现代生物学导论

IX 膜系统补充和细胞分裂

（书上6.2信号部分和3.4）

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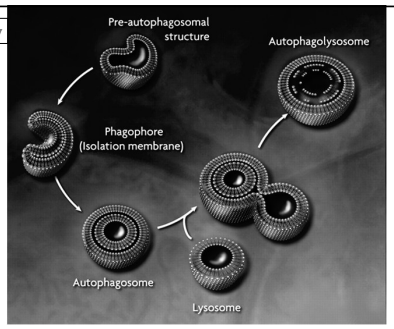
了解: 自噬, autophagy

- 2016年诺贝尔生理学或医学奖授予日本科学家大隅良典（Yoshinori Ohsumi）
- 获奖理由是“发现了细胞自噬机制。”

http://news.sciencenet.cn/htmlnews/2016/10/357666.shtm

了解: 自噬, autophagy



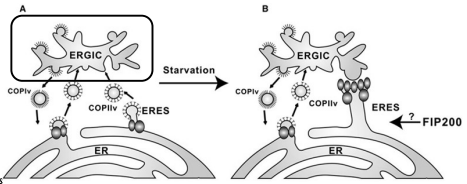
Science
2004

http://www.sciencemag.org/content/306/5698/990.full

了解: 自噬, autophagy

生命学院 葛亮

EMBO Rep. 2017，Sep;18(9):1586-1603



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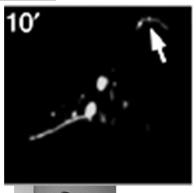
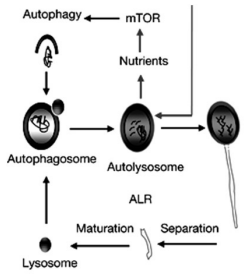
了解: 自噬



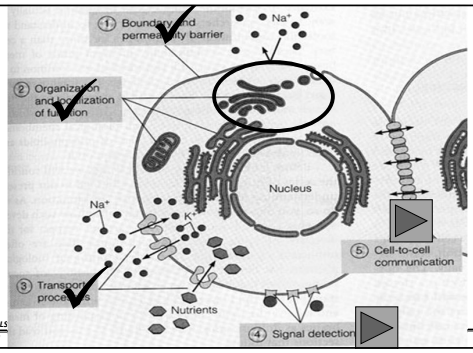
清华生命学院
俞立研究组
Nature
2010



http://www.nature.com/nature/journal/v465/n7300/full/nature09076.html

自噬, autophagy

- 细胞发生自噬非常“保守”
- 细胞自噬的出现是为了适应环境
- 自噬就是细胞自己降解自己结构的过程，即把一些暂时用不上的零件，拆解变成最小的模块，然后重新组装成自己需要的东西
- 对维持细胞内稳态以及细胞产物的合成、降解和循环再利用具有重要作用



细胞的信号转导

Cell must respond appropriately to external stimuli to survive.

参考：教材第六章第二节

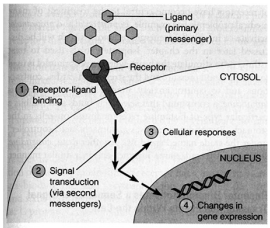
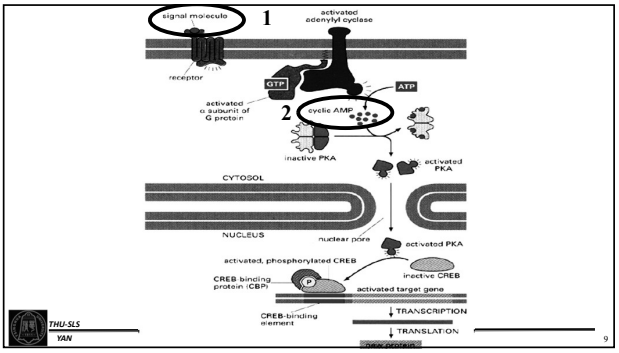
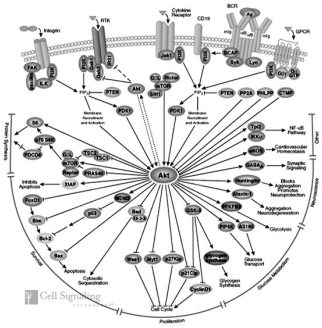


Figure 10-2 The Overall Flow of Information During Cell Signaling. Binding of ligand by a receptor activates a series of events known as signal transduction, which relays the signal to the interior of the cell, resulting in specific cellular responses and/or changes in gene expression.





细胞连接（cell junction）

✦细胞外基质与细胞连接 — 细胞社会的组织

参考《细胞生物学》

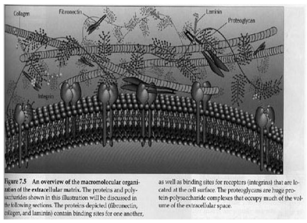
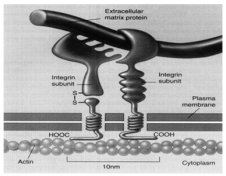
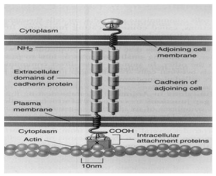


Figure 7.5 An overview of the macromolecular organization of the extracellular matrix. The proteins and polysaccharides shown in this illustration will be discussed in the following sections. The protein decorin (fibromodulin, collagen, and laminin) contain binding sites for one another, as well as binding sites for receptors (integrins) that are located at the cell surface. The proteoglycans are huge protein-polysaccharide complexes that occupy much of the volume of the extracellular space.

◈细胞间粘着分子



细胞与胞外基质的连接

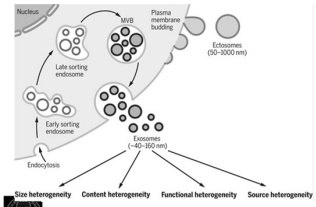


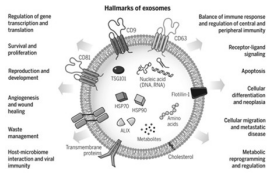
细胞与细胞的连接

了解

9.1.5 Extracellular Vesicles

In multicellular organisms, distant cells can exchange information by sending out signals composed of single molecules or, as increasingly exemplified in the literature, via complex packets stuffed with a selection of proteins, lipids, and nucleic acids, called extracellular vesicles (EVs; also known as exosomes and microvesicles, among other names).





Science. 2020 Feb 7; 367(6478): eaau6977. doi: 10.1126/science.aau6977

Original Article

Cell Research advance online publication 24 October 2014; doi: 10.1038/cr.2014.135

Discovery of the migrasome, an organelle mediates release of cytoplasmic contents during cell migration

OPEN

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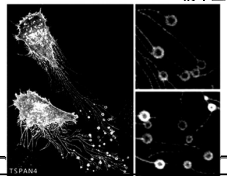
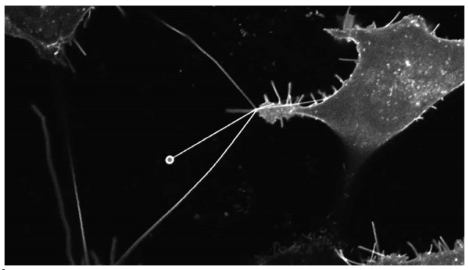




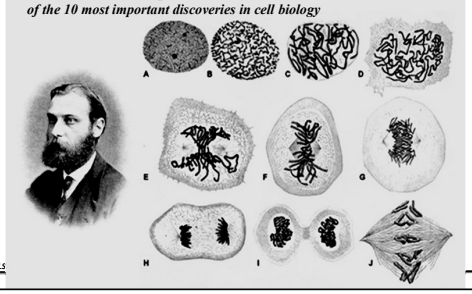
细胞的生命活动（本周和后两次课程） 提纲

- 细胞是如何分裂的（细胞周期是如何调控的）？
- 细胞是如何分化的（如何形成多种类型的细胞）？
- 细胞是如何死亡的？
- 细胞生命活动与疾病

- 细胞的最终命运无外乎两种：
  细胞分裂和细胞死亡
- 细胞分裂和细胞死亡都是细胞生命活动的基本特征
- 细胞增殖是生物繁育的基础　单细胞、多细胞
- 成体生物仍需要细胞增殖，以弥补代谢过程中的细胞损失
  每天有大量细胞死亡，需维持细胞数量动态平衡和机体正常功能
  机体创伤愈合、组织再生、病理组织修复等
  $2.5*10^7$个细胞在分裂/s
- 细胞增殖受到严密的调控机制所监控
  高等生物中，不仅要遵循细胞自身的增殖调控规律，同时还要遵守生物体整体调控机制的调节。
  不受约束而生成的细胞：免疫系统清除或癌变

Flemming Christens: Mitosis, 1870, new dyes

❖ *one of the 100 most important scientific discoveries of all times, and one of the 10 most important discoveries in cell biology*



correspondence

Celebrating 50 years of the cell cycle

To round off a year of scientific commemoration, let's raise a glass to Howard and Pelc.

Sir — This year the world has celebrated the 50th anniversary of the discovery of DNA's structure (see, for example, *Nature* **421**, 395–453; 2003). Meanwhile, however, another important scientific anniversary is in danger of slipping past unmarked.

Also in 1953, Alma Howard and Stephen Pelc published their work on cell proliferation in bean (*Vicia faba* L.) roots[1]. They grew plants with a ^{32}P isotope label and showed that it was incorporated into DNA in the nucleus only during interphase, and that it took 12 hours from the end of division until the beginning of the isotope uptake into new DNA. By analysing heterogeneous populations of meristematic cells, Howard and Pelc deduced that DNA synthesis takes about six hours, and that cells enter prophase of the next mitosis only eight hours after DNA synthesis is completed.

Howard and Pelc were the first to ascribe a timeframe to cellular life and they proposed the existence of four periods in the cell cycle: a period of cell division, the pre-S-phase (called G1), the S-phase (a period of DNA synthesis) and period G2, or the pre-mitotic period. The concept of the cell cycle was born.

Since then, cell-cycle studies have flourished. It is unfortunate, therefore, that this discovery is now almost forgotten (though not totally: see www.nature.com/celldivision/milestones/full/milestone03.html). The view of the cell cycle formed a basis for determining time parameters of the cell cycle (by labelling mitoses and other methods) and for the biochemical and molecular events that take place at each stage of the life of the cell between divisions in various groups of organisms.

As we know, the concept was later developed and the checkpoints in cell-cycle regulation and universal control mechanisms were determined by using genetics and molecular biology[2]. All these recent achievements stemmed from Howard and Pelc's study — which calls for another 50-year anniversary celebration to be held by the international scientific community.

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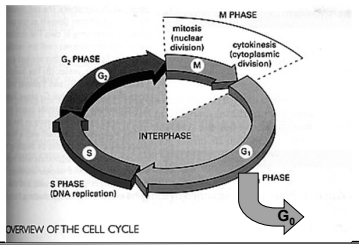
†*Timiryazev Institute of Plant Physiology, Russian Academy of Sciences, Botanicheskaya 35, Moscow 127276, Russia*

1. Howard, A. & Pelc, S. *Heredity* **6** (suppl.), 261–273 (1953).
2. Nurse, P. *Nature* **344**, 503–508 (1990).

10.1 细胞增殖及其调控

10.1.1 细胞周期（cell cycle）与细胞增殖



OVERVIEW OF THE CELL CYCLE

50年代，用^{32}P标记蚕豆根尖细胞并作放射自显影实验，发现DNA合成是在间期的某个特定时期进行的。

- 周期中细胞
- 静止期细胞
- 终末分化细胞

❖ Three categories of cells *in vivo*

(1) Cycling cells

Dividing continuously—Stem cells

(2) G_0 cells

Do not divide normally, but divide when given an appropriate stimulus: liver cells, lymphocytes

(3) Terminally Differentiated cells

Highly specialized, have lost the ability to divide until they die: muscle cells, red blood cells, nerve cells

❖细胞周期长短

Some eukaryotic cell cycle times

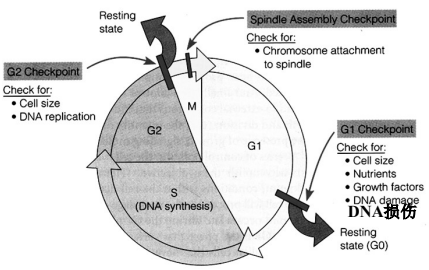
Cell Type	Cell-Cycle Times
Early frog embryo cells	30 minutes
Yeast cells	1.5–3 hours
Intestinal epithelial cells	~12 hours
Mammalian fibroblasts in culture	~20 hours
Human liver cells	~1 year

- 高等生物细胞周期时间长短主要差别在G_1期
- 早期胚胎细胞的细胞周期G_1和G_2期非常短

10.1.2 细胞周期的生化事件与检验点(checkpoint)

- 芽殖酵母的G1期晚期存在一个特定时期，被称为起始点。如果细胞继续走向分裂，则可以通过这个特定时期，进入S期。
- 在真核细胞中，被称为限制点或检验点。
- 检验点存在于各个时期。
- 起始点被认为是G1期晚期一个基本事件，影响因素包括外在（营养供给、相关激素刺激等）和内在（细胞分裂周期基因调控等）因素。
- 细胞内存在一系列特异的监控机制（检查站），可以鉴别细胞周期进程中的错误，并诱导产生特异的抑制因子，阻止细胞周期进一步运行。
- Checkpoints的主要作用是确保基因组稳定性，而不是细胞分裂的基本条件（分裂细胞具有更多的DNA损伤）

10.1.2 细胞周期的生化事件与检验点(checkpoint)



DNA损伤

❖细胞周期的检验点

G1 期: 外在因素（营养供给和相关激素刺激等）和内在因素（细胞分裂周期基因的调控）

S 期: DNA复制完成

G2 期: DNA是否完成复制，是否是否生长到合适大小，环境因素是否有利分裂等

M 期: 染色质是否与纺锤体正确装配

❖细胞周期的生化事件

G1 期: 合成细胞生长所需要的各种蛋白质（RNA）、糖类和脂类等，但不合成DNA。

S 期: 合成 DNA和组蛋白（Histones）

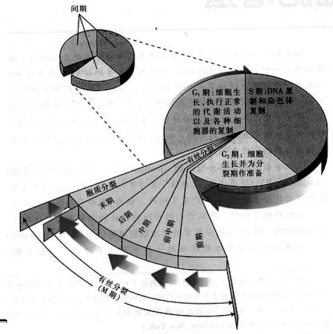
G2 期: 合成少量的蛋白质 (RNA)

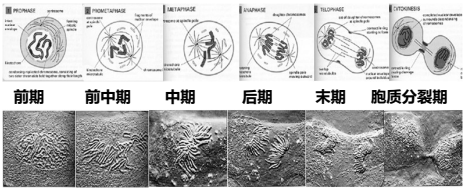
M 期: 有丝分裂（mitosis）、减数分裂（meiosis）和胞质分裂（cytokinesis）

染色质浓缩 → 纺锤体装配 → 收缩环

胞质分裂形成两个子细胞

10.1.3 有丝分裂 (mitosis)





前期 | 前中期 | 中期 | 后期 | 末期 | 胞质分裂期

- 染色质开始浓缩，
- 着丝粒处装配动粒，
- 中心体周围微管大量装配

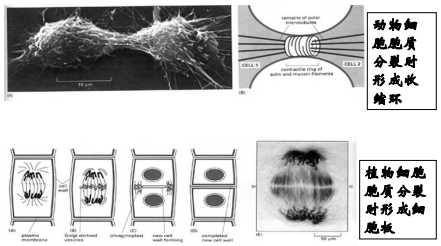
- 核膜破裂，
- 染色体进一步浓缩（X形），
- 纺锤体装配，
- 星体微管捕获染色体（动粒微管）

- 所有染色体排列到赤道板

- 染色单体分离向两极运动，
- 动粒微管变短，
- 极性微管变长

- 染色体到达两极并开始去浓缩
- 动粒微管消失，
- 极性微管继续增长，
- 核膜重装配

⇒



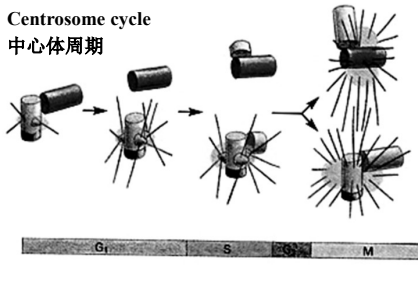
动物细胞胞质分裂时形成收缩环

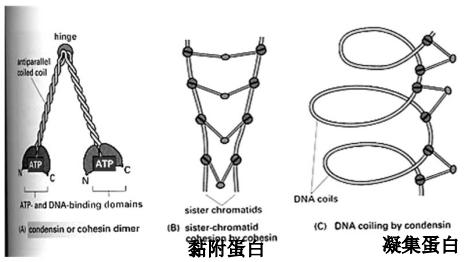
植物细胞胞质分裂时形成细胞板

请思考……

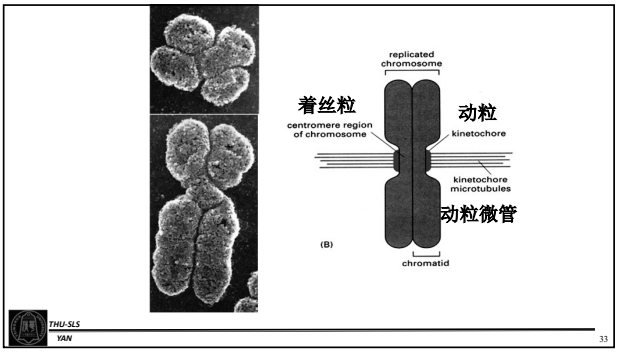
- 中心粒的复制
- 是什么驱动着染色质的浓缩与去浓缩?
- 是什么控制着染色体在赤道板上的队列? 是什么牵引着染色体向两极移动? 是什么改变了细胞的形状?
- 各种各样的细胞器在分裂中的行为?
- 生殖细胞的形成与分裂

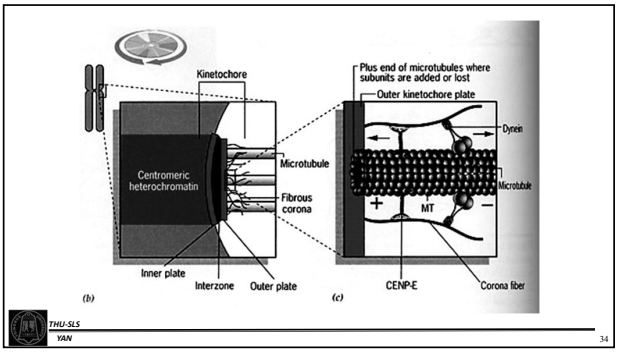
Centrosome cycle
中心体周期

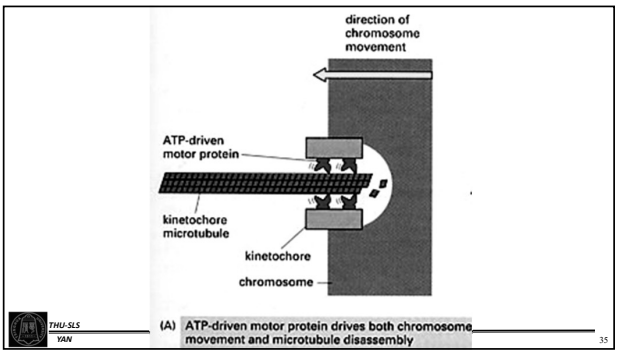


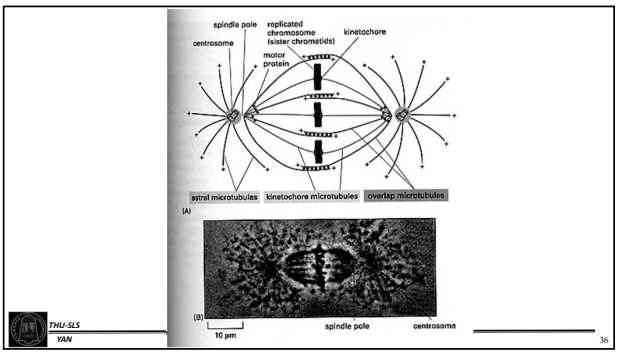


黏附蛋白　　凝集蛋白

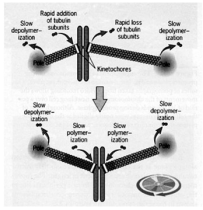




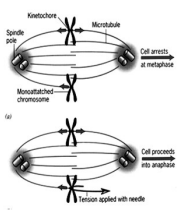




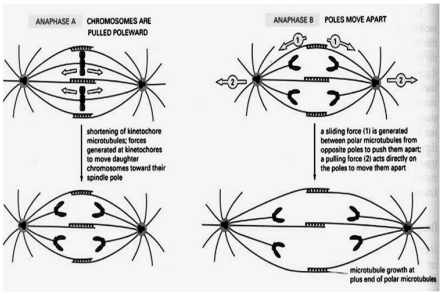
The pushing and pulling forces drive the chromosomes to the metaphase plate



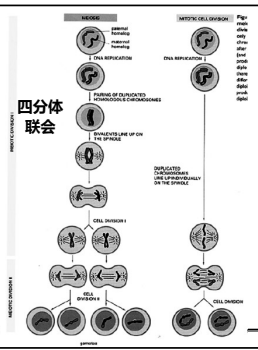
MT behavior during formation of the metaphase plate. Initially,MT from opposite poles are different in length.



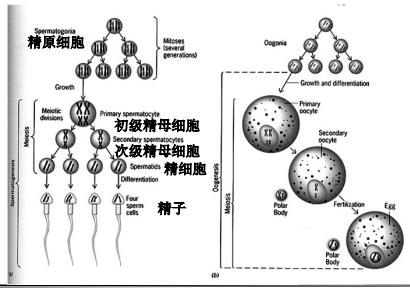
Experimental demonstration of the importance of mecha- nical tension in metaphase checkpoint control.



10.1.4
细胞的有丝分裂 (mitosis) 与减数分裂 (meiosis)



◈雌雄配子的发生



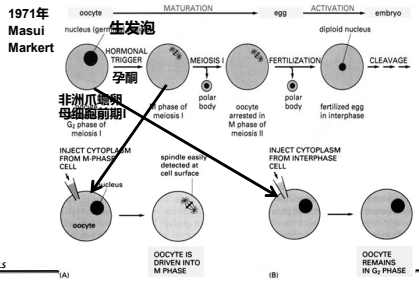
人类女性卵巢中每个卵母细胞约在出生时候进入前期I…

保持几十年

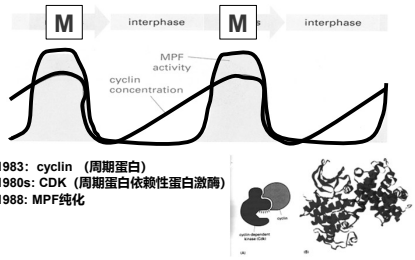
How?

10.1.5 细胞周期的调控--- MPF:引擎分子

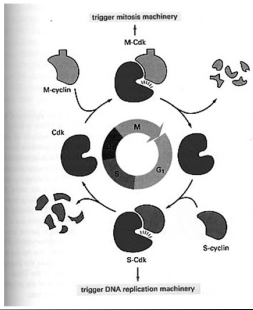
1971年
Masui
Markert



MPF的活化及其活性的周期变化



- 1983：cyclin （周期蛋白）
- 1980s: CDK（周期蛋白依赖性蛋白激酶）
- 1988: MPF纯化



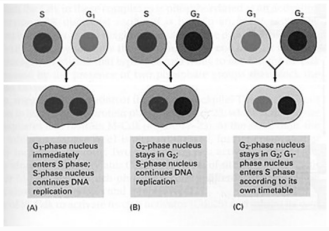
CDK 通过结合不同的周期蛋白来调控细胞周期中的不同事件

CDK 活性的终止与周期蛋白的降解相关

CDK-cyclin活性受到上游信号的调控

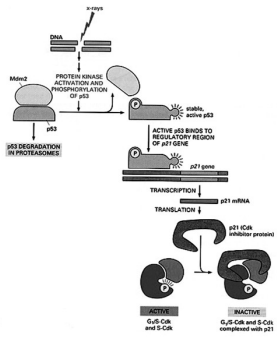
Intracellular control of cell-cycle events

❖S-phase Cyclin-Cdk complexes (S-Cdks) initiate DNA replication once per cycle



Evidence from cell-fusion exp. For a replication block.

➢ 检验点是如何实现的?



本节重点

- 了解亚细胞结构的最新发展
- 信号传导的基本概念和途径
- 细胞周期
  - 四个时相
  - M时相每个期发生的特征性事件和机制
  - 细胞周期的调控机制

作 业 见网络学堂

➢ 下节内容：细胞分化、细胞死亡（书6，11章部分内容）