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关于龙星计划

龙星计划委员会

动态

关于龙星计划

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近年来，我国经济得到了持续发展，这意味着我国不仅在产业，而且在科学技术等方面要面临全球一体化的严峻挑战。在这激烈的竞争中，优秀人才是取得胜利的关键因素（在信息领域显得更为突出）。我们高兴的看到，海外一批中国留学生现已学有所成，在诸多信息科学前沿领域做出了重大贡献。

龙星计划就是组织一批在美国学术界已有成就、有一定地位的原中国留学生，不定期回国就某一领域，在中国各地大学，系统地讲授一门美国研究生课程（每门课程15-30课时）。同时，就所讲课程的学术领域、有关课题与国内科学家及研究生共同讨论研究。这对提高我国科研水平和培养优秀人才都将起着重要作用。

（1）龙星计划委员会（下称委员会）分为两部分，即海外部分和国内部分。分别由一位主任主持工作。委员都是国内某一技术领域专家。委员会负责遴选讲者、确定承办单位和课程设置等工作。 设在中国科学院计算技术研究所的龙星计划办公室为龙星计划顺利实施提供必要的支撑保障。

委员会每年征求授课讲者和承办单位，公布学术交流领域。各大学提出申请后由委员会进行选择。龙星计划每年评估学术交流活动情况，为下一年课程安排做参考。

（2）每年组织6-12人次回国讲学、短期工作。每次讲授一门研究生课程，计15-30小时。课程仅面向中国计算机学会会员招生，免收学费，食宿自理。CCF会员申请信息地址：http://www.ccf.org.cn/c/2017-02-22/582915.shtml 。

（3）承办单位负责组织学员及提供各种信息，以保证课程的圆满成功;负责给课程提供必要的设备、场地等;负责给讲者提供市内多方面的服务（如交通、住宿等）信息。

CCF龙星计划

肿瘤系统生物学

Cancer Biology: an informatics perspective

徐鹰

南方科技大学医学院

Main Topics

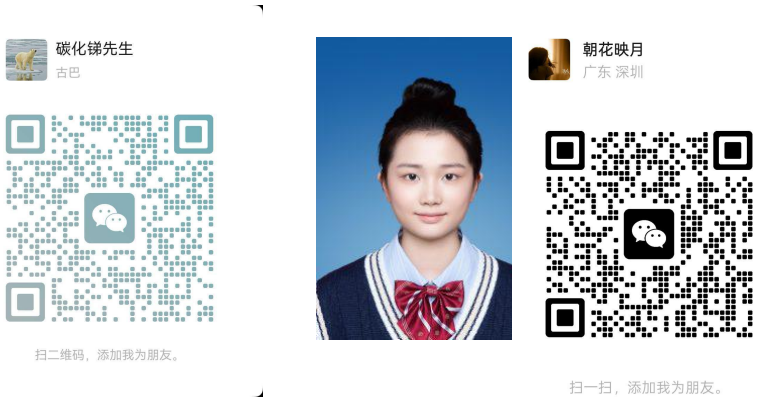
- Lecture 1 （7月28号）：肿瘤研究背景、肿瘤特征、慢性炎症与组织修复、肿瘤发生的必要条件
- Lecture 2 （7月29号）：肿瘤的演化框架：化学稳态失衡、维持平衡的代谢重编程、基因突变的作用
- Lecture 3 （7月30号）：压力应激与表观调控、我们演化模型的各种应用、转移后肿瘤的特有生物学

Questions To Study

- What is cancer?
- What drives a cancer to start, progress, metastasize?
- Why cancer characteristics tend to be organ-specific?
- What dictate age-dependent cancer occurrence rates?
- What drives drug resistance by cancer cells?
- Why metastasized cancers behave differently from their primary counterparts?

Format

- Lectures: 9:00 – 12:00pm each day, July 28 – 30, 2026
- Reading: handouts posted online at https://sysbio.med.sustech.edu.cn/ICSB2026.html
- Teaching Assistants
  - Mr Bocheng Shi（石博诚）
  - Ms. Yinghua Zhao（赵英华）



2026年春季南方科大MED232的考试题

期中考试

1. **第一部分：检验你对所学知识的了解程度**（每题 5 分）【在以下，肿瘤是指恶性肿瘤】

a. 根据已有的测序数据，每一种已测序的慢性炎症基因组都有大量基因突变。根据课堂学到的知识，肿瘤基因组中的突变起到的主要作用是什么？解释你的答案。

d. 如果给你一组疾病组织及疾病旁正常组织的转录数据，你如何根据这些数据的分析来确定这组疾病组织是否为恶性肿瘤？解释你的答案。

e. 是什么决定了一个肿瘤的增殖速度？解释你的答案。

f. 为什么肿瘤对葡萄糖的需求比正常细胞高出 20-30 倍？请解释你的答案。

j. 有些慢性炎症会癌变，另一些则不会癌变，如关节炎、两者的主要区别是什么？

m. 我们认为肿瘤的发生是疾病组织的化学微环境造成的。那你认为处于同一环境的 T 细胞

n. 一个广泛的临床观察是：越缺氧的肿瘤，恶性程度越高。你认为它的底层原因是什么？请解释你的答案。

o. 根据这学期学到的知识，你认为系食者得癌症的概率明显低于食肉者的概率的原因可能是什么？解释你的答案。

p. 绝大多数肿瘤的脂肪代谢都上调。根据这学期学到的知识，你认为这是什么原因？解释你的答案。

q. 两位有同样类型肿瘤的患者（同样性别、类似年龄及健康状态），一位活了很久，但另一位很快就走了。给出造成不同结果的可能原因，并解释你的答案（根据这学期学过的知识）。

期末考试

1. **第一部分：检验你对所学知识的了解程度**（每题 5 分）

a. 为什么抑制肿瘤的增殖将导致肿瘤细胞的死亡？

组织细胞

）的异同点分别是什么？解释你的答案。

b. 为什么肿瘤组织细胞的糖代谢都大幅上升，而其它重大疾病，如老年痴呆（AD）组织细胞的糖代谢则下降？

h. 请给出一个例子，来说明“基因突变是肿瘤发生的终极原因”这一说法是有问题的，并解

明这一说法在逻辑上站不住脚的。

发展的主要恶性循环包括哪些重要的生物过程，及它们的逻辑关系。解释你的答案。

变是肿瘤发生的终极原因”这一说法是有问题的，并解

n. 肿瘤患者的血糖水平普遍较健康群体的要高，且有统计意义。你认为两者可能的关系是什么？请解释你的答案。

水平上升的现象，而且血钾水平越高，死亡率越高。根的解释。

l. 如果让你设计 AD 早期血液标识，你会集中考虑 AD 的哪几个特有生物过程中的蛋白？请给出三个例子，并解释你的答案。

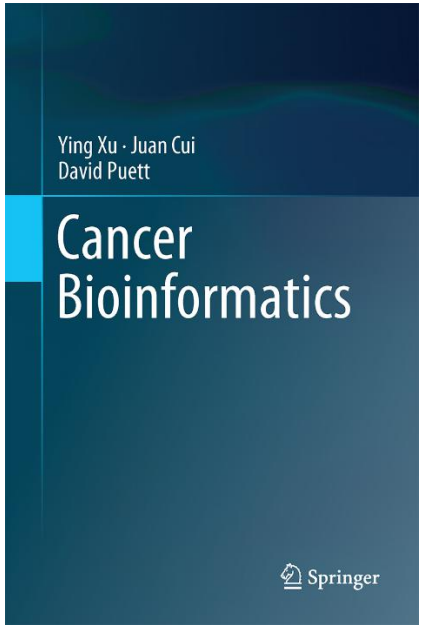
m. 你认为糖尿病的发病原因是什么？解释你的答案。

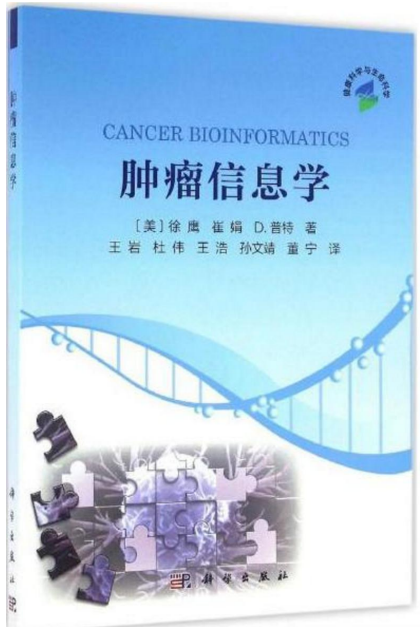
n. 肿瘤患者的血糖水平普遍较健康群体的要高，且有统计意义。你认为两者可能的关系是什么？请解释你的答案。

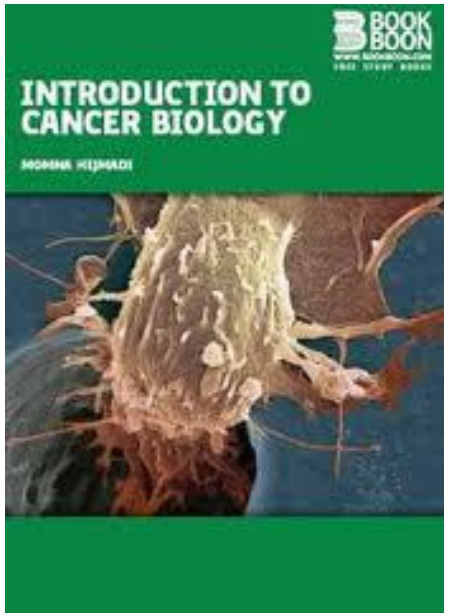
o. 请给出一个可能驱动糖尿病患者的血糖水平越来越高的原因。解释你的答案。

Reading Material and References

- All lecture and reading material are downloadable from online
- “Introduction to cancer biology” (a free on-line book), by Momna Hejmadi
- “Cancer Bioinformatics”, Springer (2014)







Expectation of the Students

- Read the short book “Introduction to cancer biology” and the suggested literature
- Active participation in in-class discussions and no private in-class conversations
- Have your phones switched off and absolutely no phone calls in class!

Lecture I

Introduction to Cancer Biology:

Study of cancer from an informatics perspective

Table of Content

What is Cancer According to Literature

- A cancer is often defined as a collection of cells that grow uncontrollably by disregarding the rules imposed on normal cells/tissues, which can invade and colonize other tissues
- While the definition is simple, we do not have a detailed understanding about what causes a cancer and what drives the disease.
- Yet, as we will learn later, this definition may not capture the true essence of the disease.

A Historical Perspective

- A case of breast cancer was identified and clearly documented by Egyptian physician Imhotep 4,50 years ago
- It is Greek physician who named the disease *kartinos* 2,200 years ago, Greek word for crab, now coming down to us as *cancer*
- Multiple theories were developed in the past 1,000 years, particularly since 19th century when surgeries, along with anesthesia and antibiotics, were widely used to treat human illness
- The first major breakthrough in understanding of cancer at the molecular level is the observation by German biochemist Dr. Otto Warburg that cancer cells tend to use glycolytic fermentation pathway regardless of the level of available O2.

A Historical Perspective

- In 1960's, Warburg stated: Cancer … has countless secondary causes; but there is only one prime cause, (which) is the replacement of respiration of oxygen in normal body cells by a fermentation of sugar.

- He went on to further state: … the de-differentiation of life takes place in cancer development. The highly differentiated cells are transformed into non-oxygen-breathing fermenting cells, which have lost all their body functions and retain only the now useless property of growth … What remains are growing machines that destroy the body in which they grow

Otto Warburg 1931
Nobel prize winner

A Historical Perspective

- The first oncogenic virus was discovered by Peyton Rous of Rockefeller Institute in 1916 (received Nobel Prize in 1966)
- Rous excised a sarcoma in a chicken, ground and injected the soluble filtrate into chickens; then a sarcoma would develop
- After years of intensive research, the transmissible agent was identified as the Rous sarcoma virus (*RSV*)
- The actual oncogenic element in the retroviral genome was a mutated gene *SRC*

A Historical Perspective

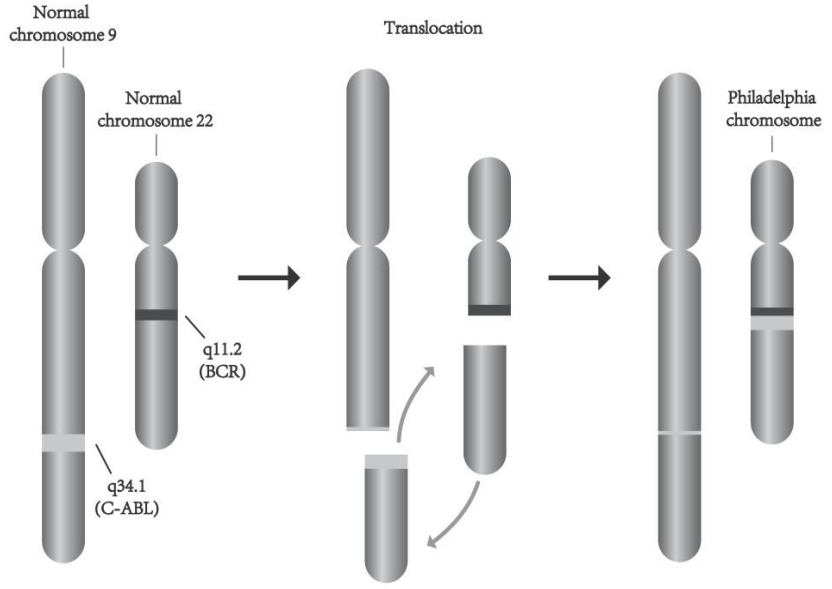
- The concept of oncogene was coined in 1969 by NIH scientists, George Todaro and Robert Heubner
- The first confirmed oncogene was discovered in 1970 and was termed SRC by Dr. Steve Martin
- For demonstrating over-expression in human SRC can transform normal cells to cancer cells, Bishop and Varmus received Nobel Prize in 1989，开始了肿瘤是基因突变结果的时代

Bishop and Varmus, 1989
Nobel prize winners

A Historical Perspective

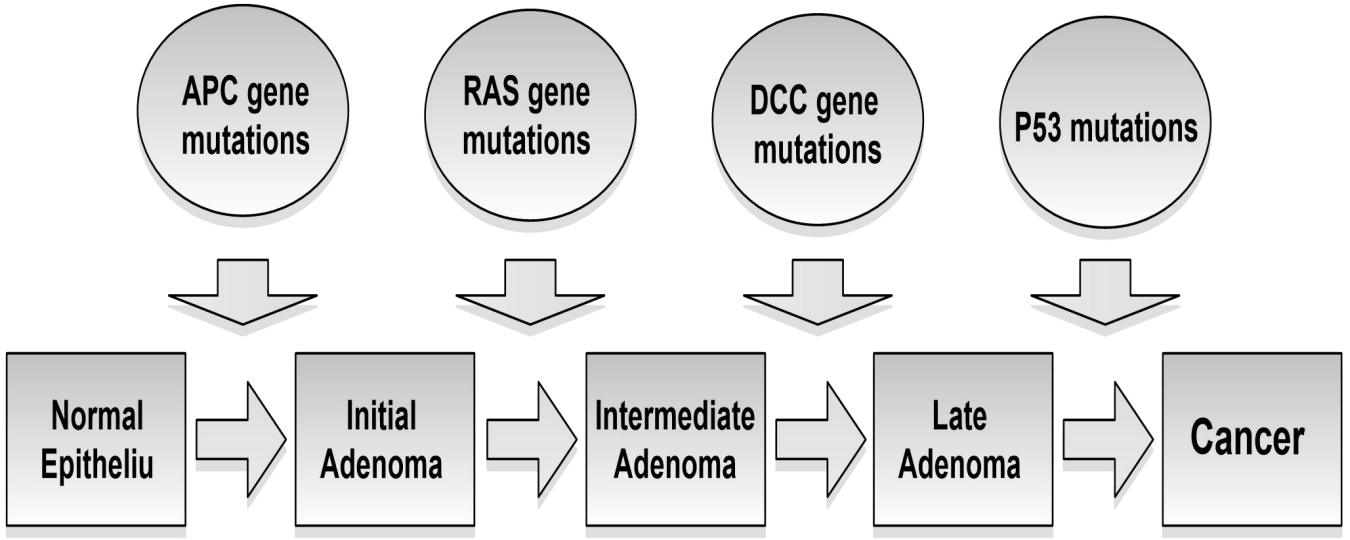
- The discovery of (proto)oncogenes by Bishop and Varmus and tumor suppressor genes by AG Knudson, both in 1970s, laid a foundation for the now popular theory that cancer is the result of genomic mutations. This theory has dominated the thinking in cancer research for ~50 years

- Philadelphia chromosome is believed to be the cause of CML, a type of blood cancer



A Historical Perspective

- The first mutation-driver model of cancer was proposed in 1990 by Fearon and Vogelstein based on the observation that vast majority of colorectal cancers have mutations in the APC gene



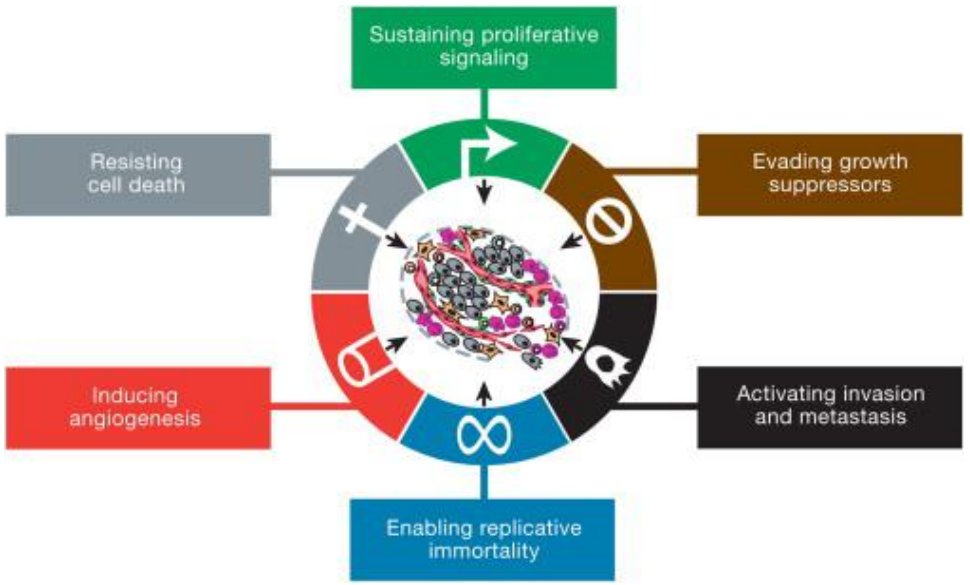
Bert Vogelstein

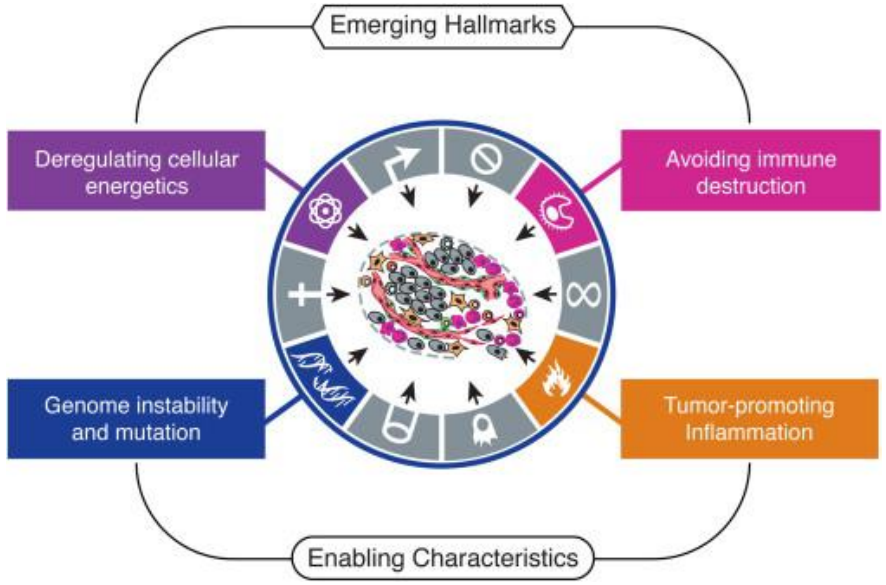
Phenotypic Characteristics of Cancer

- While substantial amount of information has been generated about cancer (over 3 million research articles), it remains largely unclear what really constitutes a cancer at the cellular and tissue level!

- Hanahan and Weinberg published two seminal papers “The Hallmarks of Cancer” and “The Hallmarks of Cancer: the next generation”, which for the first time defines the distinguishing molecular level characteristics of a cancer

Hallmarks of Cancer



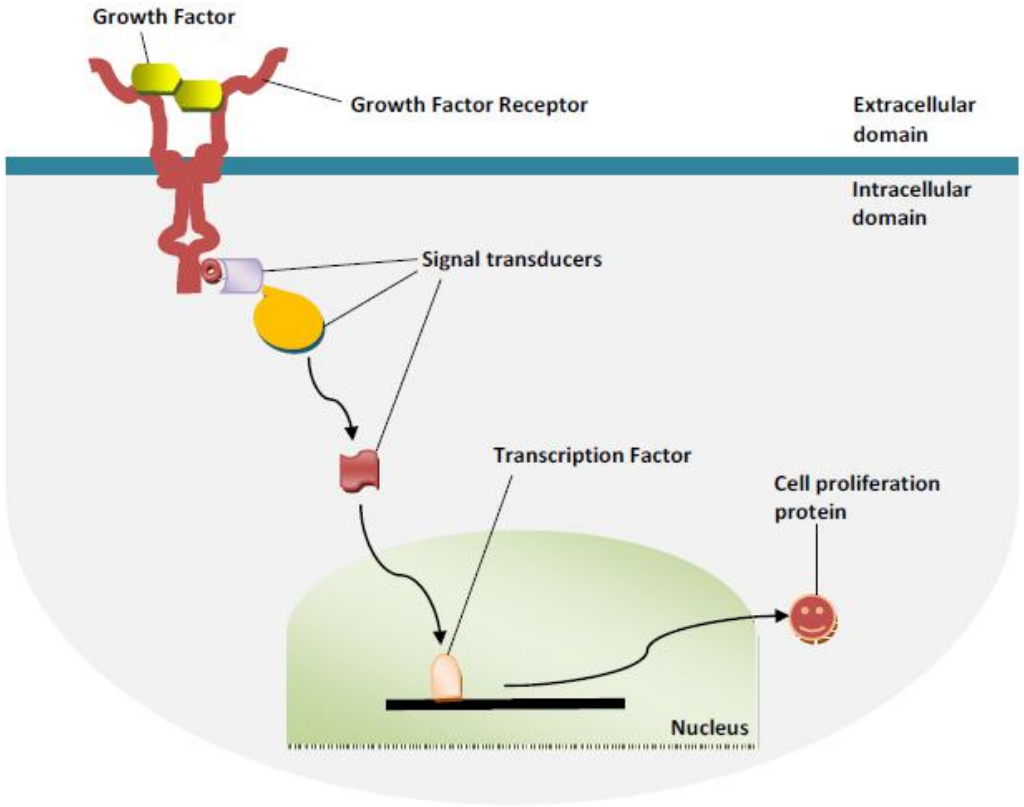


- Sustained proliferative signaling
- Evading growth suppressors
- Resisting cell death
- Enabling replicative immortality

- Inducing angiogenesis
- Activating invasion/metastasis
- Reprogramming energy metabolism
- Avoiding immune destruction

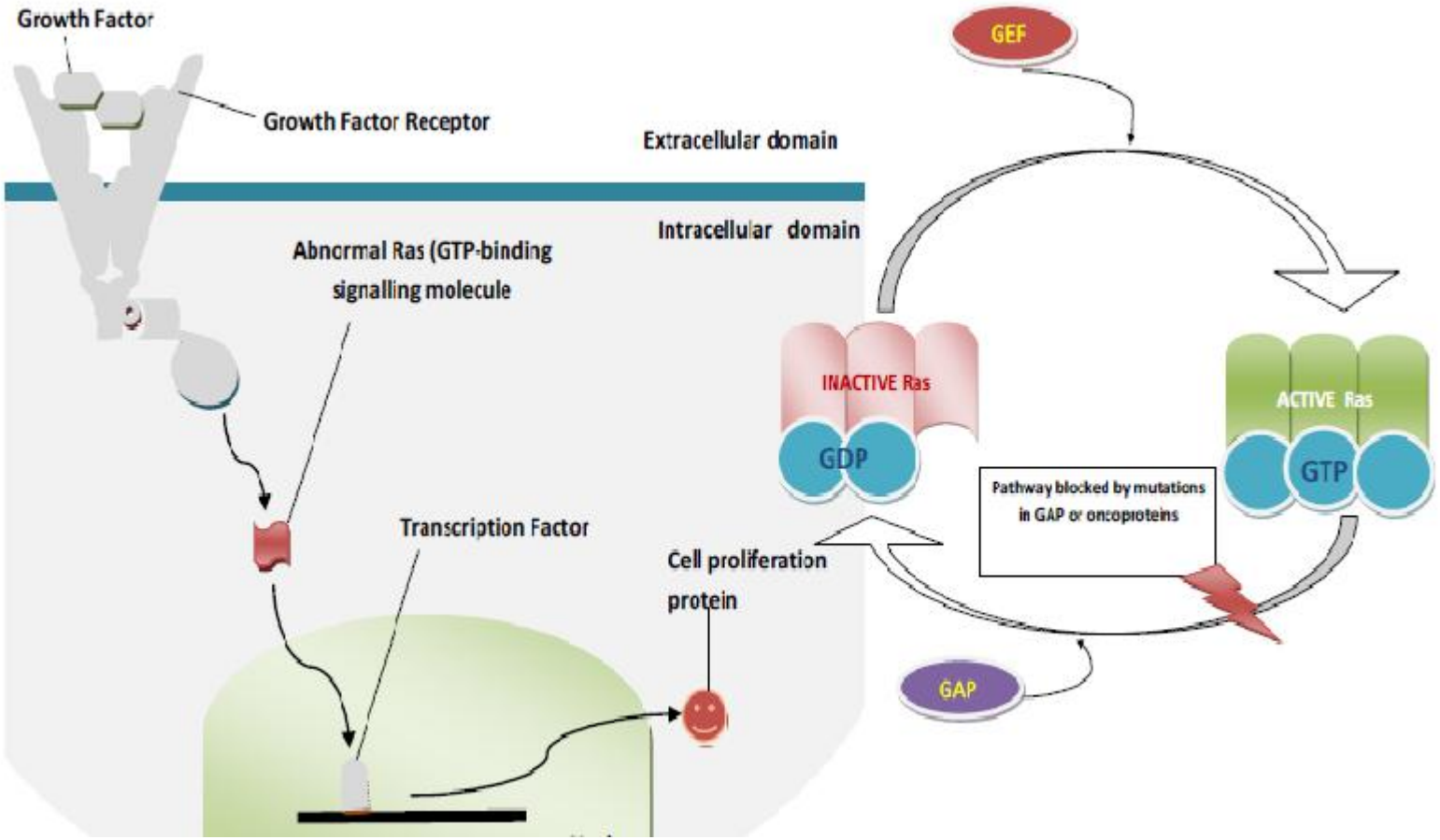
I: Sustained Proliferative Signaling

- Normal cells will proliferate only when they receive "growth signals"
- Cancer cells, for "unknown" reasons, grow without necessarily having such signals



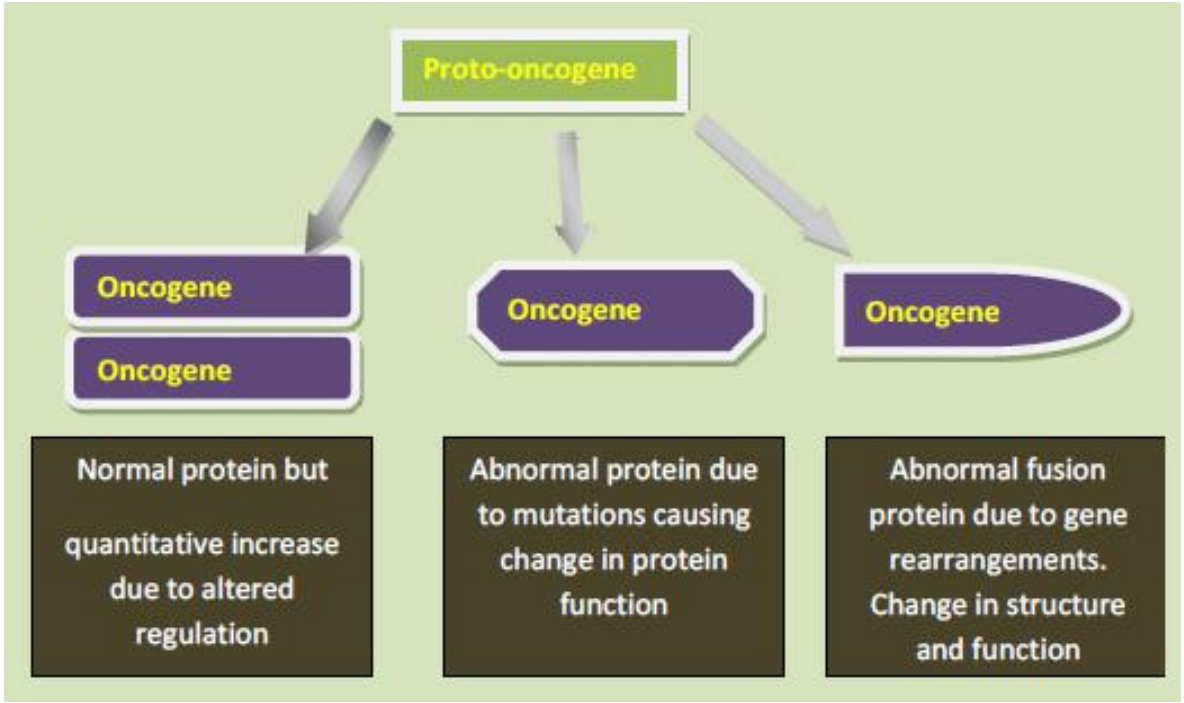
Sustained Proliferative Signaling

- Abnormal signaling by Ras (as an oncogene)



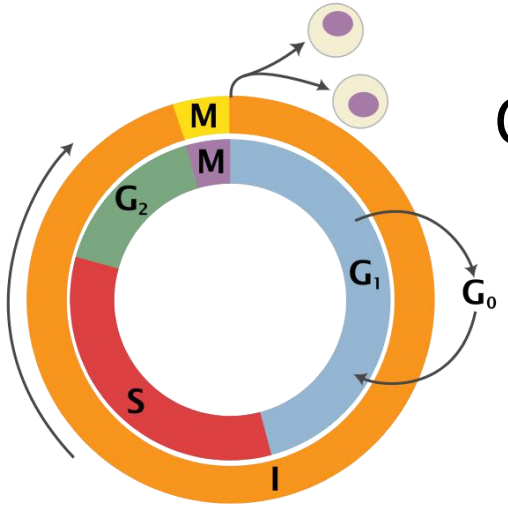
Oncogenes

- Oncogenes are genes whose over-expression or mutations can lead to cancer
- Hundreds of oncogenes have been identified
- Different cancers may have their own main oncogenes



II: Evading Growth Suppressors

- Like growth signals, there are anti-growth signals to stop cells from division



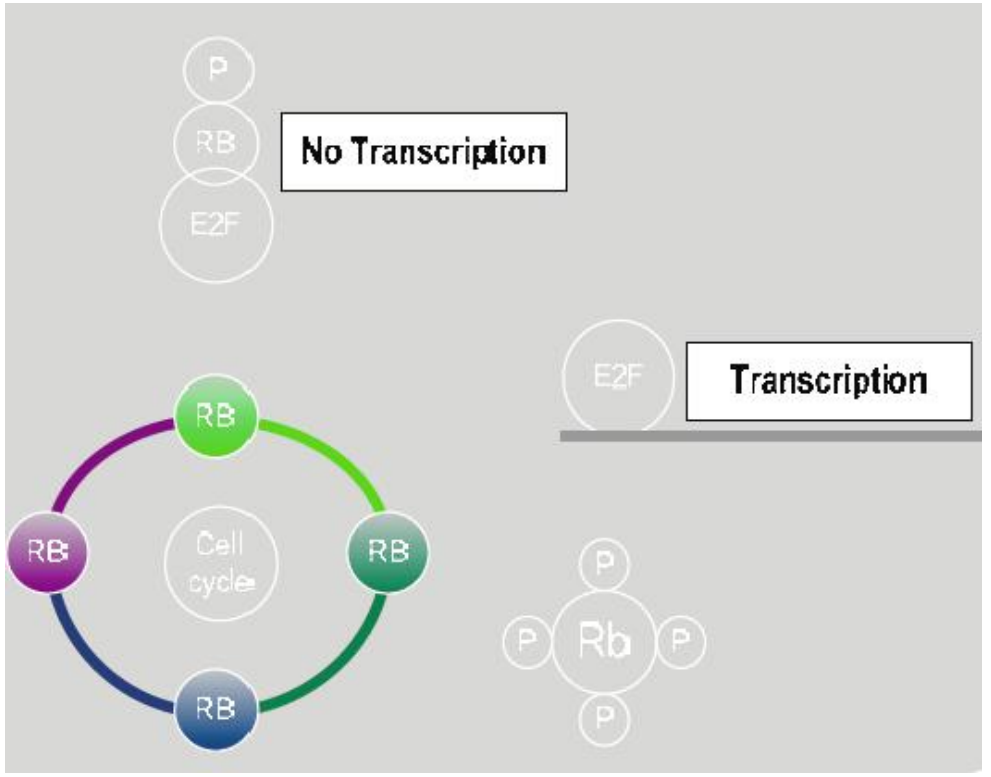
Cell cycle

Anti-growth signals can force dividing cells into the quiescent phase (G0) of the cell cycle

Evading Growth Suppressors

- RB (retinoblastoma) protein is one such anti-growth protein, which binds to the regulators of the cell cycle
- P53 is another anti-growth protein

Cancer cells somehow have learned to by-pass the anti-growth mechanism through having mutations or repression of proteins like RB and P53



Tumor Suppressor Genes

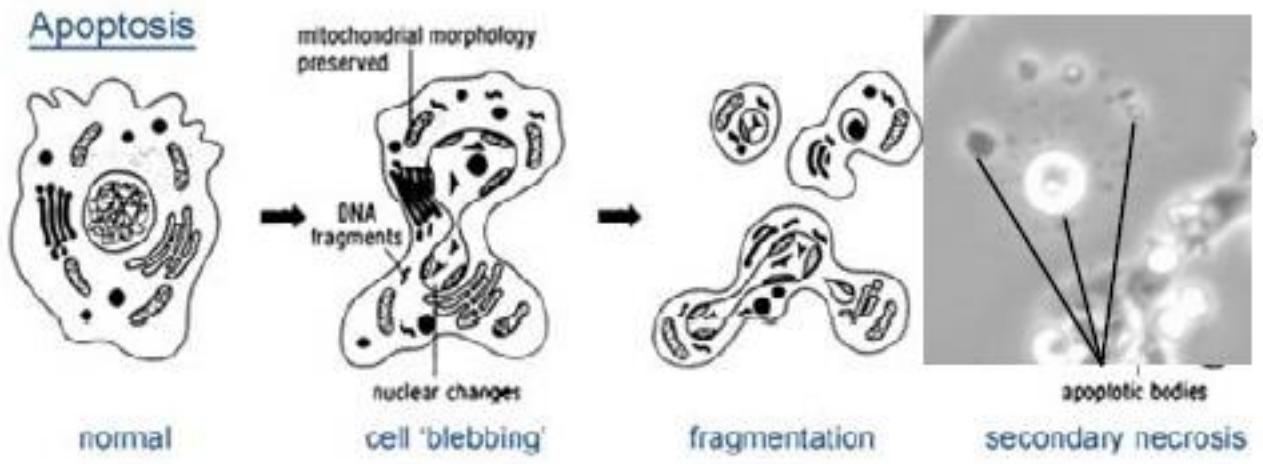
- Genes that encode proteins capable of inhibiting cell division, like RB, are called tumor suppressor genes
- In cancer genomes, multiple tumor suppressor genes may have loss-of-function mutations
- A few hundred tumor suppressor genes have been identified for different cancers

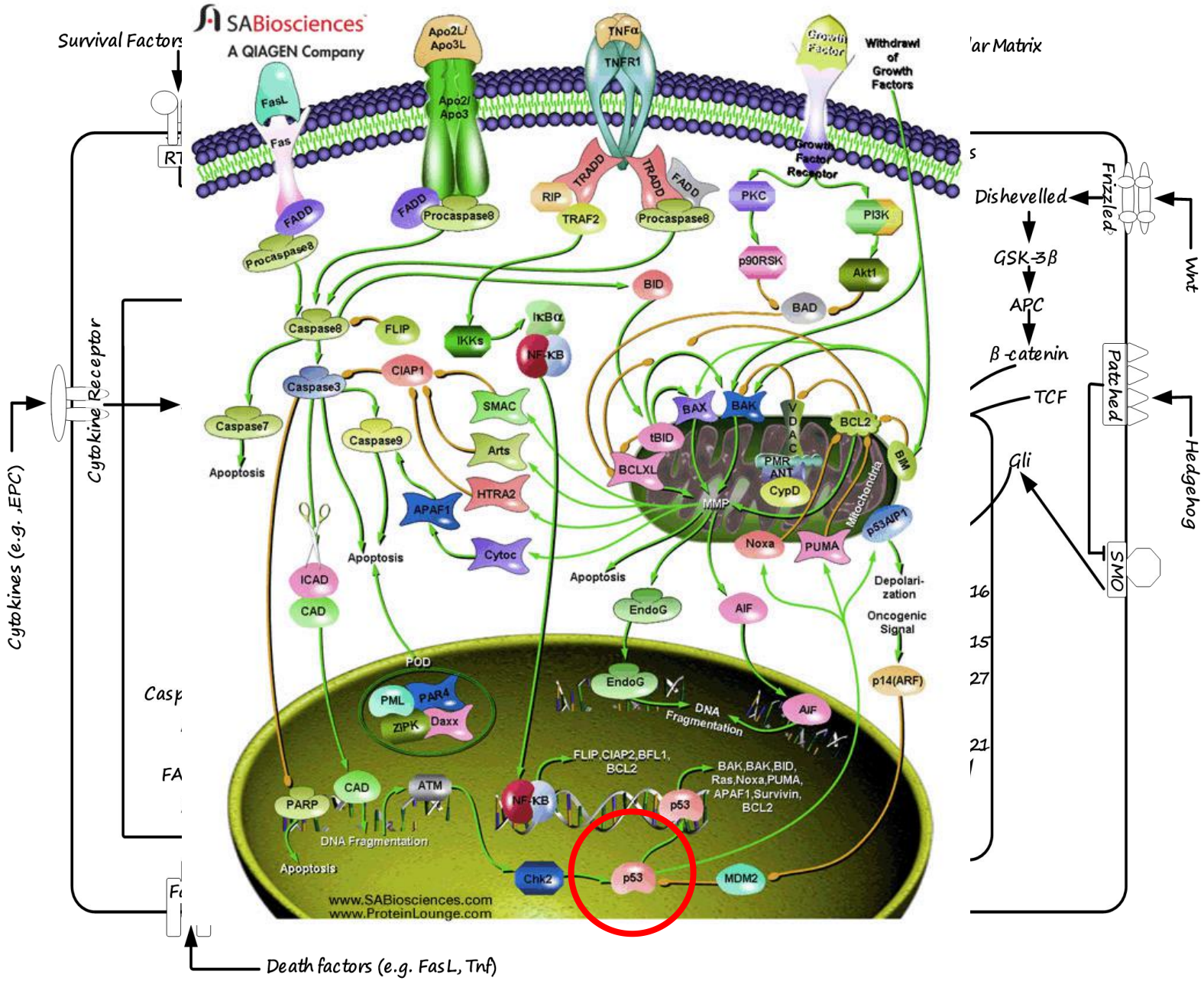
Later we will learn that there could be a fundamentally different way to look at oncogenic and tumor suppressor mutations!

III: Resisting Cell Death

- A cell constantly surveys its internal state including access to oxygen and nutrients, integrity of its genome and balance of its cell cycle pathways

- If malfunction or damage is detected, the cell activates cell death (apoptotic) pathway to kill itself

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Survival Factors
Cytokine Receptor
Cytokines (e.g. ,EPC)
Death factors (e.g. FasL, Tnf)
Withdrawl of Growth Factors
Growth Factor Receptor
Apo2L/ Apo3L
Apo2/ Apo3
TNFα
TNFR1
FasL
Fas
FADD
Procaspase8
TRADD
RIP
TRAF2
PKC
PI3K
p90RSK
Akt1
BAD
BID
Caspase8
FLIP
IKKs
IκBα
NF-KB
CIAP1
Caspase3
Caspase7
Caspase9
Apoptosis
SMAC
Arts
HTRA2
APAF1
Cytoc
ICAD
CAD
BAX
BAK
VDAC
BCL2
tBID
BCLXL
PMR ANT
CypD
MMP
Mitochondria
BIM
Noxa
PUMA
p53AIP1
EndoG
AIF
Depolari-zation
Oncogenic Signal
p14(ARF)
POD
PML
PAR4
ZIPK
Daxx
DNA Fragmentation
FLIP,CIAP2,BFL1, BCL2
BAK,BAK,BID, Ras,Noxa,PUMA, APAF1,Survivin, BCL2
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PARP
p53
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SMO
16
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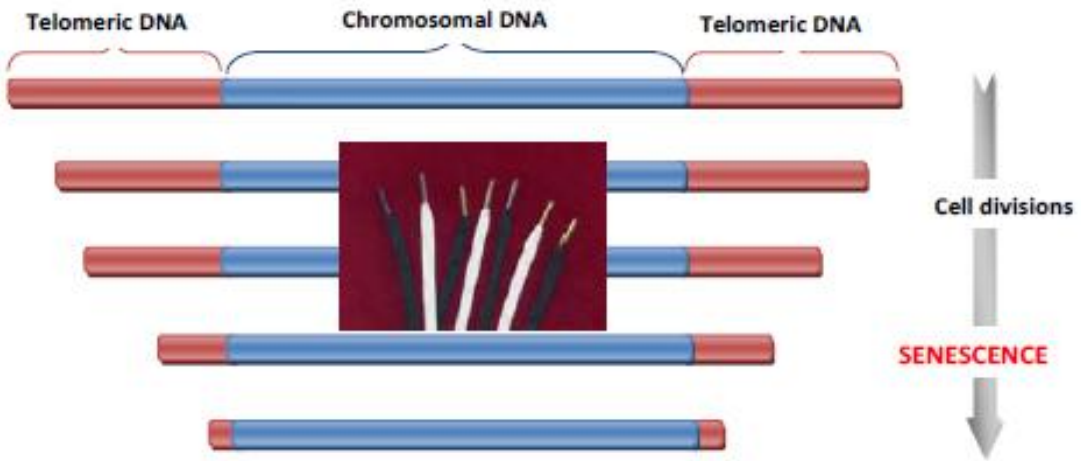
21

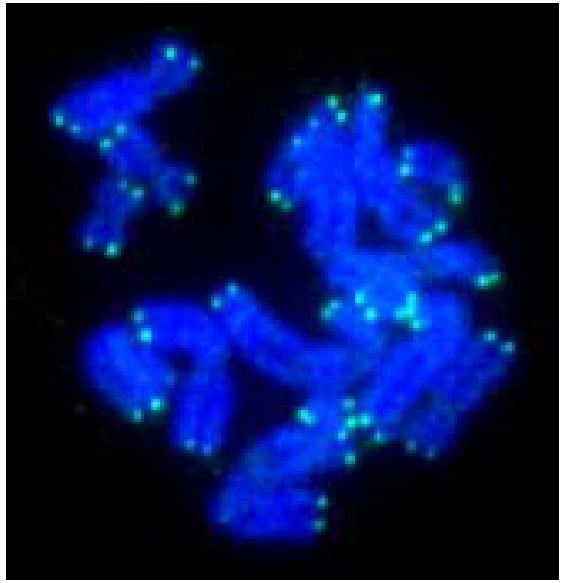
Resisting Cell Death

- Cancer cells all learned to by-pass the apoptosis process to avoid to be killed
- They use (at least) two pathways to avoid apoptosis by impairing the sensing of and signaling about abnormal internal status or the execution apoptosis
- One main mechanism is through having mutations in the main regulator, p53, of apoptosis
  - 50% of the cancer genomes have mutations in p53

IV: Enabling Replicative Immortality

- Normal human cells can divide 60-70 times and then reaches the end of its natural life
- Cells all keep a biological clock that keeps track of their ages





Enabling Replicative Immortality

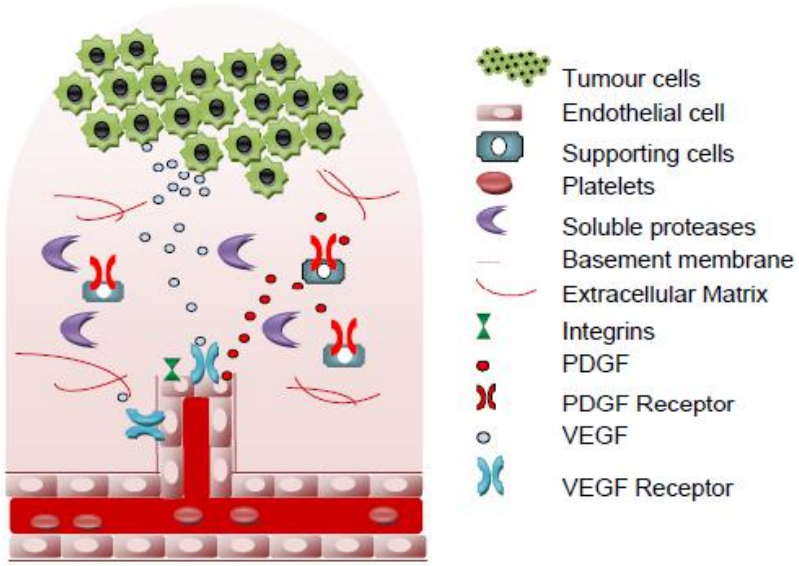
- Cancer cells learned to protect their telomeres, so they do not get shortened when cells divide, hence making cancer cells immortal
- They use telomerase to add to the ends of telomeres after each division to maintain their lengths
- This is an encoded mechanism in human cells but has been used only by embryonic stem cells

V: Inducing Angiogenesis

- All cells, healthy or diseased, need oxygen and nutrients, which can be provided only through blood vessels
- Human bodies are well designed so every cell is within 100 um of a capillary
- Cancer cells need additional blood supply to support its rapid growth

Inducing Angiogenesis

- Angiogenesis is a process that grows new blood vessels from the existing ones, which is used during wound healing or menstruation
- Cancer cells learned to send out angiogenic signals to endothelial cells lining nearby vessels to grow new vessels

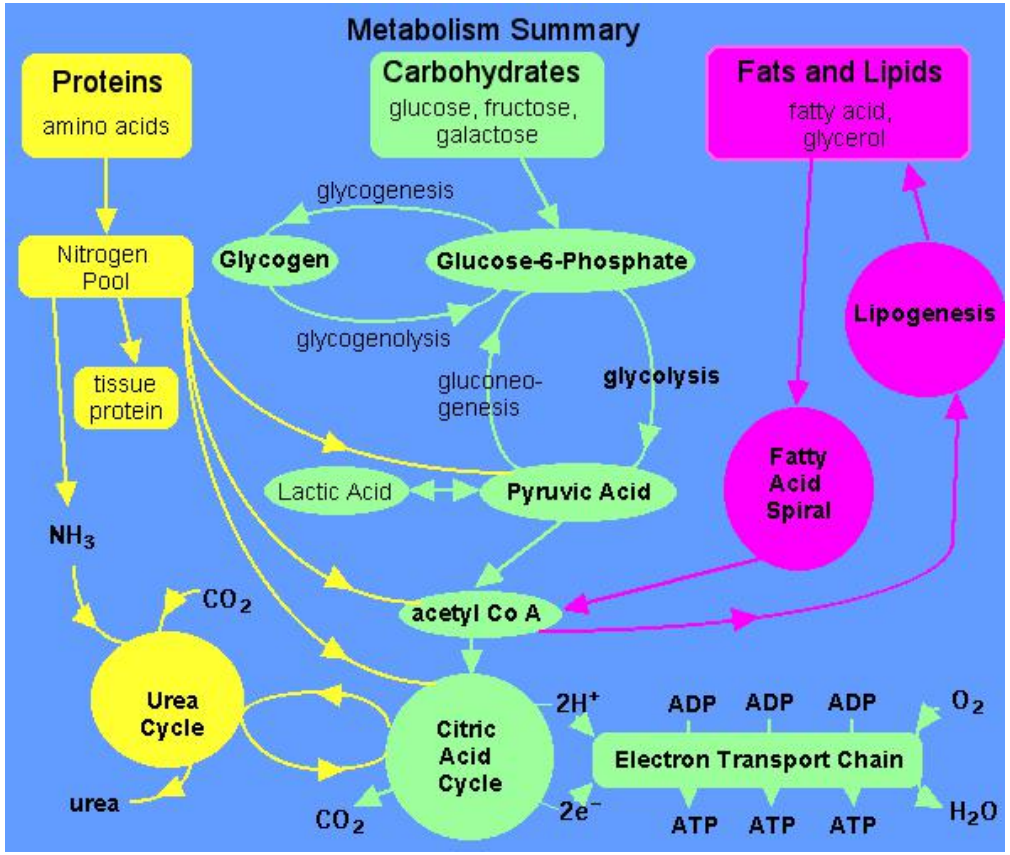


Inducing Angiogenesis

- Without angiogenesis, a cancer will not be able to grow big nor able to spread to other parts of the body
- Cancer becomes dangerous only after it starts to have its own blood vessels
- One type of cancer treatment is to kill tissue cells cells with messy blood vessels

VI: Reprogrammed Energy Metabolism

- Human cells have multiple ways to convert nutrients to energy (ATP)
- Oxidation of pyruvate through utilization of electron transport chain requires oxygen
- Glycolysis does not require oxygen and uses lactate as the electron receiver



Reprogrammed Energy Metabolism

- Otto Warburg observed in 1927 that cancer cells use glycolytic fermentation in addition to oxidation of pyruvate regardless of the O2 level (Warburg effect)

- Oxidation of pyruvate is by far the most efficient energy metabolism per glucose

- It seems that all cancers utilize suboptimal energy metabolisms, which may be a key reason for their explosive growth – a paradox

Reprogrammed Energy Metabolism

- While Warburg effect was widely observed in cancer tissues, no generally accepted explanation has been developed
- This remains to be one of the most intriguing issues related to cancer development
- We will present a model to answer the question

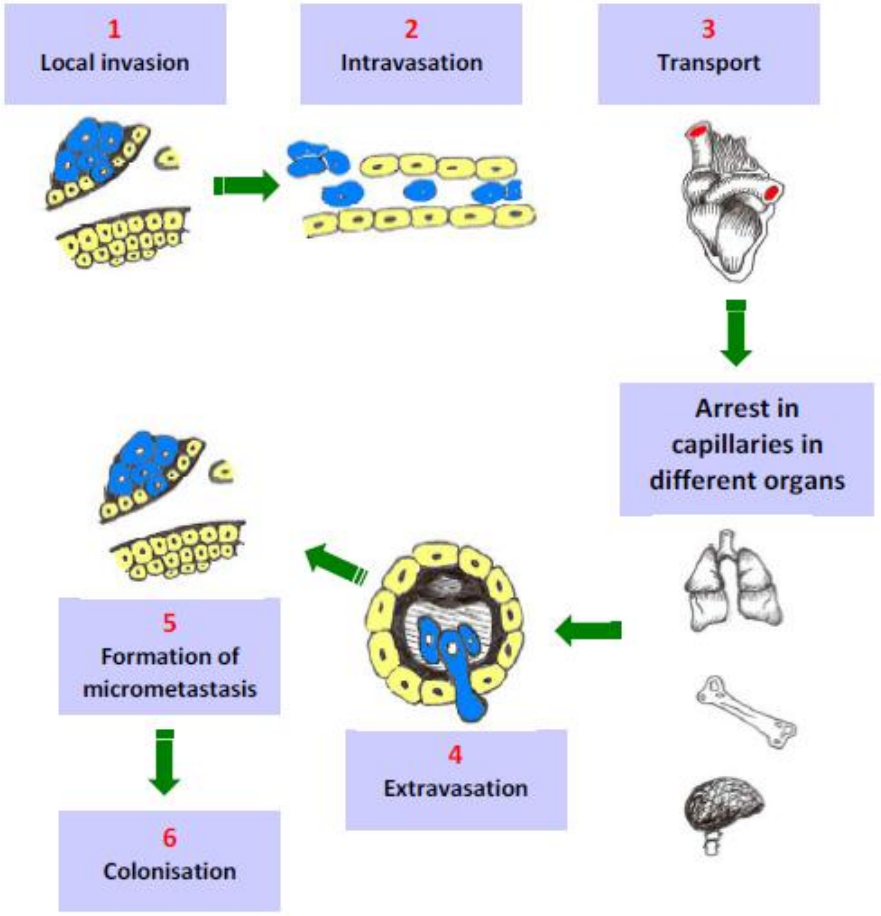
VII: Avoiding Immune Destruction

- Cancer development and immunity are linked at the root
  - Cancer is often considered as a wound that will not heal
  - Immune system responds to two things: (a) invasion of pathogens, and (b) tissue damages

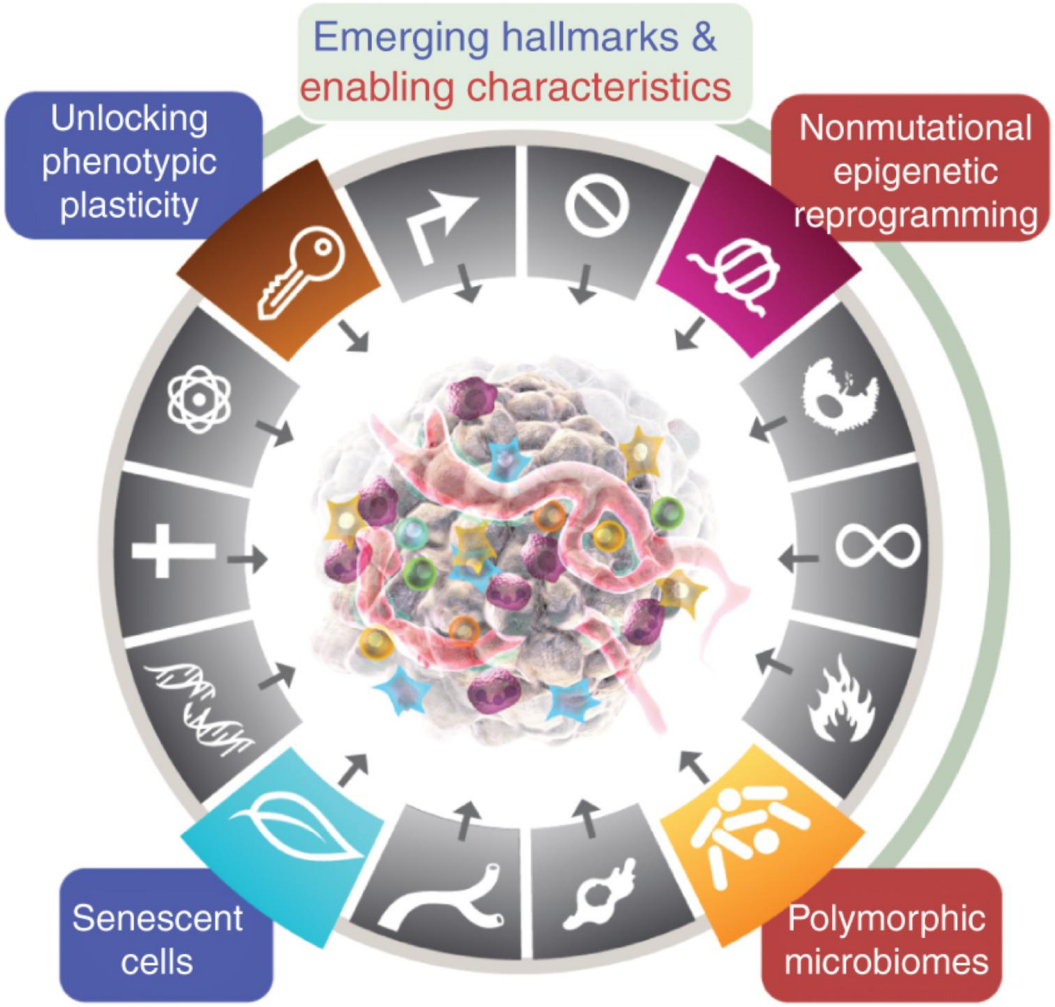
- Cancer studies using immune-deficient mice may not necessarily lead to cancer related discoveries; the same can be said about cell-based cancer research

VIII: Activating Invasion/Metastasis

- What makes cancer really deadly is its ability to invade neighboring cells and spread to other organs
- Over 93% of the cancer related deaths are due to metastatic cancers
- … and yet, our previous view about metastatic cancers may not be correct!



Hallmarks of Cancer: new dimensions



Cancer discovery (2022)

Hallmarks of Cancer: new dimensions

- Unlocking phenotypic plasticity: cancer cells can de-differentiate, differentiate and trans-differentiate to various cell types
- Senescent cells: Cell senescence is irreversible and tend to release various molecules that trigger immune responses. Cancer cells seem to be able to switch between senescence and proliferation state
- Non-mutational epigenomic reprogramming: tumor microenvironment can trigger abnormal changes in folded DNA structures, altering encoded transcription programs
- Polymorphic microbiomes: There are interactions between gut microbiota and cancer tissues

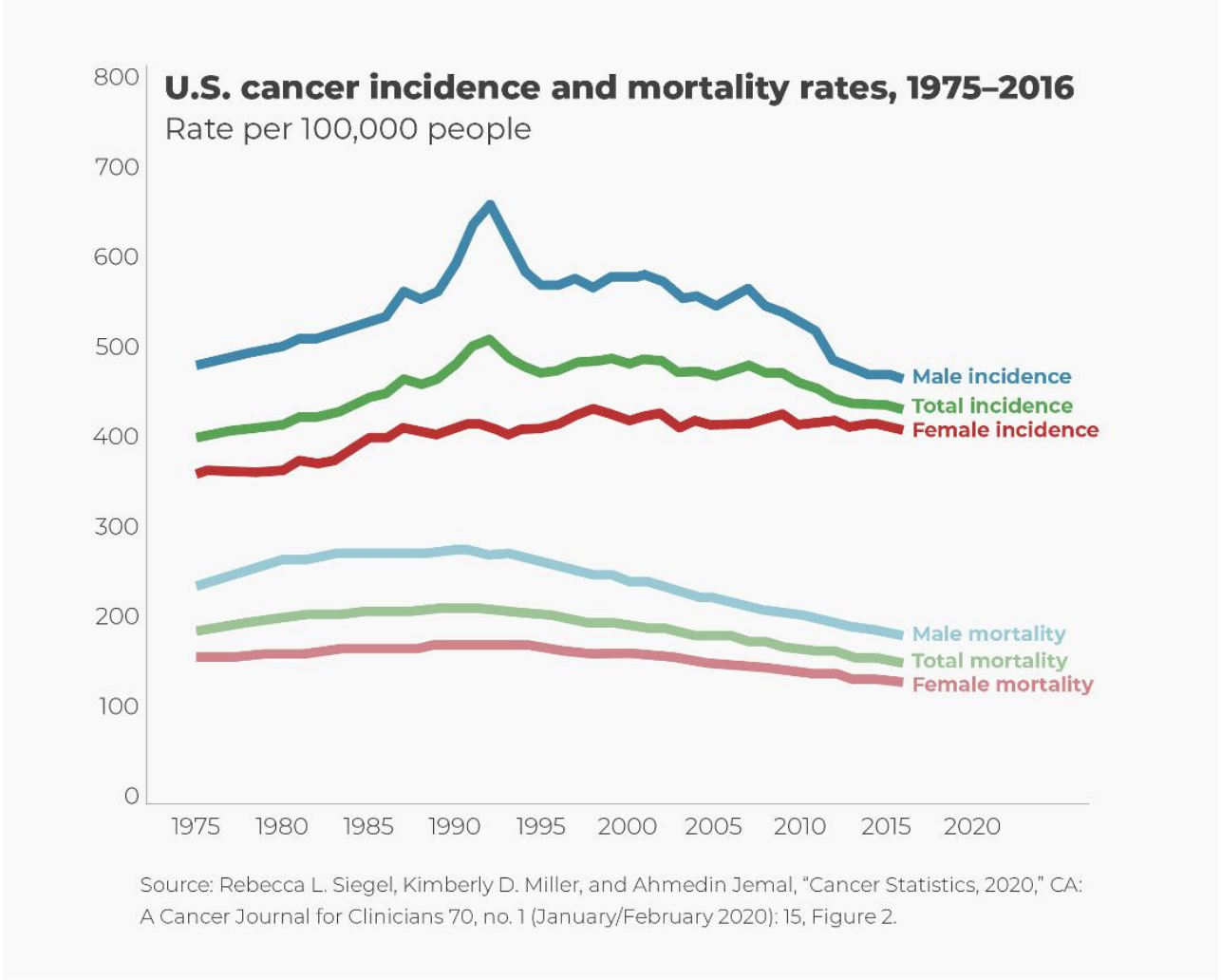
Cancer Hallmarks

- The first two papers have been widely used as the guiding framework in cancer research
- They have clearly captured some of the key phenotypic characteristics of cancers in general
- They represent the state of the art in understanding of cancers
- BUT they did not touch on the root issue of cancer: what drive cancers to evolve?
- Issues discussed in the third paper are not cancer specific

Cancer Hallmarks

-
- It is noteworthy that all the hallmarks of cancer (discussed above) are cellular processes encoded in our genome but used for other purposes rather than for cancer cells to develop

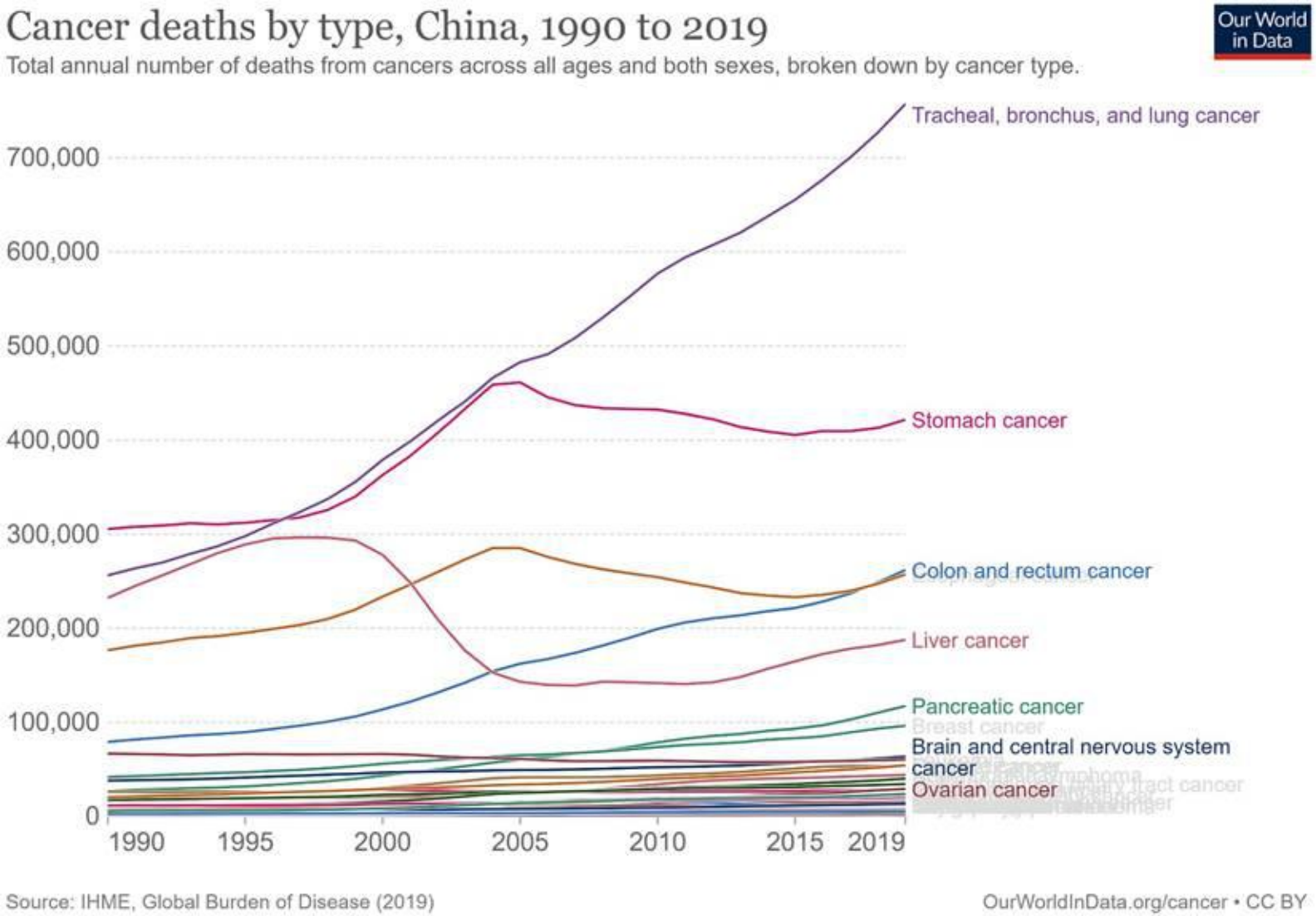
The State of Art

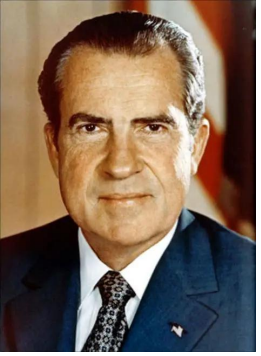


Source: Rebecca L. Siegel, Kimberly D. Miller, and Ahmedin Jemal, "Cancer Statistics, 2020," CA: A Cancer Journal for Clinicians 70, no. 1 (January/February 2020): 15, Figure 2.

肿瘤死亡率降低的重要原因是禁烟、早期发现、早期治疗

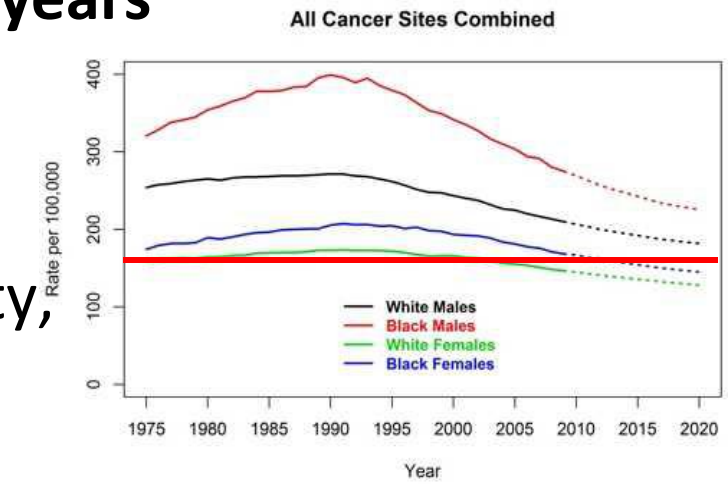
Cancer Death Rates in China





War on Cancer (1971 --)

- Encouraged by the rapid development of cell biology, U.S. President Richard Nixon signed in 1971 the legislation **'War on Cancer**,' aiming to eliminate the pain and death caused by tumors to humans **within 25 years**
- James Watson repeatedly stated, including an article in the New Work Times, that: on the whole the 'war on cancer' has **made no dent** in the overall cancer mortality, except for **some rare cancers**



- In 2021, U.S. President Joe Biden changed the name to **Cancer Moonshot** with a revised goal: **halving the death rate** from cancer within 25 years.

思考

- 组学大数据并没有在质上提升我们研究、解决疾病的能力 -- 对于绝大多数复杂疾病，包括肿瘤、老年痴呆、糖尿病、抑郁症，我们的认识似乎还停留在很表面的水平

- AI技术在提升我们的分析能力方面已有了长足的进步，但我们还没有看到对疾病认识上质的突破，我们可能需要新的思维方式来研究肿瘤及其它复杂疾病

- 咱们先来看看产生肿瘤的环境 - 慢性炎症、组织修复、肿瘤发生的必要条件

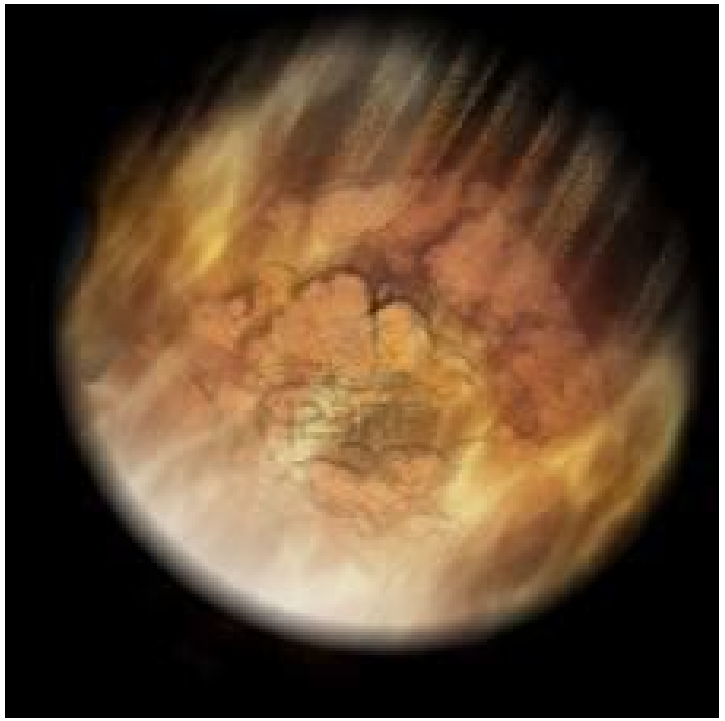
- 目前的肿瘤研究可能缺了些什么？

Oxygen and Life

- Chronic inflammation has been found to be associated with cancer development, but the mechanism remains not well understood
- Chronic inflammation can be characterized as over-production of H_2O_2 and $\cdot O_2^-$ by innate immune cells, causing local hypoxia and oxidative stress
- Question: what happens when human cells are under hypoxic condition for an extended period of time?

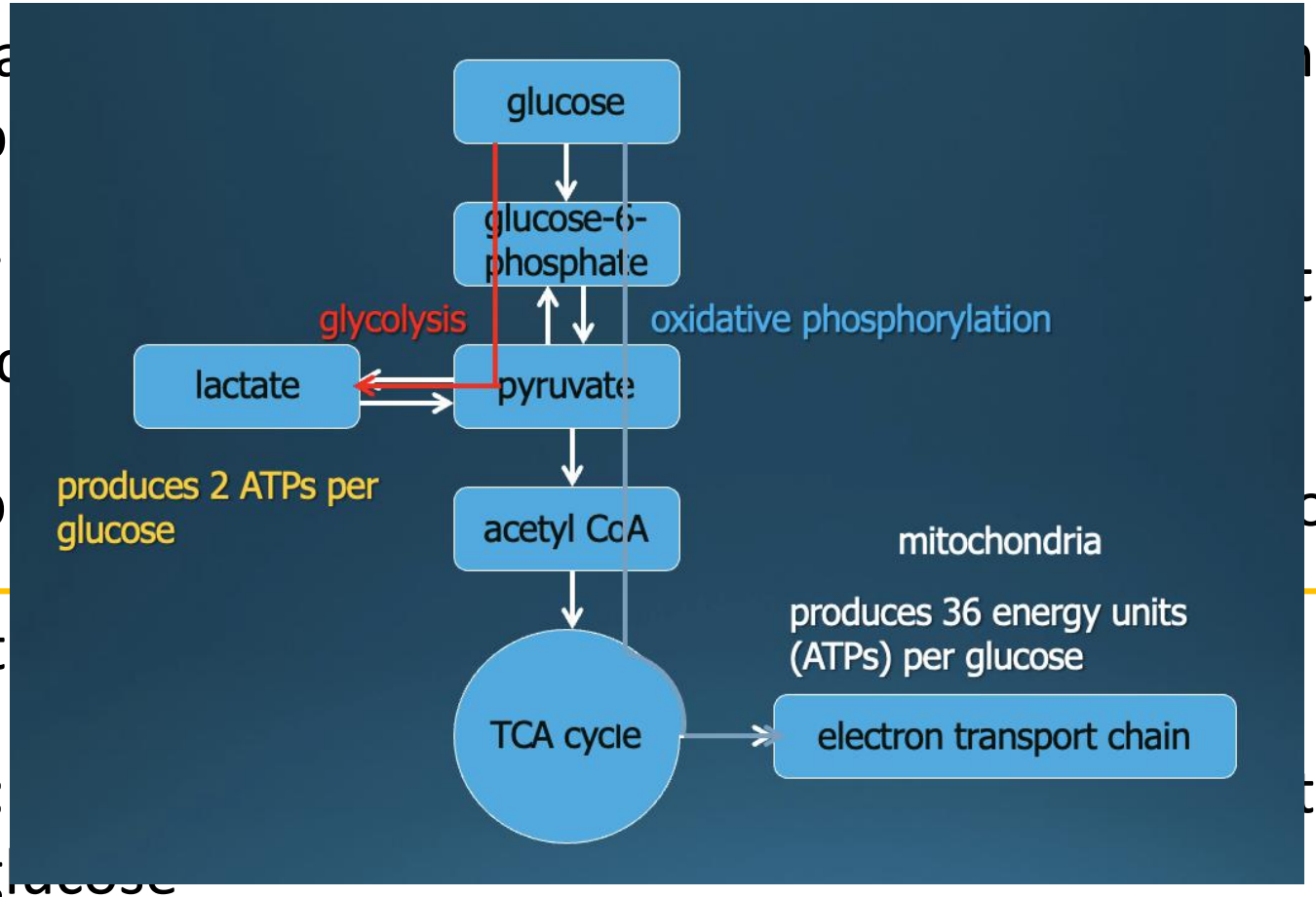
Oxygen and Life

- The emergence of O_2 ~2.8 billion years ago made it possible to have complex organisms developed, including human
- Human as a population has never lived under hypoxia for extended period of time

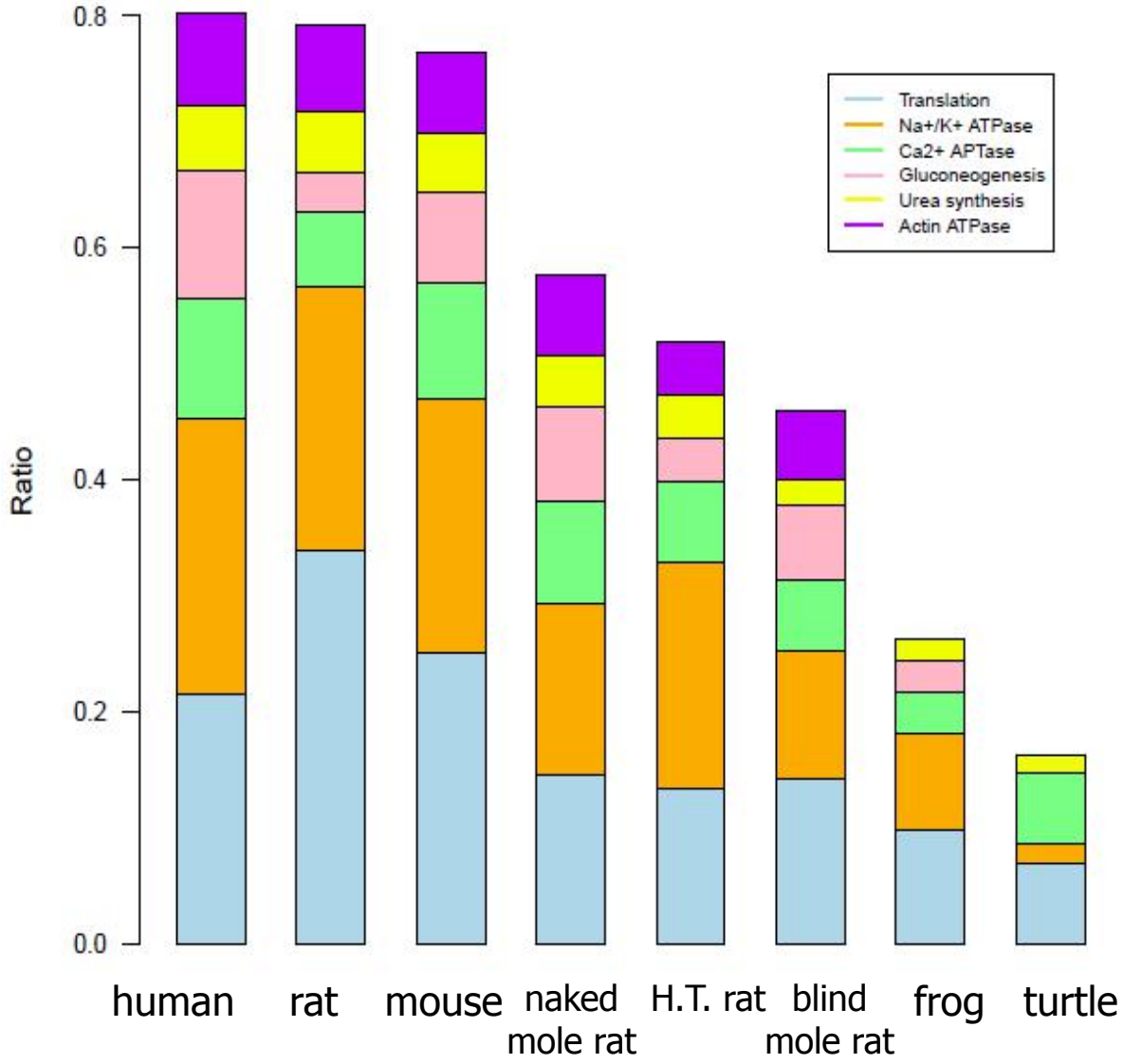


Energy Supply under Hypoxia

- Under hypoxia … entation from oxidative resp…
- The cells will i… the reduced energy produc…
- Under x% hyp… ordingly
- This leads to t…
- The reason is: … to deal with the influx of the g…



Energy Demand under Hypoxia



- Human, rat and mouse have only little reduction in energy demand under hypoxia *versus* normoxia
- Frog and turtle have significant reductions
- Naked and blind mole rats have substantial reductions

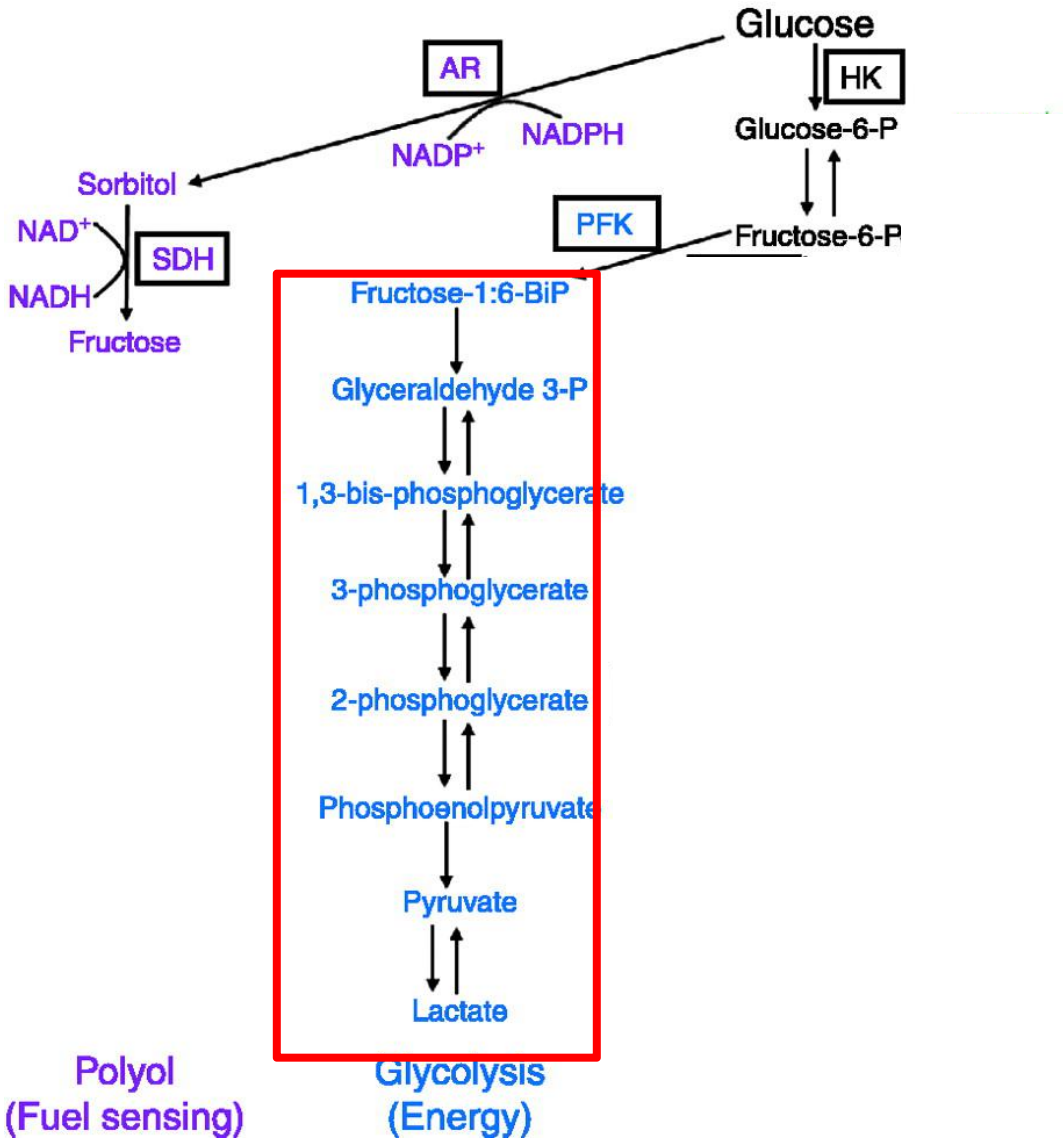
Energy Demand and Supply under Hypoxia

- This is the result of evolution as human has never lived in hypoxic environment for long during the past evolution and hence has not learned which energy-consuming activities to shut down
- Very interestingly, one difference between these two groups of organisms is that one develops cancer and the other virtually do not develop cancers
- Hence the energy gap may have something to do with the fundamental potential of an organism to develop cancer

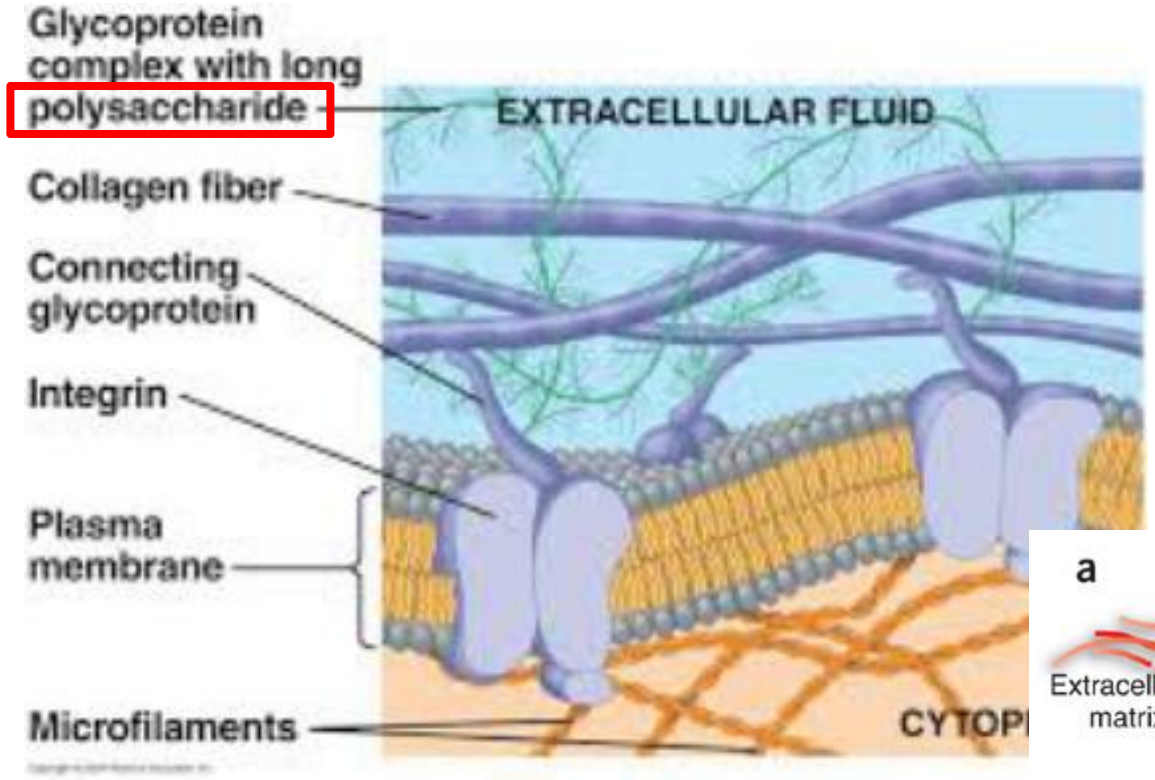
Energy Gap and Implications

- The continual accumulation of glucose metabolites will lead to cell death if the accumulation is not channeled out
- What is the connection between the accumulation of glucose metabolites and cell proliferation?
- Oncogenes have been proposed to be the link but that may not work since most of the affected cells are probably not signaled to proliferate, which involves many parts and coordination

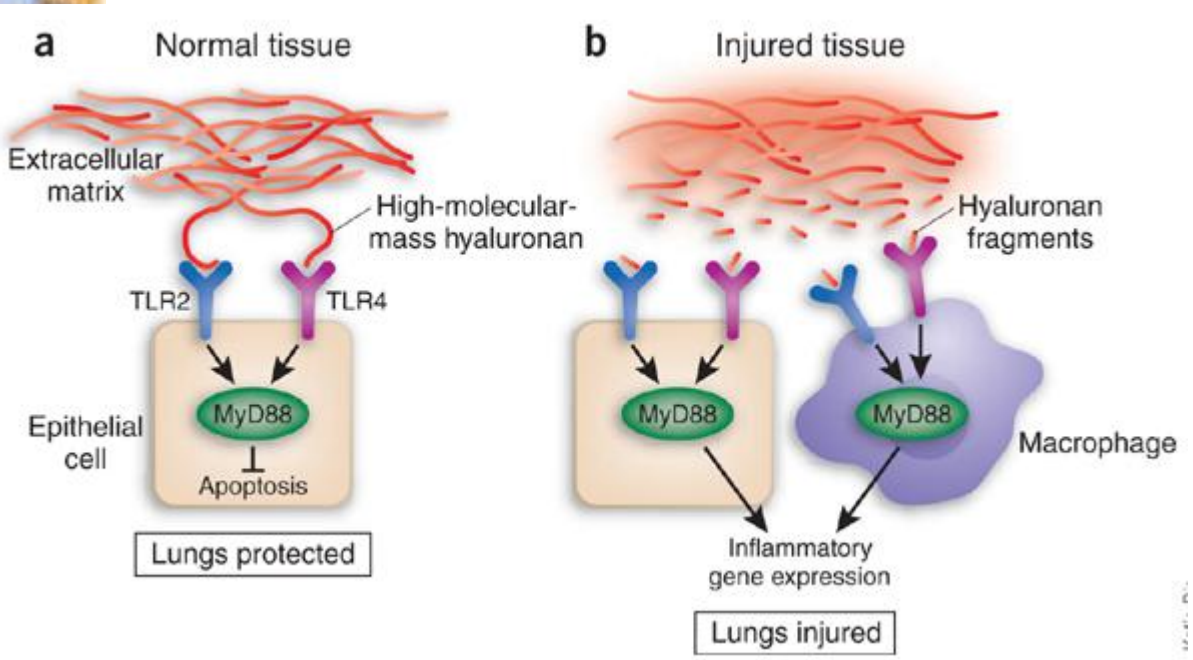
Accumulation and Cell Proliferation



Hyaluronic Acid and Function

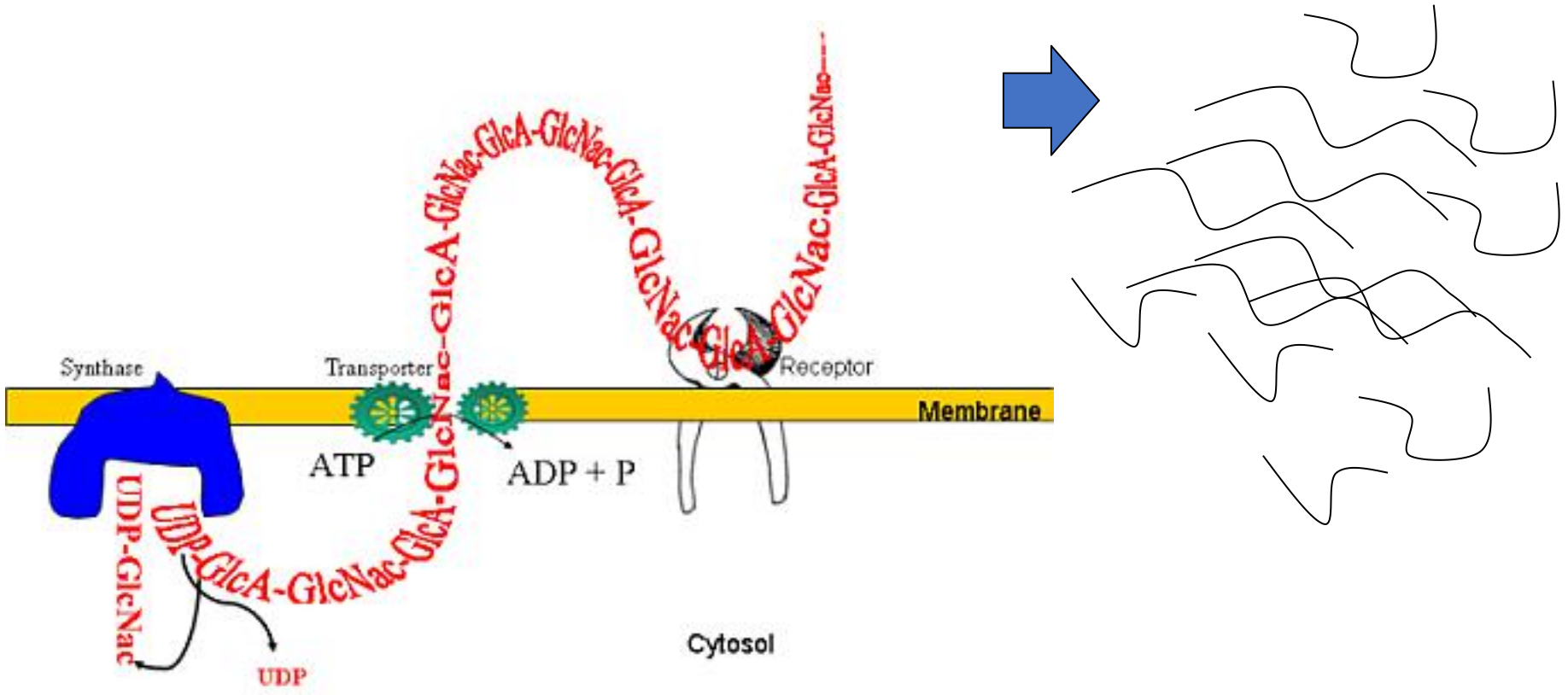


Hyaluronic acid fragments serve as a wide range of signals for tissue injury and repair



Hyaluronic Acid and Hypoxic Cells

- Synthesized hyaluronic acids will be exported out of cells and then degraded into fragments, hence providing all the signals for continuous growth



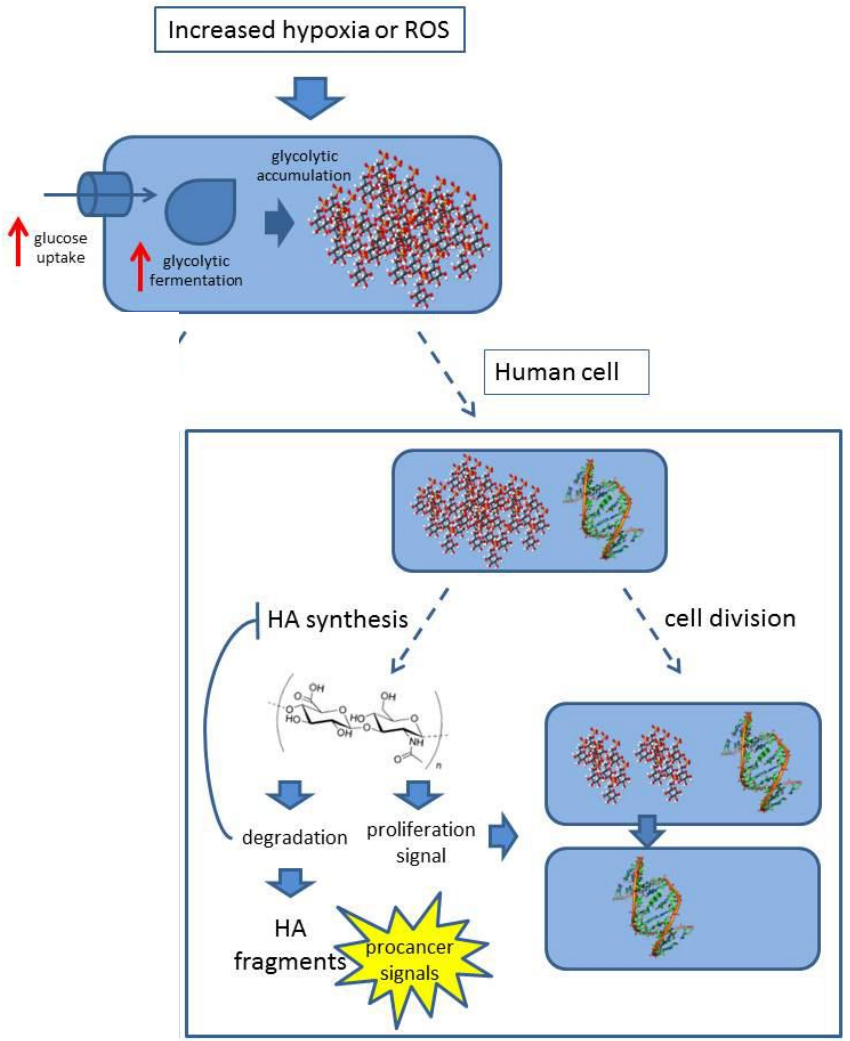
Hyaluronic Acids and Tissue Repair

- Hyaluronic acids of different sizes serve as different signals for tissue injury and repair
  - Inflammatory signals to recruit immune cells
  - Cell survival through repressing apoptosis
  - Cell-cycle control
  - Cell growth
  - Loss of contact inhibition
  - Anchorage-independent growth
  - Angiogenesis

Virtually all the signals needed for tumor cell proliferation

(Short) hyaluronic acids of different sizes serve as different signals, all related to tissue repair and cancer development

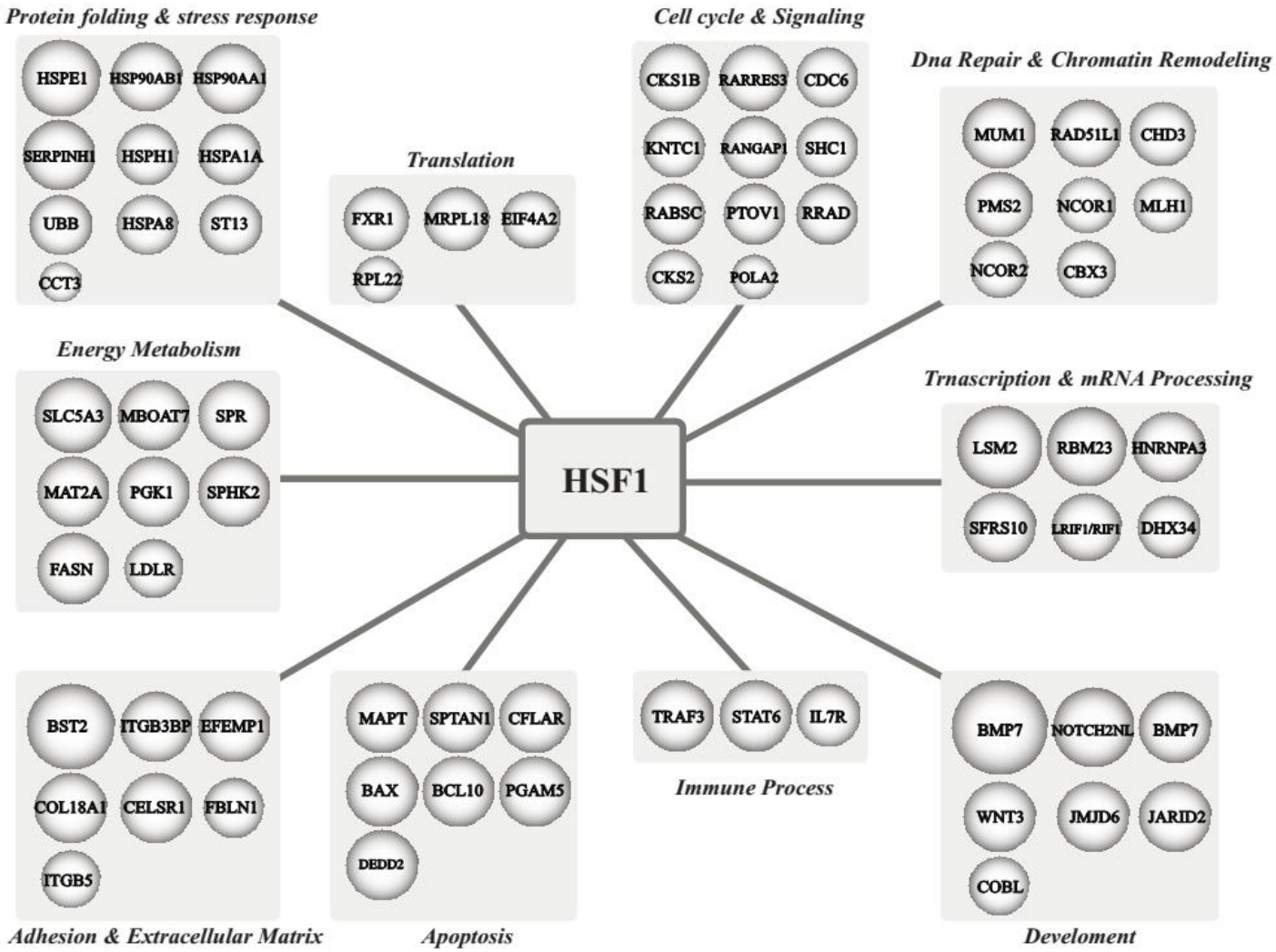
Size (saccharides)	Function	References
High-molecular-mass HA > 1000–5000	Suppression of angiogenesis	Feinberg and Beebe (1983)
	Immune suppression	McBride and Bard (1979), Delmage et al. (1986)
	Inhibition of phagocytosis	Forrester and Balazs (1980)
	Suppression of HA synthesis	Lueke and Prehm (1999)
HA fragments		
~1000	Induction of inflammatory chemokines	Noble et al. (1993)
	Stimulation of PAI-1	Horton et al. (2000)
	Stimulation of urokinase	Horton et al. (2000)
10–40	Induction of CD44 cleavage	Sugahara et al. (2003)
	Promotion of tumor cell migration	Sugahara et al. (2003)
8–32	Stimulation of angiogenesis	West et al. (1985), Sattar et al. (1994), Slevin et al. (1998, 2002)
	Stimulation of tumor neovascularization	Rooney et al. (1995)
~15	Suppression of smooth muscle cell proliferation	Evanko et al. (1999)
12	Endothelial cell differentiation	Takahashi et al. (2005)
	Up-regulation of PTEN in tumor cells	Ghatak et al. (2002)
10	Displacement of matrix HA on oocyte surface	Camaioni et al. (1993)
	Displacement of proteoglycans from cell surface	Solursh et al. (1980)
6	Suppression of HA cable formation	de la Motte et al. (2003)
	Induction of NO and MMPs in chondrocytes	Knudson and Knudson (2004a, b)
	Induction of HAS2 in chondrocytes	Knudson and Knudson (2004a, b)
4–6	Induction of cytokine synthesis in dendritic cells	Termeer et al. (2000, 2002), Taylor et al. (2004)
	Transcription of MMPs	Fieber et al. (2004)
4	Up-regulation of Hsp 72 expression	Xu et al. (2002)
	Suppression of apoptosis	Xu et al. (2002)
	Induction of chemotaxis	R. Savani, personal communication
	Up-regulation of heat shock factor-1	Xu et al. (2002)
	Up-regulation of Fas expression	Fujii et al. (2001)
	Suppression of proteoglycan sulfation	Solursh et al. (1980)



cancer

Model: hypoxia -> accumulation of glycolytic metabolites -> hyaluronan synthesis and fragmentation -> signaling for tissue damage and repair; hence starts the tissue-repair process and opens the door for cell proliferation in a tissue environment

Master Regulator of Proliferation



Essential Roles of Hyaluronic Acids

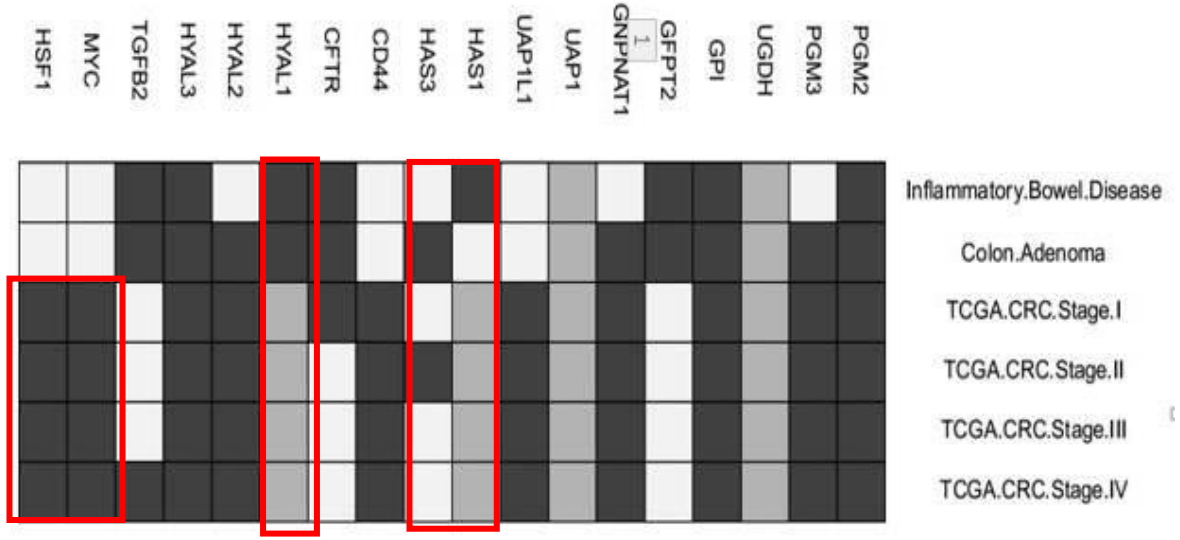
- Persistent production of hyaluronic acid production provides continuous signals for affected cells to
  - overcome virtually all tissue-level constraints for cell division such as contact-inhibition and anchor-dependence of ECM
  - overcome apoptosis
  - generate angiogenesis
  - …..
- Virtually all conditions for a cancer to take place

A good project to demonstrate this via a mouse cancer model

- **Hypothesis**: Persistent production of hyaluronic acid may be a prerequisite for large-scale genomic mutations since otherwise DNA repair mechanisms will fix all mutations

Synthesis of Hyaluronic Acid

- The key conditions for activation of hyaluronic acid synthesis pathway:
  - plenty of glucose metabolites, particularly G6P
  - hypoxic condition
  - availability of TGFβ (available when tissue is inflammatory)
- That is, under inflammation-induced persistent hypoxia, hyaluronic acid will be synthesized, exported and fragmented

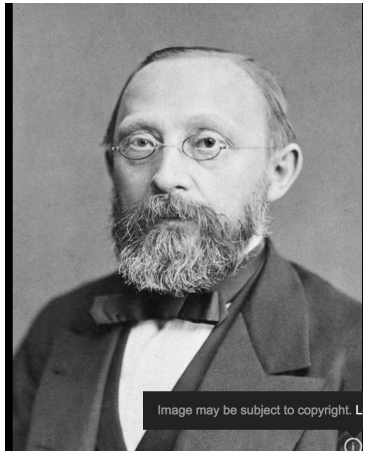


Chronic Inflammation and Cancer

- Chronic inflammation has long been known to be associated with cancer development, which can be traced back to as early as over 150 years ago (Rudolf Virchow)
- Recent studies suggest that inflammation is a critical component of any cancer
- However, the causal relationships between the two are currently unknown

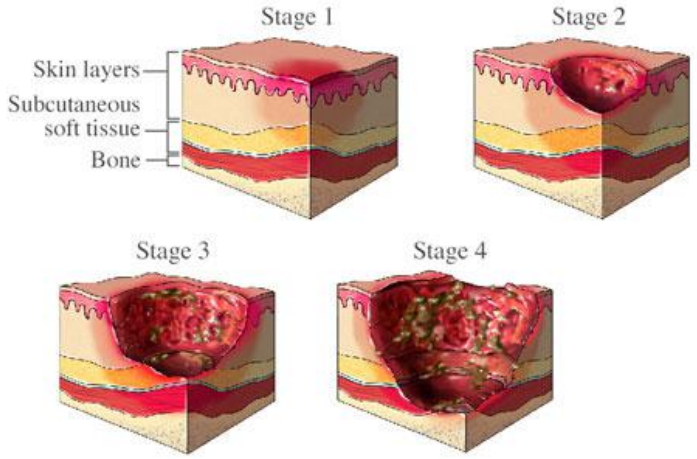
Coussens and Zena, Nature (2002)

Rudolf Virchow

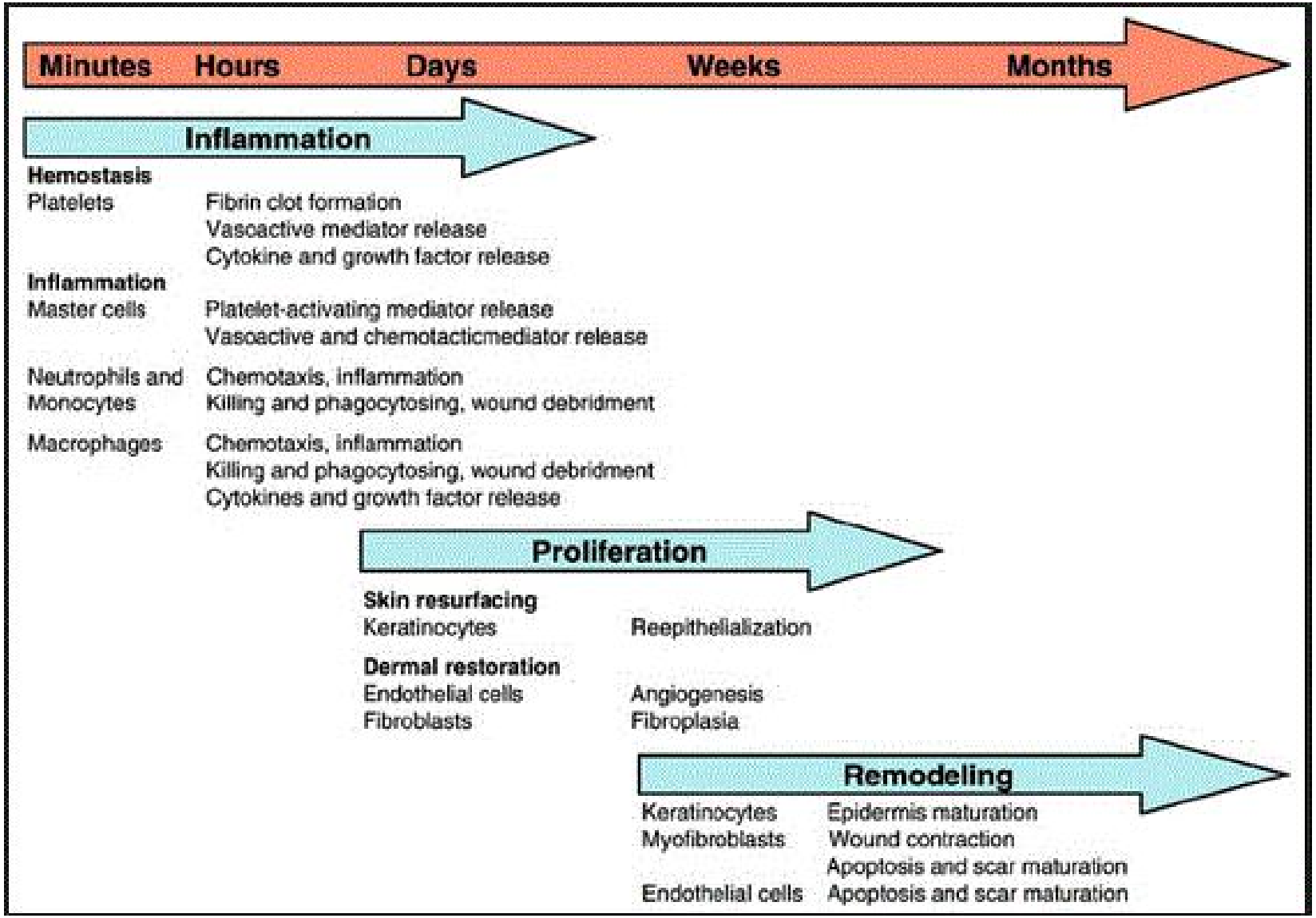


Tissue Injury

- Tissue injuries fall into acute and chronic types, separated by the amount of time used to heal
- The prominent distinct features of chronic injuries from acute injury include
  - proliferation of connective tissue and tissue degeneration
  - primary immune cells are lymphocytes, macrophages
  - major chemical signal include bradykinins and prostaglandins



Three Phases of Tissue Repair

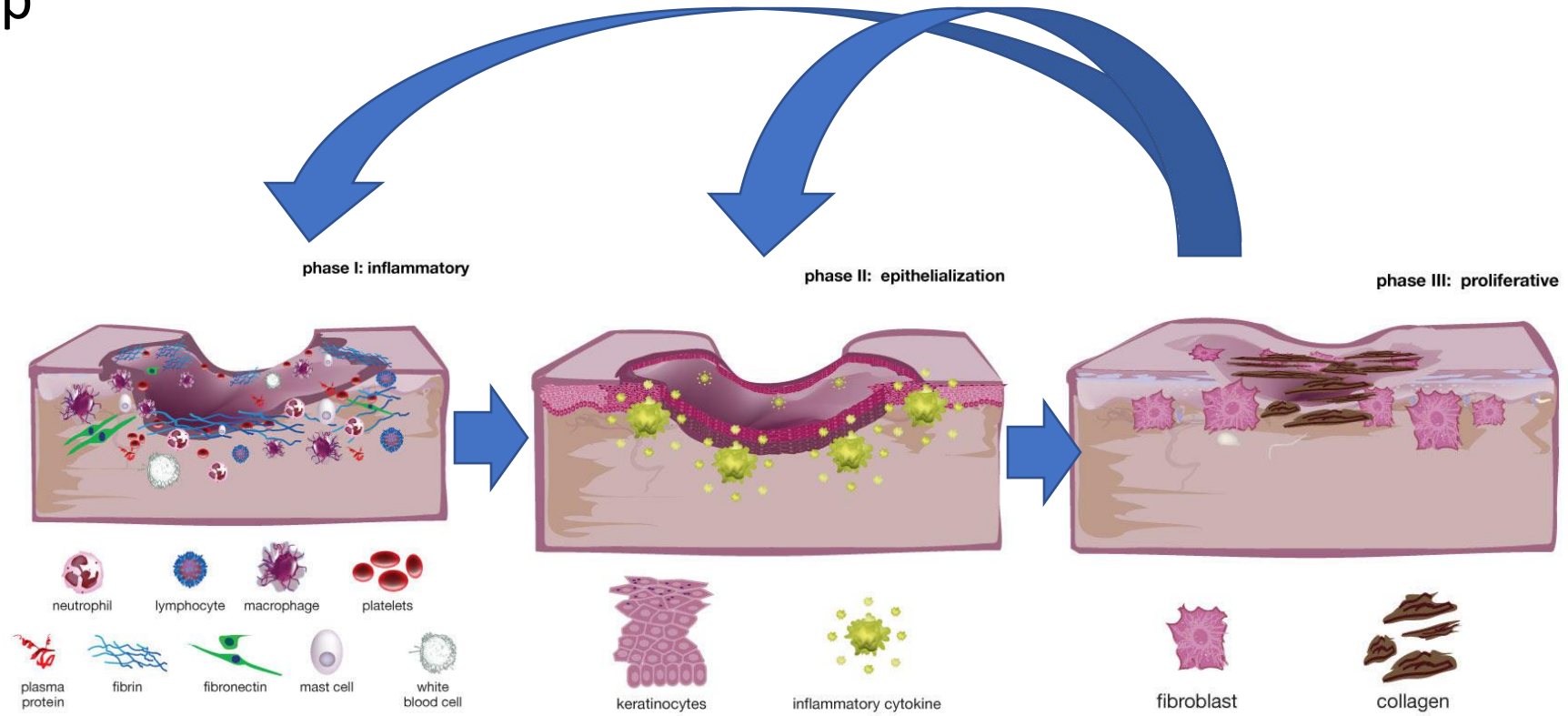


Causes of Chronic Inflammation

- Chronic inflammation leads to a progressive shift in the type of cells present at the site of inflammation and is characterized by simultaneous destruction and healing of the tissue from the inflammatory process.
- In comparison with acute inflammation that is mediated by granulocytes (a type of white blood cell), chronic inflammation is mediated by monocytes/macrophages and lymphocytes.
- Key steps in tissue repair:
  - re-epithelialization, fibrosis, and angiogenesis

Causes of Chronic Inflammation

- A key in forming chronic inflammation is that some “criteria” in terminating some phases of the tissue repair process could not be met, leading to the entrapment of the process in one or more phases of the repair process and forming an “infinite” loop



Causes of Chronic Inflammation

- The general observation has been that various stressors can prolong an acute inflammation to a chronic one characterized by reduced mitochondrial activities, hence reduced ATP production, and elevated oxidative stress.

- A previous paper suggests that the following three factors may play the predominating roles (Wound Healing Essentials: Let There Be Oxygen, 2009):
  - Oxygen level, iron and ascorbate

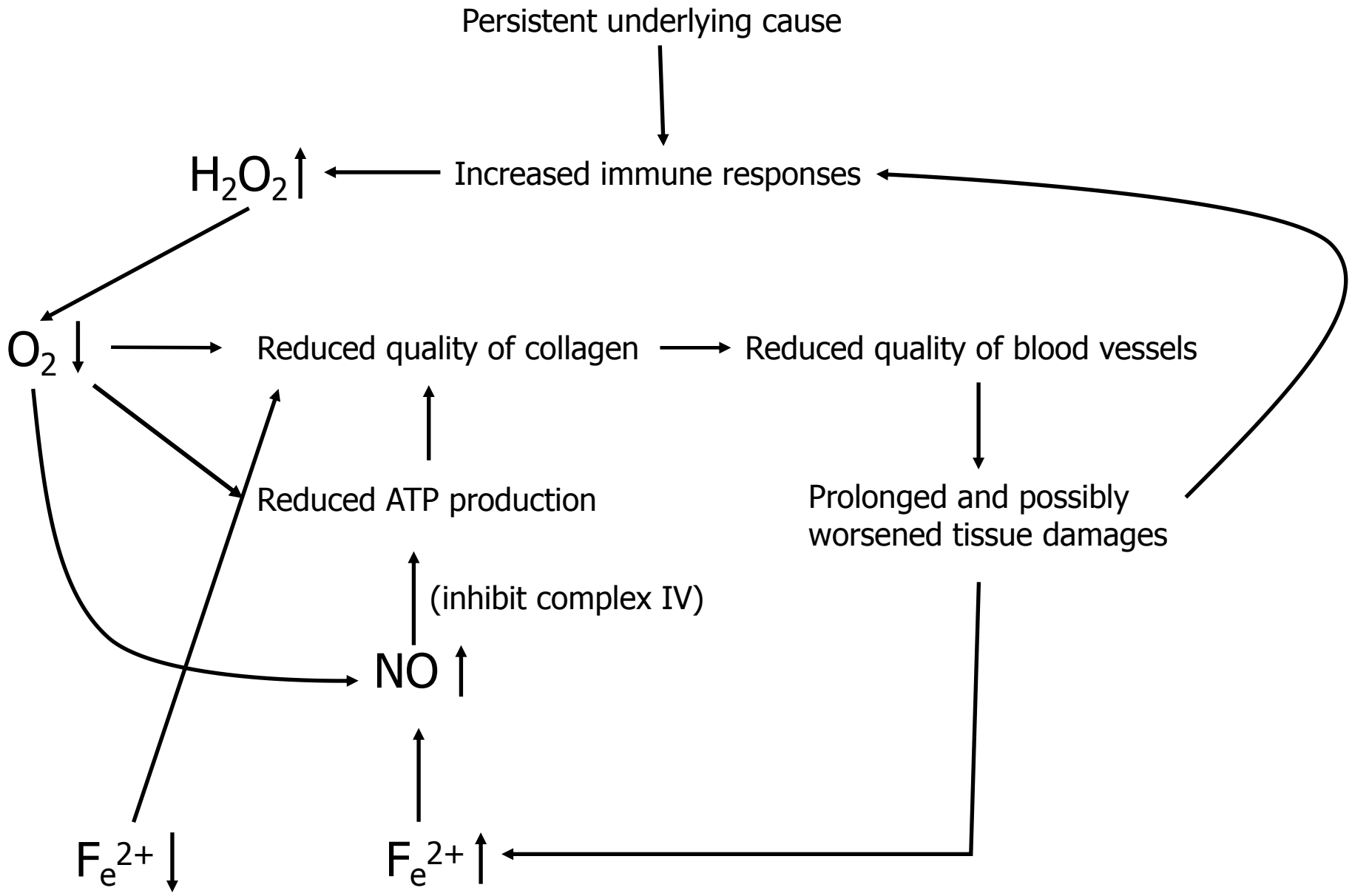
O2 and Wound Repair

- Three major factors contribute to wound tissue hypoxia:
  - generation of reactive oxygen species (ROS) by way of respiratory burst
  - increased O_2 demand of the healing tissue, and
- Angiogenesis: Both O2 and ascorbate are essential to building a healthy new blood vessels (mostly by way of healthy collagen structures)
- Collagen deposition provides the matrix for angiogenesis and tissue remodeling. Maturation of collagen is highly O_2-dependent.

Iron and Wound Healing

- Iron deficiency impairs wound healing as collagen synthesis requires hydroxylation of lysine and proline, and co-factors ferrous iron and vitamin C.

- Iron over-concentration can lead to increased ROS, slowing down healing and prolonging inflammation


Persistent underlying cause
Increased immune responses
H_2O_2 ↑
O_2 ↓
Reduced quality of collagen
Reduced quality of blood vessels
Reduced ATP production
Prolonged and possibly worsened tissue damages
(inhibit complex IV)
NO ↑
F_e^{2+} ↓
F_e^{2+} ↑

Chronic Inflammation vs. Cancer Development

- All data suggest that cancer comes out of chronic inflammation but why some chronic inflammation is cancer prone while others are cancer independent

Summary

- Cancer is a wound that will not heal
- An acute inflammation becomes chronic because of the lack of O_2, iron, or Vc
- Hypoxia, inflammation, and hypoxia can induce each other, so at steady state, they are equivalent
- Persistent production and fragmentation of hyaluronic acid chain is a prerequisite of cancer development
- The lesson: we need to look at cancer development from an evolutionary and systems perspective.