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Subject: Autophagy and Cancer

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Autophagy:

Autophagy is self-digestion of the cell organelles.

The mechanism of autophagy is that specific membrane will surround the organelle which will be degraded forming **autophagosome**, which will fuse with a lysosome forming **autophagolysosome**, and lysosomal enzymes will digest the organelle.

One of the pathways involved in autophagy is the **mTOR pathway.** mTOR will balance the process. If the cell can survive by degradation of few organelles, then only autophagy will be activated. However, if the damage is really severe, this will lead to autophagy mediated apoptosis.

Advantages of this pathway:

1- When cells lack molecular machinery of apoptosis.
2- It provides cells with an opportunity to repair the damage prior to death.

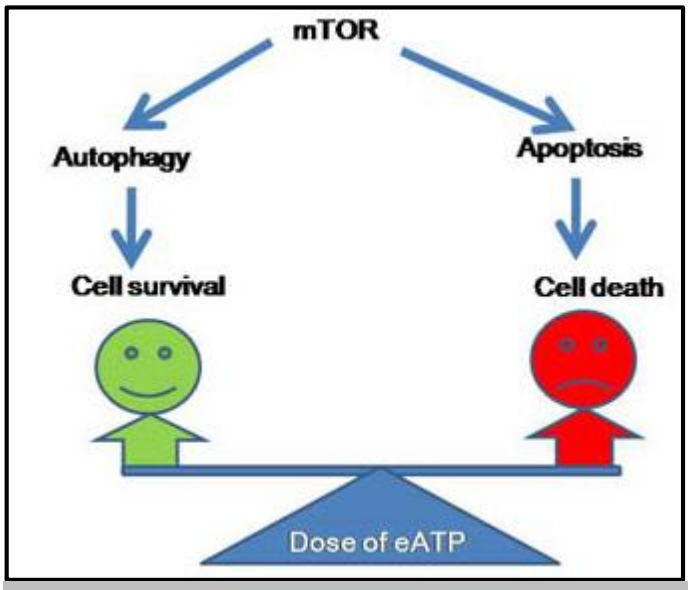

Figure 1

Cell Fate:

All the processes we were talking about in the last lectures, namely cell proliferation and apoptosis, are necessary for the normal development and tissue regeneration (during embryogenesis or during life).

See figure 2, Cells will proliferate and differentiate to develop different body tissues (Fibroblasts, endothelial cells, smooth muscle cells, epithelial…).

Note: If the cell was a stem cell (ex: from bone marrow), it will divide in two ways. One for self-renewal and the other one for differentiation. This is called ***asymmetric division***. While other proliferating cells (ex: osteoblasts) will only differentiate (symmetric division).

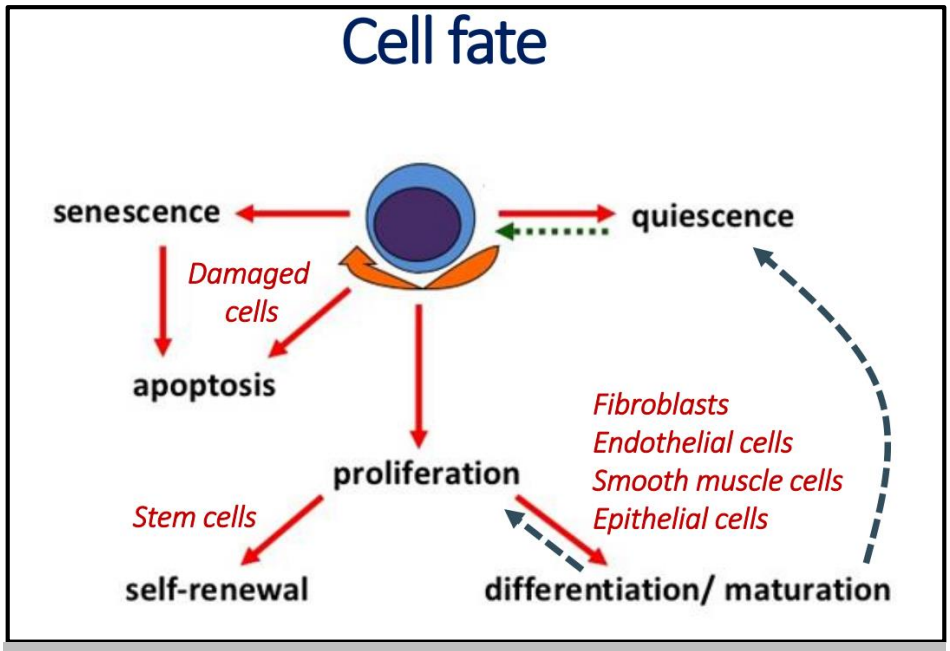

Figure 2

If the cells get old and start function abnormally. They will enter senescence, and targeted later on for apoptosis.

Also if the cell is damaged (ex: many misfolded proteins), this will activate apoptosis.

-End of Slide 11-

Now we will talk about cancer from cellular perspective.

Cancer is abnormal proliferation of cells caused by mutations, viruses…

Tumorigenesis is the development of the tumor.

Tumor can be benign (not invasive) or malignant/cancer (invasive).

The initiation of tumorigenesis is caused by what is called **carcinogen**.

Carcinogen: A substance/factor that induces mutations in cells affecting their function and control.

So when cells are exposed to carcinogens, they will be mutated and lose their control, as a result they will start to proliferate faster than normal tissue cells. Some tumor cells will have more and more mutations and the cells will have new properties giving them advantages (to the tumor) to proliferate and to resist the immune system and other environments.

Note: The microenvironment surrounding cells is called a **niche**. Niche is very important for cells survival and differentiation (ex: one of the factors affecting embryonic stem cells differentiation is the niche). However, some tumor cells due to mutations will have the ability to survive different environments becoming more invasive.

More mutations and more cells selection happens and this will end up with abnormal **heterogeneous** growth (so the same tumor will have different cell populations).

There are many types of cancers that can develop in the human (over 140). Most of the time the **environmental factors** will initiate tumor development. Other causes include radiation, viruses, bacteria, chemicals, chronic inflammation and inflammatory diseases (ex: Crohn's disease)

- UV radiation for example mainly affects skin causing skin cancers. UV radiation also damages DNA repair mechanisms.

- Other examples of carcinogens include Phorbol esters, Ethidium Bromide (intercalating agent, used in gel electrophoresis), Hormone supplements, Aflatoxin, tobacco…

- When viruses use cell machinery to replicate, they may cause transformation of the cells making them divide uncontrollably.

  Examples:
  - Hepatitis B and C viruses can cause liver cancer. Because when liver is damaged it will start repair, the liver will regenerate itself, liver cells will then get exhausted and have uncontrollably divisions resulting in cancer.
  - Papilloma virus can cause cervical cancer. It inserts its genome in the cell's DNA and this is related to tumor development.
  - Not all viruses induce tumors, Ex: Adenovirus **can't** produce tumors.

  So there is different mechanisms and different types of cancers depending on the type of the virus.

Features of cancer cells:

- ***Uncontrolled growth***. Also cancer cells don't have specific number of divisions like normal cells (because cancer cell can preserve the length of telomeres by the action of telomerase).

- Cancer cells lose it junctions and contact with other cells and ECM. And this will facilitate their movement and invasion (this property is beneficial for metastasis).

- Autocrine growth stimulation. A cancer cell will produce certain ligands that bind to its surface receptors inducing signaling pathways involved in cell survival and proliferation. Also, cancer cells can proliferate **without** the presence of growth factors by making the receptor of these factors constitutively active.

- They lose **contact inhibition**. Normally, when cell touches other cells it will stop dividing and won't grow over each other. This is not found in cancer cells.

- They lose **density dependent inhibition**. When growing cells become very dense, normally this will inhibit further division. Again, this is not found in cancer cells.

- The ability of invasion by synthesis of different types of proteases that digest ECM, basal lamina and surrounding tissues.

- ***Angiogenesis*** (synthesis of the cancer's own blood vessels). This will bring nutrients to cancer cells and also help in metastasis.

- Lose of apoptotic ability. This is the way that cancers become resistance to drugs, because they don't die.

- ***Lack of differentiation/anaplasia*** (because terminally differentiated cells don't divide). Remember stem cells divide for self-renewal and for differentiation. However, cancer cells have mutations that inhibit differentiation so it will only divide to the same type of cell.

Note: This point doesn't conflict with heterogeneity of the cancer, because heterogeneity is a result of mutations accumulation not cells differentiation.

Proto-oncogenes: Genes normally found in cells, involved in cell division and proliferation. If they were mutated, they won't be controlled and cancer occurs.

Note: if the gene is **normal**, it's called **proto-oncogene**. If it get **mutated**, it's then called **oncogene**.

Tumor suppressor genes (ex: p53): These genes protect the cells from problems, they may stop cell cycle or induce apoptosis. If they get mutated they will lose their function and cancer will develop.

The first discovered oncogenes were the **viral oncogenes**. The virus expresses these oncogenes using the cell machinery to produce viral proteins. When virus infect the cell, they will be inserted in different regions on the cell's genome and produce various proteins and induce transformation.

Example: ***RAF kinase***. In human cell DNA there are sequences that encodes for a regulatory protein domain and a kinase domain (RAF kinase). The viral protein (called GAG protein) which is expressed from a certain viral oncogene is inserted in front of the kinase domain so the kinase domain is kept and the GAG replaces the regulatory domain. This would ***constitutively activates*** the kinas domain so we will have RAF (an intermediate in signaling pathway) always phosphorylated and activated resulting in more cell proliferation and survival.

Note: In the book, there is a very big table that contains different types of viral oncogenes and their related type of cancer. For Example, BCR-ABL causes leukemia, Src causes sarcoma, RAS causes Kirsten sarcoma…

- Any mutation in any part of a signaling pathway can lead to cancer, this mutation could involve a hormone, a receptor, a transducer. So if the mutation leads to over activation this could lead to cancer.

Examples:

- If ***a receptor tyrosine kinase*** is over activated due to a mutation that affects the kinase domain, this will activate the signaling pathway.

- A mutation can happen in a regulatory part (enhancer for example) of a receptor gene, if this regulator is over expressed It will lead to over

expression of the receptor so more ligands can bind and more activation of the related signaling pathway.

- If a gene translocation happens, it is going to be inserted within another gene in the new chromosome and it will disrupt this gene and problems in the protein may happen and this may lead to activation of cell proliferation and cause cancer.
  Example: ***Platelet derived growth factor (PDGF***) fuses with a transcription factor called TEL resulting in over activation.
  Note: Translocation means that a part of a gene or a whole gene is translocated from one chromosome to another chromosome.

- Mutation in RAS protein, Glycine substituted with Valine, although they both are non polar but this substation results in over activity of RAS and it will act as an oncogene.

- β catenin (a transcription factor). This factor is inactivated normally by being a part of a protein complex. There is a protein called ***WNT***, if this protein binds to its receptor, the destruction complex, which B-catenin is part of it, will disassociate and β catenin will move to the nucleus and activate gene expression. Moreover, WNT targets other genes including c-MYC (an oncogene when it gets over activated) and CyclinD (cell cycle regulator) so if these are over produced I expect cancer transformation.

How do oncogenes affect cell survival? There are different pathways. For example, by activating a signaling pathway that activates bcl-2 which will inhibit apoptosis resulting in cell survival.

Or by the AKT pathway, over activation of this pathway will induce survival.

Oncogenes also affect differentiation. They will stop differentiation at a certain point, so the cells can proliferate and keep dividing.

Note: The remaining 4 slides are self-study (included in the exam).

The End