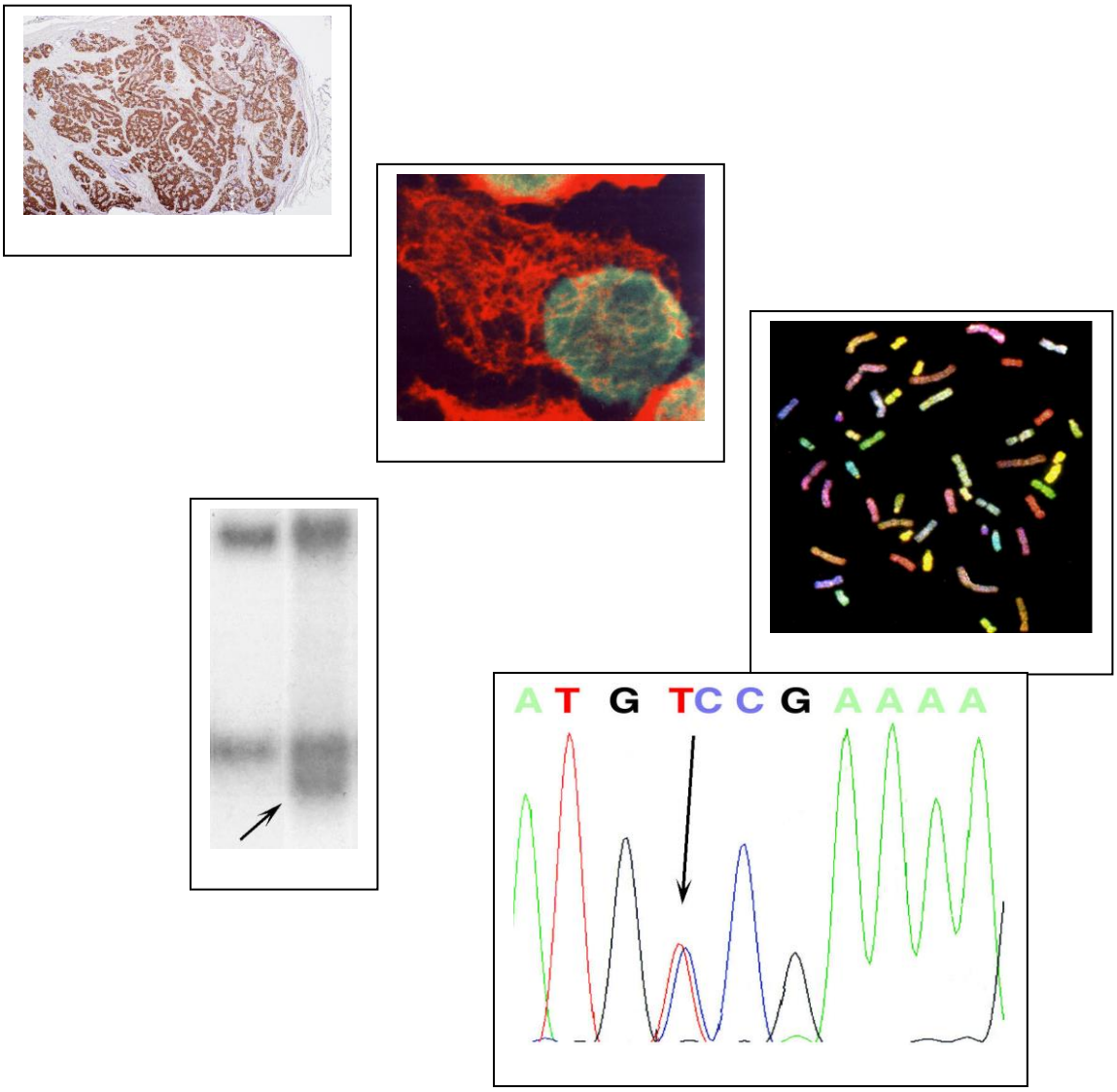
SCI2037

Cell Biology



University College Maastricht

Period 4

February 5th - March 30st, 2018

Contents

Introduction

In this course students have an opportunity to get acquainted with the exciting and nowadays quite popular discipline cell biology. This discipline has been profiting from the development and improvements of recombinant DNA technology and is a driving force in fundamental and biomedical research. This has resulted in recent years in some extraordinary developments, such as the sequencing of the whole genome of many organisms including humans, the cloning of different mammals and the development of DNA "chip" microarray and next generation sequencing technology to analyze the presence, expression and sequence of all human genes on a small glass slide or DNA chip. And every week newspapers still inform us about additional genomes and diseases that have been genetically unraveled.

In this course you are challenged to discuss, at the molecular level, different cellular and genetic processes that are the basis of life as we know it. The course cell biology builds on the knowledge obtained in the UCM course 'Introduction to Biology'. The aim of the course is to familiarize students with further knowledge in the field of cell biology, which enable you to better understand and appreciate the newest developments in these research areas.

The course consists of 10 tasks. Each task will be presented in the form of two tutorial group meetings and/or a lecture. The tasks deal with general cell biological topics such as the role of membranes, membrane transport of small molecules, the nuclear architecture, the organization of the genome, regulation of transcription and translation, protein trafficking, the cell cycle and maintenance of genomic integrity, programmed cell death and senescence. The last task dealing with cancer is serves as an integration task; knowledge of the previous topics is required to appreciate what the consequences can be when a cell goes astray and the defense mechanisms of the body fail.

Course coordinators

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Attendance requirement

The attendance requirement for eleven out of the twelve tutorial meetings is 85%. You are allowed to miss two regular tutorials without further consequences. If you miss more meetings, you will have to apply for an additional assignment (request forms are available at the Office of Student Affairs). In order to qualify for an additional assignment you have to have valid reasons for all missed sessions. If you don't meet the *SCI2037* attendance requirement, you are not eligible for a resit. You automatically fail the course if you miss over 30% of the scheduled meetings.
The presentation session in the sixth week of the course is mandatory and is not considered one of the regular tutorial meetings to which the 85% attendance requirement applies.

Readings

In addition to the main course book *Molecular Biology of the Cell* by Alberts *et al.* (2008), other books may be helpful in studying learning goals from the cases. Many of those are available in the UCM Reading Room and/or in the library at the FHML (UNS50). Students are encouraged and required to use books or other different sources of information in addition to the main course book.
Main course book:

- Alberts et al. (2015). *Molecular Biology of the Cell*. (6th ed.). Garland Science, New York

Other books and suggested readings:

- Alberts *et al.* (2014) *Essential cell Biology.* (4th ed.). Garland Science, New York
- Baliga, B.C. and Kumar, S. (2002) Role of Bcl-2 family of protein in malignancy. *Hematol Oncol 20(2)*, 63-74
- Brown, C.J., Lain, S., Verma, C.S., Fersht, A.R., Lane, D.P. (2009) Awakening guardian angels: drugging the p53 pathway. *Nat Rev Cancer 9(12)*, 862-873
- Goh, A.M., Coffill, C. R., Lane, D. P. (2011) The role of mutant p53 in human cancer. *J Pathol 223(2)*, 116–126
- Hanahan, D., Weinberg, R.A. (2000). Hallmarks of Cancer. *Cell 100(1),* 57-70
- Hanahan, D., Weinberg, R.A. (2011) Hallmarks of Cancer: The Next Generation. *Cell 144(5)*, 646-674
- zur Hausen, H. (2002) Papillomaviruses and cancer: from basic studies to clinical application. *Nat Rev Cancer 2(5)*, 342-350
- …

Assessment

This course contains three elements of assessment:
1. a written exam consisting of open questions (60% of the overall course grade);
2. a written assignment (25% of the overall course grade – for more information, see below);
3. a presentation on the topic of the paper (15% of the overall course grade – for more information, see below)

Written assignment

The purpose of the written assignment in this course is to allow students to further discuss, develop and elaborate on a subject related to the topics discussed in the tutorial groups. Besides subjects proposed by the

tutor, the students are free to come up with their own ideas. The topics need to be discussed with and approved by the tutor in week 4 the latest.
Note: You are not allowed to use a paper from either this course or another course which you failed in the past and improve that and hand that in. Your choice of topic and approach need to be new in that sense. However, they may obviously fit your academic interests as expressed in other courses at UCM and your curriculum.

Format of the paper

The report should be between 2750 to 3250 words, excluding references. If the word count is between 2500-2750 or 3250-3500, 0.5 points are subtracted from the final grade for the report. If the word count is below 2500 or above 3500, the report will not be graded and considered a fail. As it is a rather short report, do not make too many subdivisions and use the structure that will be presented in the workshop in this course.
The essay should include a minimum of 6 references (maximal 3 internet sites). When you use information from a scientific article, university textbook or internet source, make sure you include the reference. Not doing so, is a form of plagiary. Do not take this lightly. Copying and pasting pieces of text from the internet is as much a form of plagiary as is copying from a book!
In addition to scientific articles or university textbooks, there is nothing against using the internet as a source. However, if you use an internet site, always put a reference to it in your report; omitting to do so and being caught in doing it, results in an annulment of the whole report.
Reports are to be handed in before the deadline (see overview below). This deadline cannot be extended. Failure to comply with it loses you all credits on the writing assignment.

Presentation

The purpose of the presentation in this course is to allow students to discuss their paper topics and possible issues related to it and to receive feedback.
Format of the presentation
Every student has (max.) 10 minutes for the individual presentation. The presentation should be prepared in Powerpoint and may contain a maximum of 12 slides. A laptop and beamer will be available.
The assessment of the presentation will be based on:

- The quality of the introduction (are you able to explain the context and relevance of your research question in such a way that the audience has enough insight to understand the context and reasons for your topic?)
- The quality of the presentation of the problem (are you able to explain the problem and capable of explaining why the solutions you provide are the best solutions?)
- The handling of questions/discussion (are you able to answer questions and discuss the problem?)

The presentation should be theoretically informed. You do not have to explain basic concepts discussed in the course, since you are presenting to students from your own discipline. However, don't take all background knowledge for granted!

Resit

Students who initially fail the course, but who have complied with the compulsory attendance requirement and took part in all of the assessment during the course, are eligible for one resit.
The overall grade for this course consists of a grade for the exam (60%), the written assignment (25%) and the presentation (15%). The resit serves the purpose of lifting your overall grade to sufficient/above 5.5. It does not replace the overall grade. Hence, the resit can be either on the exam OR on the written assignment

OR on the presentation. In case of a resit, you will have to redo that part of the assessment for which you received the lowest grade. In case of redoing the paper, you can either rewrite the original paper, incorporating the feedback you received, or choose a new topic and write a totally new paper.
In order to receive a grade for the exam you will have to do a serious attempt at passing the exam. If it is not deemed a serious attempt you will not receive a grade and you will not qualify for a resit. The same thing holds for the written assignment and the presentation. If it is not deemed a serious attempt you will not receive a grade and you will not qualify for a resit.

Overview of meetings, lectures and deadlines

Week 1	Meeting 1	Pre-discussion Task 1	
	Meeting 2	Post-discussion Task 1	
		Pre-discussion Task 2	
	Lecture		
Week 2	Carnaval break		
Week 3	Meeting 3	Post-discussion Task 2	
		Pre-discussion Task 3	
	Meeting 4	Post-discussion Task 3	
		Pre-discussion Task 4	
	Lecture		
Week 4	Meeting 5	Post-discussion Task 4	
		Pre-discussion Task 5	
	Meeting 6	Post-discussion Task 5	
		Pre-discussion Task 6	Topic declaration and approval by tutor
	Lecture		
Week 5	Meeting 7	Post-discussion Task 6	
		Pre-discussion Task 7	
	Meeting 8	Post-discussion Task 7	
		Pre-discussion Task 8	
	Lecture		
Week 6	Meeting 9	Post-discussion Task 8	
		Pre-discussion Task 9	
	Meeting 10	Post-discussion Task 9	
		Pre-discussion Task 10	
	Lecture		
Week 7	Meeting 11	Post-discussion Task 10	
	Meeting 12	mandatory Presentations	
	Lecture		
Week 8		Exam	
		Friday March 31st 2017 : Deadline final report – upload in EleUM > Safe Assignment and drop a hardcopy in OSA mailbox	

Please check the schedule provided by the Office of Student Affairs and announcements on EleUM as well.

Tasks

Task 1: Cellular constituents, Cytoskeleton, Cell adhesion and ECM

Cells, prokaryotic and eukaryotic, can be considered as boundary enclosed boxes in which complex processes operate in strictly coordinated ways so that the box can survive. In prokaryotic cells, all the life necessary processes are present in one single compartment, in eukaryotic cells, several membrane bound compartments are present in which each of them has a specific structure and function. The internal organization in space and time of regions or compartments and their mutual communication is possible due to the presence of an internal molecular transport system with specific motor devices. These system is also involved in shaping the cells and in some cases, even important movements. An important requirement of this transport system is that it should allow the cell not only to response to changing environmental conditions but also to reproduce in a proper way, in other words, the system should be pretty dynamic.
Cells are the building blocks of multicellular organisms. This seems a simple statement, but it raises deep problems. As we know, cells are not like bricks: they are small, deformable, and often motile objects, filled with an aqueous medium enclosed in a flimsy plasma membrane. Yet, they can combine in their millions to form a structure as massive, as strong, and as strictly ordered as a horse, a giraffe or a giant redwood tree. How can cells be joined robustly, with their membranes intact? The cells can stick together mechanically using several building materials which allows loose or very tight constructions. Several types of junctions will allow the cells not only to stick together in order to form larger units but they should still be able to socialize with each other and exchange material using certain types of passageways. In order to build up large units, a strict coordination with the internal transport system is inevitable.

Recommended literature

Textbooks

Alberts et al. Molecular Biology of the Cell, 6th edition, 2015: Chapter 16

Further reading:

Alberts et al. Essential Cell Biology, 4th edition, 2004: Chapter 17

Task 2: Membrane Transport of Small Molecules

In order to live and grow, cells exchange molecules with their environment. The plasma membrane acts as a barrier that controls the transit of molecules in and out of the cell. Because the interior of the lipid bilayer is hydrophobic, the plasma membrane tends to block the passage of almost water-soluble molecules. This barrier function is crucially important because it allows the cell to maintain concentrations of solutes in its cytosol that are different from those in the extra-cellular fluid and in each of the intracellular membrane-enclosed compartments. To make use of this barrier, cells have had to evolve ways of transferring specific water-soluble molecules across their membranes in order to ingest essential nutrients, excrete metabolic waste products, and regulate intracellular ion concentrations. A few of these solutes, such as CO_2 and O_2 for example can simply diffuse across the membrane, but the vast majority cannot. The transport of inorganic ions and small water-soluble organic molecules such as sugars and amino acids across the lipid bilayer is achieved by specialized transmembrane proteins, each of which is responsible for the transfer of a specific ion, molecule or group of closely related ions or molecules.

Which tools are available to a cell to maintain its internal environment and cope with changing environmental conditions? There are two main classes of membrane proteins that mediate the transfer of small molecules: carrier proteins and channel proteins. The first-class moves molecules from one side of the membrane to the other by changing their shape. The second-class forms tiny hydrophilic pores in the membrane through which solutes can pass by 'diffusion'. Is there a need of an energy source? Most channels proteins let through inorganic ions only and are therefore called ion channels. Because these ions are electrically charged, their movements can create powerful electric forces across the membrane, enable nerve cells to communicate, ultimately carrying out the astonishing range of behaviors of which the human brain is capable.

An important feature of microorganisms, plants and animals is the movement of water into and out of cells. Water has the natural tendency to flow across cell membranes as a result of osmotic pressure. But is this mechanism sufficient to maintain the water balance of for instance the epithelial cells of the kidney?

Recommended literature

Textbooks

Alberts et al. Molecular Biology of the Cell, 6th edition, 2015: Chapter 11

Further reading:

Alberts et al. Essential Cell Biology, 4th edition, 2014: Chapter 12

Task 3: Cellular Communication

Nowadays we use Skype, WhatsApp, texting, e-mail, etc. to communicate with each other. But how do cells communicate, and what information do they exchange?

Unicellular organisms must be capable of recognizing their surroundings and responding to them. They have to find nutrients and must be able to locate partners for their 'social lives'. The communication between cells in a multicellular organism is much more complex. Individual cells have to be capable of sensing the wide ranges of signals coming in from their surroundings and responding appropriately to them. The various cells and organs within a multicellular organism each have their own functions, and the organism as a whole can only function properly if the cells or organs are communicating correctly amongst themselves. Even during embryonic development, the cells are exchanging signals that will ultimately determine what the cell should do, what its purpose will be in the organism and whether it should die or continue to live. Later on in life, things can go completely wrong if the communication between the cells does not work properly.

If you think about it carefully, cells must produce signal molecules that can reach target cells somehow, either in their direct vicinity or over great distances. Conversely, target cells must have receptors to let them receive the signals. These signals could be molecules secreted by other cells, or could come from contact with other cells or a substrate. It should be clear that more than a single type of receptor is needed if the wide varieties of responses are to be explained. The cell may do a variety of things in response to one or more signals, for instance change its metabolism, move, proliferate or die. Evidently, the cell must be capable of passing the signals that are received on the outside of the cell into the interior, where they are translated into an appropriate response.

Recommended literature

Textbooks

Alberts et al. Molecular Biology of the Cell, 6th edition, 2015: Chapter 15

Further reading:

Alberts et al. Essential Cell Biology, 4th edition, 2014: Chapter 16

Task 4: The Nucleus: Nuclear scaffold, DNA and its organization

The *Human Genome Project* (also called *HUGO*) recently revealed that our genome harbors approximately 30,000 genes divided over 23 or 24 chromosomes (in total $3x10^9$ base-pairs, length: 1 meter). Each human cell contains two copies of each of these chromosomes, except for the germ cells that harbor only one copy of all chromosomes. A gene comprises a small part of the double-stranded DNA chain and codes for a discrete hereditary characteristic, usually corresponding to a protein or RNA. Hugo found in one of his books that the mean length of a gene was approximately 10,000 base pairs. "How is that possible", he wondered, "because this means that only $3x10^8$ base pairs (10% of the human genome) are harboring the human genes, how about the other 90% of DNA?" A fellow student told him that there is indeed a large part of the human DNA non-coding, and that this so-called spacer or "junk" DNA is lying between the genes as well as within the genes. Besides unique DNA, particularly lying within gene sequences, the human genome also harbors different forms of repetitive DNA. Some forms only occur in chromosome-specific areas (e.g., satellite DNA), while other repeats are lying all over the genome (e.g., microsatellites).

Hugo was amazed about the fact that only a small proportion of the DNA was actually coding for RNA or proteins. But when he continued reasoning he figured out that the total length of DNA in 1 cell is 6.4×109 × 3.4×10-10 meters ≈ 2 meters. How does a cell organize its genome in such a way that it will fit into a nucleus with a radius of a few µm? The organization of the DNA must be very compact and dynamic at the same time to allow replication and transcription. What keeps the nucleus together and how is the exchange of constituents between the nucleus and the cytoplasm regulated?

Recommended literature

Textbooks

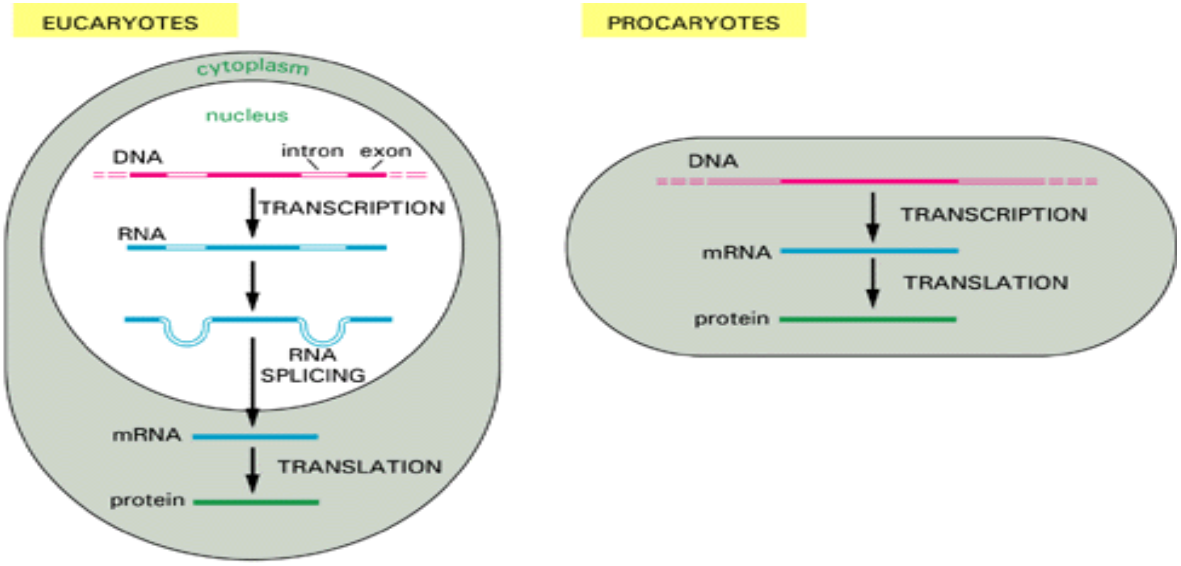
Alberts et al. Molecular Biology of the Cell, 6th edition, 2015: Chapter 4

Further reading:

Alberts et al. Essential Cell Biology, 4th edition, 2014: Chapter 5

Task 5: Genes and their Expression

"So what are all these genes coding for", Hugo asked his uncle, the molecular geneticist. "That is a good question, one a lot of scientists would like to know", he said. "Let me tell you how cells read the DNA:"The genetic information present in the nuclear DNA is used to synthesize RNA and proteins, which are involved in the maintaining of the cell structure as well as the molecular processes occurring within cells. Two steps are required for protein synthesis: firstly, DNA is copied into a messenger molecule, the mRNA, in the nucleus (= transcription), and secondly the mRNA is translated in a protein in the cytoplasm (= translation) (see figure). Let's tackle transcription first. "How does the cell recognize the start and end of a gene, and why are not all genes always active in a cell? A liver cell most likely uses other genes as compared to a skin cell. How is that regulated?" Hugo asked. "Just read your new biotechnology book", his uncle said, "and realize, that regulation of transcription is not that simple. Transcription (and also translation) is regulated differently if you compare eukaryotes and prokaryotes. For instance, eukaryotic genes contain coding and non-coding parts that have to be removed, in eukaryotes the finished mRNA has to be transported out of the nucleus and even then the stability of the mRNA can be controlled by something called RNA interference".



Recommended literature

Textbooks

Alberts et al. Molecular Biology of the Cell, 6th edition, 2015: Chapter 6, Chapter 7

Further reading:

Alberts et al. Essential Cell Biology, 4th edition, 2014: Chapter 7 pages 223-238

Task 6: Translation of the Genetic Code

After studying the chapter on gene regulation in his biotechnology book as suggested by his uncle, gene regulation starts to make sense for Hugo. Every step required for the process of gene expression can be controlled. Now the cell has to face the next step i.e. how to read the information contained within the mRNA and translate this information into a protein. Clearly the mRNA sequence has to be decoded and the resulting peptide chain has fold in a correct way.

Again a basic question arises. Is the complete mRNA translated and if not which parts are and where does translation starts and stops. Clearly if deciphering the code is hampered by specific types of mutations the reading frame can be distorted. Even if the reading frame is not hampered a single mutation can have a serious impact on protein function. How is that possible?

Fortunately, in most cases the genetic code is deciphered in a correct way. However, not all polypeptide chains fold in the same way. Some proteins form long helical filaments e.g. actin others are globular proteins in which the polypeptide chain folds up into a compact shape like a ball with an irregular surface. Some proteins contain more than one polypeptide chain; some are stabilized by cross linkages; some are anchored in membranes others are dissolved in the cytoplasm etc. Is this folding mediated? Can proteins also be targeted for destruction?

Recommended literature

Textbooks

Alberts et al. Molecular Biology of the Cell, 6th edition, 2015: Chapter 3, Chapter 6.

Further reading:

Alberts et al. Essential Cell Biology, 4th edition, 2014: Chapter 4, Chapter 7 pages 238-250

Task 7: Proteostasis: Intracellular compartments and Protein Sorting.

Just when Hugo thinks he's got the picture of gene expression, translation and folding straight, a fellow student came up with a very basic question. How do the proteins know where to go in the cell? Some proteins function in the cytosol, in the nucleus, in organelles; some are located in the cytoplasmic membrane and serve for instance as receptor and even others are exported outside of the cell? An example of the latter is collagen. These molecules are produced by e.g. fibroblasts and are soluble as long as they are inside the cell but become insoluble and form large fibrils once outside of the cell? Are these proteins modified posttranslationally, Hugo wonders. Now he thinks about it he remembered terms like glycoproteins and phosphoproteins.

Recommended literature

Textbooks

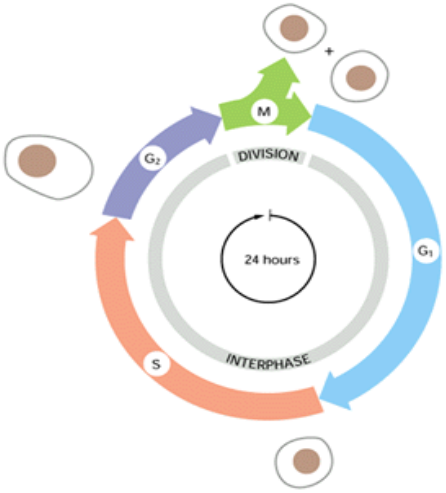
Alberts et al. Molecular Biology of the Cell, 6th edition, 2015: Chapter 12

Further reading:

Alberts et al. Essential Cell Biology, 4th edition, 2014: Chapter 15 pages 492-502

Task 8: The cell cycle and preservation of the genetic code

Later, by understanding more on the translation process of the genetic code, Hugo wondered how a cell would regulate cell growth and division. He remembered from the biology lessons at secondary school, that the cell cycle has different phases (see figure) and that there are a couple of genes playing a key role during the cell cycle, in particular cyclins, cyclin-dependent kinases and the retinoblastoma protein pRb.



It looks simple, but if you think about it carefully, everything suddenly seems less straightforward than it first appeared. What triggers the cell to start proliferation? How does the cell make sure that it only duplicates its DNA once during a single cycle? How does the cell know what the next step after DNA replication is, in other words what stage of the cycle it is in? How does the cell ensure that all the chromatids are correctly split across the daughter cells? Hugo reasoned that to prevent unrestricted proliferation, the cell must have a variety of controls or "checkpoints". The proliferation can then be stopped at that point if the conditions are unfavorable or even harmful, such as for example when the DNA is damaged. He remembered from television a documentary some years ago, in which researchers from the University of Maastricht tested the effect of UV light (from the sun) on the skin of two groups of students lying on the beach. One group received UV-protection cream, while the other group got a non-protecting cream. Since UV-light can cause alterations in the DNA, skin tissue of the latter group showed an increased synthesis of the protein p53, also called "the guardian of the genome". The program clearly stated, that p53 functions as part of the cell-cycle control system that determines at certain DNA damage checkpoints if DNA may be repaired prior to cell division, or if a cell is so much damaged that it should be condemned to death (by a process called apoptosis). Such an important function implicates, that inactivation of p53 would lead to increased DNA damage in cells and a high chance to develop chromosome alterations, ultimately resulting in cancer. Indeed, approximately 50% of all human cancers show p53 inactivating alterations.

Recommended literature

Textbooks

Alberts et al. Molecular Biology of the Cell, 6th edition, 2015: Chapter 17

Papers

Goh AM et al. The role of mutant p53 in human cancer. J Pathol 2011; 223: 116–126.

Brown CJ et al. Awakening guardian angels: drugging the p53 pathway. Nature Rev Cancer 2009, 9: 862-873.

Zur Hausen H: Papillomaviruses and cancer: from basic studies to clinical application. Nature Rev Cancer 2002, 2: 342-350

Further reading:

Alberts et al. Essential Cell Biology, 4th edition, 2014: Chapter 20

Task 9: Apoptosis and Senescence

An organism cannot just grow indefinitely. Somehow it must regulate its cell number. During the embryonic growth phase cell not only proliferate but also die in order to shape organs or structures. It is know that during the development of our extremities, cells must die in the interdigital spaces to allow the proper development of our fingers. In the nematode *Caenorhabditis Elegans* the developmental fate of every single somatic cell has been mapped. In the adult hermaphrodite 131 of the 959 cells will die. Apparently this process is programmed and conserved in evolution.

Later in life an organism has developed a defense mechanism to protect itself from cells going astray. You better can sacrifice a few cells or induce a kind of permanent senescence than face the possible consequences of cells going astray. Every individual cell in our body seems to have a molecular mechanism that is capable of inducing cell death as a response to cellular stress. Furthermore, some cells of our immune system make use of this underlying mechanism to induce this programmed cell death in their target cells. Apparently this molecular mechanism can be triggered from the outside or from the inside of the cell. Somehow the cell is broken down from within and cells dying in this way are disposed of in an efficient way without invoking an inflammatory response. If you look carefully in tissues an occasional cell can be seen that is rounded up, forming vesicle like structures and showing fragmented, highly condensed DNA.

Recommended literature

Textbooks

Alberts et al. Molecular Biology of the Cell, 6th edition, 2015: Chapter 18.

Papers

Baliga & Kumar: Role of Bcl-2 family of protein in malignancy. Hematological Oncology 20, 63-74, 2002

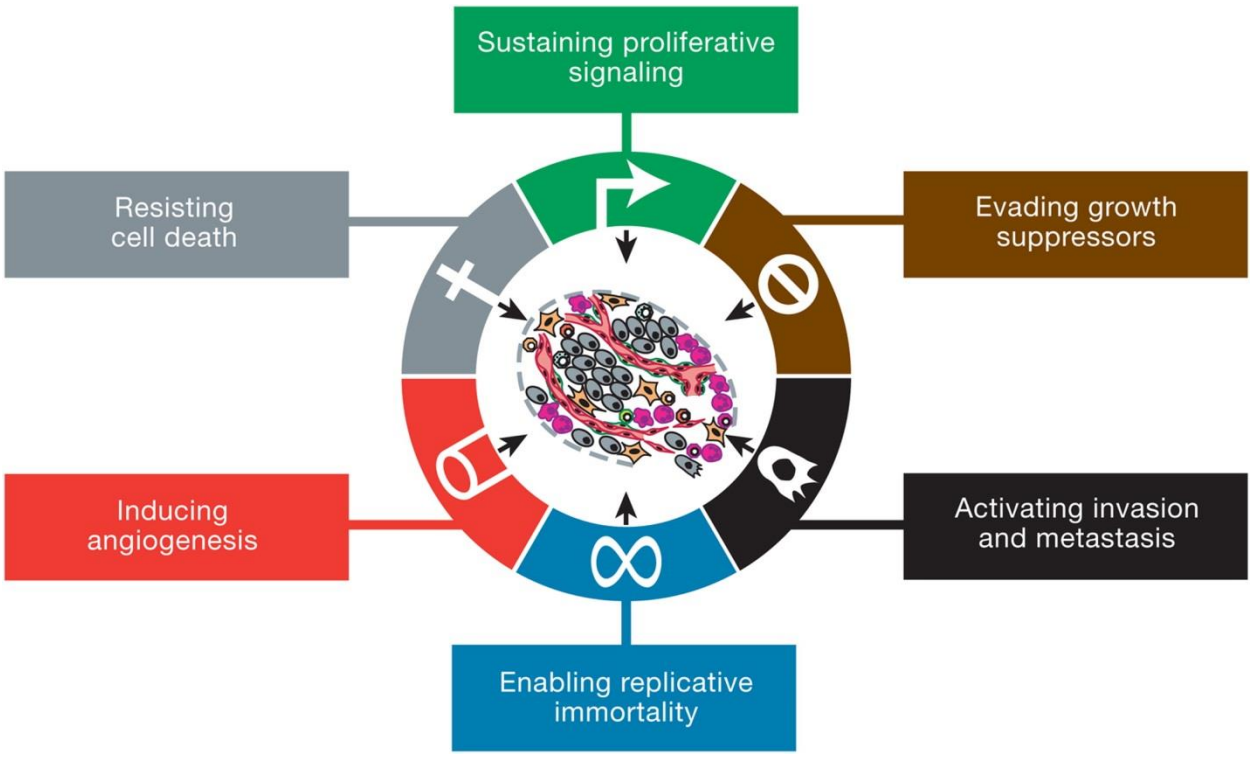
Further reading:

Alberts et al. Essential Cell Biology, 4th edition, 2014: Chapter 18, Chapter 21, pages 726-737

Task 10 Hallmarks of Cancer

Ms. Jones rings her daughter Janet one day. She seems very upset, so Janet immediately asks what is bothering her. Barbara says she discovered a lump in her breast when taking a shower. The lump felt different to the normal lumpiness she was used to feeling in her breast. She immediately called her general practitioner (GP). Fortunately, he could see her the same day. “Do you think it could be cancer? What is cancer exactly?” pressing questions she is asking her daughter.

Janet now knows from her study that cells cannot suddenly just become cancerous. You might think that all they do is grow quickly, but that is not the case. You also have things like fibroids, rapidly growing tissues that are not malignant. Janet remembers a diagram from an article that summarized a number of features that a cancer cell has to have. When she examines the diagram closely, is seems as if the cancerous cell is no longer responding appropriately to signals from its environment. It keeps on growing, even without growth factors and apparently does not start apoptosis. How did that work - signal transduction and apoptosis? Moreover, it would appear that the tumor cell is able to make blood vessels grow and that the cells can migrate into surrounding tissues or even wander around the whole body. Where had she seen this before? Finally, she is astonished at the fact that tumor cells can keep on dividing. She had only just been learning the chromosomes get shorter at the ends each time the cell divides and that this is the reason why cells are only able to divide a limited number of times. So what is going on with the tumor cells?



Recommended literature

Textbooks

Alberts et al. Molecular Biology of the Cell, 6th edition, 2015: Chapter 20,

Papers

Douglas Hanahan, Robert A. Weinberg. Hallmarks of Cancer. Cell 2000, 100: 57-70

Douglas Hanahan, Robert A. Weinberg. Hallmarks of Cancer: The Next Generation. Cell 2011, 144: 646-674.

Further reading:

Alberts et al. Essential cell Biology, 4th edition, 2014: Chapter 20 pages 712-726