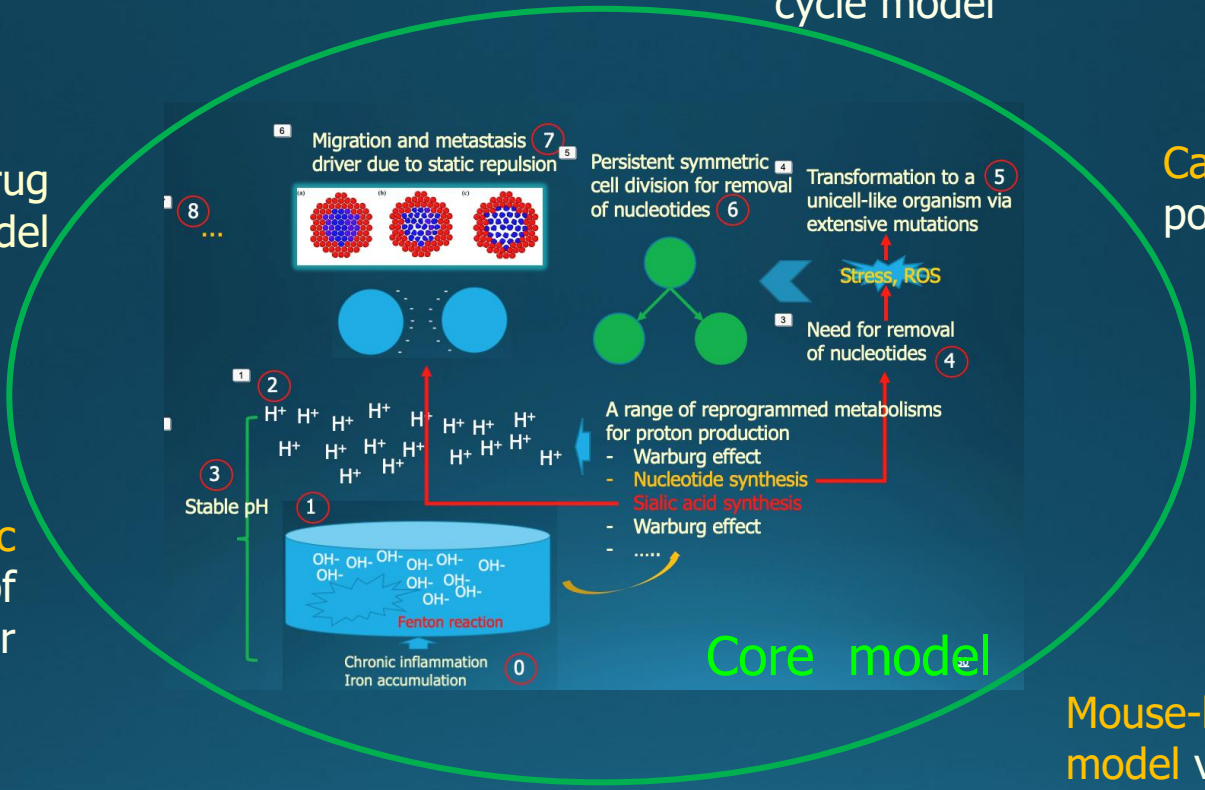
– 唾液酸合成
– 瓦博格效应
。。。
1
静电排斥
细胞迁徙
维持pH
稳定
缺氧压力
内部碱性化
耐药
芬顿反应
$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + \cdot OH$
$+ O_2^-$
转运器系统性
突变以维持进
出物质的平衡
转移后肿瘤是
另一种疾病
适应过氧压力
慢性发炎（H_2O_2，
$\cdot O_2^-$ 浓度上升）
局部铁Fe^{2+}积累

Future Work: An Expanded Model

Post-metastatic cancer model

Cancer cell cycle model

Cancer drug resistance model



Cancer cell polarity model

Organ-specific characteristics of cancer

Mouse-based model validation

Cancer-immune interplay model

Speculation with strong support: It is the distinct combinations of MRs that give rise to a variety of cancerous behaviors

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.

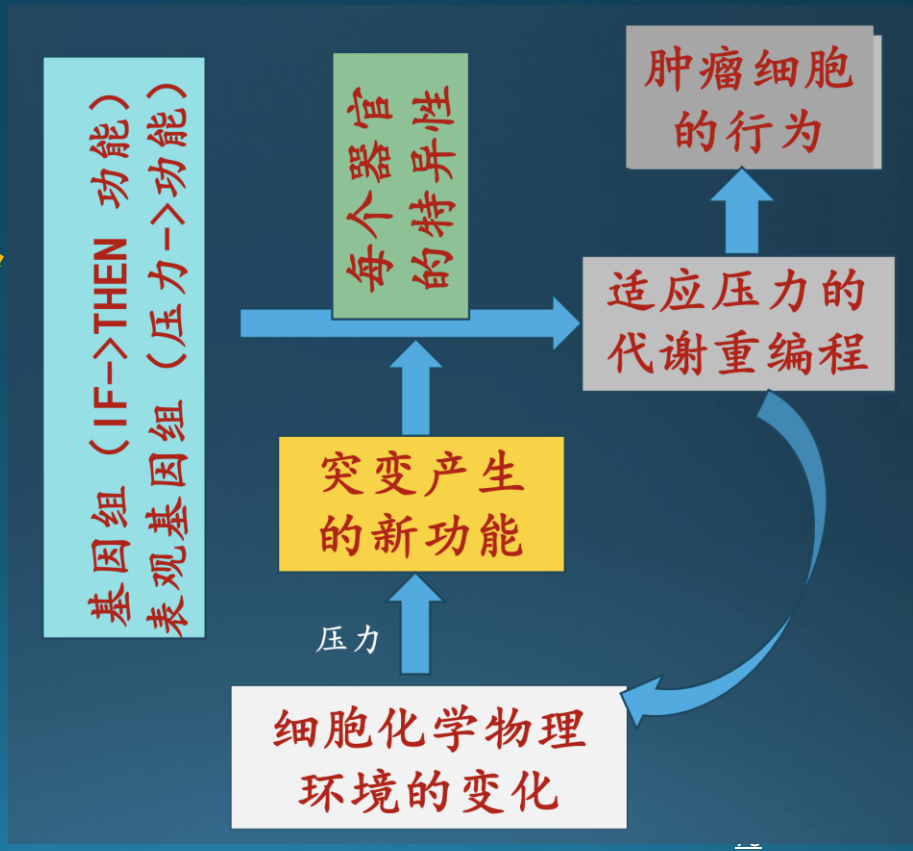
- It generally takes two types of factors for a cancer to take place, namely endogenous driving forces for cell proliferation and exogenous growth factors specific to individual cancer types

- If this is experimentally validated, cancer could be potentially treated through stopping the availability of growth factors needed by individual cancers.

肿瘤演化动力学

我们建立了一个新的，有高度可操作性的肿瘤演化模型，但仍有大量的问题需要解决

- 是什么决定了不同器官的肿瘤发病率
- 是什么决定了一个肿瘤的恶性程度
- 是什么决定了每个器官肿瘤的特性
- 建立一个有高度预测能力的、定量的肿瘤演化动力学模型



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 transcriptomic and genomic data

Becoming A Cancer Systems Biologist:

the more the better

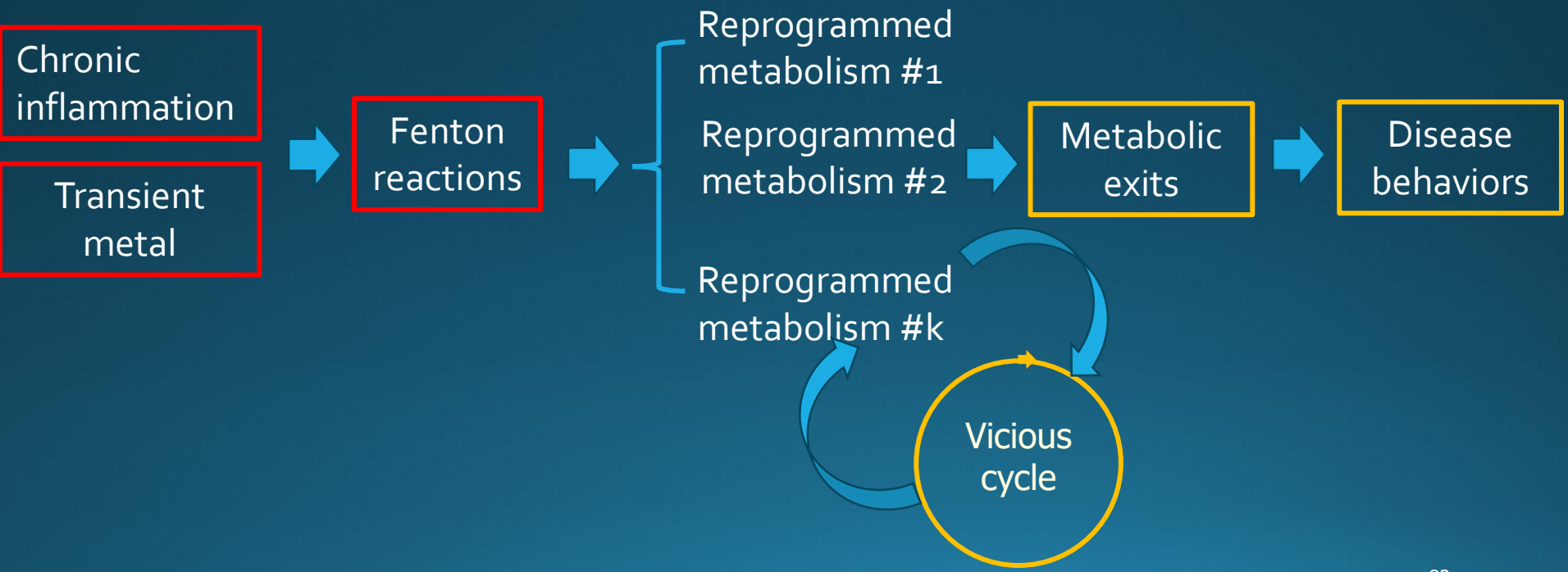
- Able to interpret hundreds of biological pathways enriched by differentially expressed genes in cancer vs. controls
- Capable to build qualitative disease evolution model based on statistical analyses such as Bayesian networks
- Able to build quantitative dynamic models for cancer evolution using existing mathematical frameworks
- Capable to develop 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 disease such as Alzheimer's disease, diabetes, Parkinson disease .....



Take-Home Message

- Cancer development requires fundamental changes in the underlying cell types, to enable persistent symmetric cell division
- Such changes are probably largely at the cell polarity level via mutation and repression at the epigenetic level
- Omic data provided considerable supporting evidence but more work is still needed.