**Microbiology sheet 21**

\*This will be the last lecture in virology which is “Tumor Viruses”

Tumors in general are generated from different tissues in the body.

**Types of Cancers:**

* Leukemias (derived from lymphoid cells)
* Carcinomas (derived from epithelial or endothelial cells)
* Sarcomas (derived from connective tissue cells)

Slide #2:

Tumors are caused mainly by environmental conditions almost 85%,whereas a fewer (15%) are due to viruses mainly liver and cervical tumors.

Slide #3:

1. In general cells during their growth they undergo regulation mechanisms if anything is defected the cell goes through apoptosis, while in tumors this regulations is missing.

2.the other thing is that cells have shelf life they can live for one day or one year or ten years,unlike here in tumor cells they will be immortal they will not die they ll continue to grow and divide .

3. They will intake a lot of sugars, and thus those patients will lose weight.

4.In the tissue culture at least the y will grow independently. Normally, in tissue cultures when cells get in contact this contact will inhibit and stop their growth unlike here it will be loose and it will go over and over and over.

So in these cell cycles there will be no regulation, this loss of regulation might occur due to any of these factors :

* + a- Growth signaling pathways activated **(oncogenes – RNA tumor viruses).** The protooncogenes of the RNA viruses generally they are a type of retroviruses
  + b-Pathways to prevent cell proliferation are disrupted **(tumor suppressors – DNA tumor viruses).** When talking about DNA viruses we talk about tumor suppressor genes that will undergo a certain mutation and disrupt their function.

So, we either talk about protooncogenes or tumor suppressor genes.

The growth of those cells in vitro at least we can see certain characteristics, normally the cells will form a single cell layer if there was one tumor cells we will notice the growth of which will be in the form of a tumor ie not forming a single layer.

cells,those transformed cells increase they growth,they will lose their inhibition and they will have specific antigens produced from the cell membranes generally antigens are not found in the normal tissue they are only found in the abnormal tissue. And then this abnormalities can be detected by genetic testing; you look for the DNA or the RNA of these cells and look for any abnormality affecting mainly the oncogenes or the tumor suppressor genes.

Another important thing also is that some cells they produce what we call **Conality**, because they are generated from a single cell so all the tumors they will have exactly the same characteristics and antigens and this is what conality is.

-the doctor mentioned the hallmarks of cancer as in the slides and said that these are mainly the characteristics of tumor cells.

What about the viruses that causes those tumor cells:

Generally we have RNA viruses and DNA viruses that produce these types of tumors.

So DNA viruses there is a group that causes tumors as mentioned in the slide and also the RNA viruses mainly Retroviruses that causes HTLV1 and Falviviruses mainly Hepatitis C virus.

Normally, the growth of viruses they grow in a cell, that cell will be lysed and then the virus will be generated. The genome will be responsible for the production of all viral proteins.

In the case of tumor viruses, generally these viruses they will not cause a lytic or death of the cell, the nucleic acid will be integrated in the host cell nucleic acids and it will usually be converted into a **transformed** cell it will not die and it will have the characteristics previously mentioned. So in tumor viruses there is no lytic infection which means the cell will not be destroyed because of this it will be transformed. So the transformed cells again also are usually not controlled,reduced adhesion,motile, they can invade other tissues ie metastasize, and they are able to produce tumors and those are frequently having chromosomal abnormalities.

Referring to *slide number #14 The* viruses again as we mentioned will produce new antigens which are called tumor antigens or transplantation antigens. For example if we took Human Pappilloma Virus which causes a tumor in cervix cancer and these are generally the serotypes of that virus which mainly cause that disease, mainly HPV16 causes that disease,now there is a vaccine against it which can prevent it ( cervix cancer).

Hepatitis B&C causes hepatocellular carcinoma and this is mainly found in South East Asia in China and Japan .

We ll also talk about Herpes group Epstein Barr virus producing Burkitts lymphoma associated with Hodgkin’s Disease ,PTLD, nasopharyngeal and gastric carcinoma. Again Herpes Simplex type 8 which causes Kaposi Sarcoma in those patients. So these are generally the viruses which we can see.

So if there is no regulation we will end up with the neoplasia in the DNA.

What will the tumor viruses do to the cell?

Refer to the graph in *slide #16*

Now, what about the protooncogenes and the oncogenes?

-Protooncogenes are proteins that are important in the regulation of the cell growth, (remember when we talk about cell division we talk about four phases G1 S G2 and mitosis so the viruses to be able to grow they need the S phase to be active. If we have a regulation in that cell at this stage then that cell can go through apoptosis) so these viruses generally the protooncogenes they are genes that stimulate the normal cell growth and control them,Oncogenes however they become proteins which will change the cell to be proliferating out of control and produce tumors. Refer *to slide #17* and memorize it.

Generally in genetics an abnormality is either a deletion or a gain, in the oncogenes generally there is a gain of function,when we activate them those genes will induce certain function in the cell and that function is not normal but they will **induce** it. When we talk about tumor suppressor genes here we are talking about loss of function which means if there was a mutation in the tumor suppressor gene the function of which will be lost and we will end up with a tumor. ‘This is generally is an autosmal dominant type while there is a recessive type.’ I have no idea what this means.

*Slide #19* shows you the DNA viruses that targets suppressor genes not the oncogenes as previously mentioned. E1A responsible for the Retinoblastoma suppressor gene and E1B responsible for the p53 suppressor gene and so on as in th e slides.

These viruses again also the newly produced antigens due to the mutations of the gene generally those they have some similarities in a normal functioning proteins in the body for example EBV LMP1 antigen mimics CD40 ( remember we saw CD40 in the T-cell interaction with B-lymphocytes) so if we have that tumor suppressor gene mimicking this one then we will have activation of the B-lymphocytes without any control. Or the E5 gene of bovine papillomavirus that mimics the platelet degradatation growth factor this factor is very imp receptor to produce function of these cells. Polyomavirus SRC signaling pathway.HHV8 this one will end up viral D cyclin and viral IL6, D cyclin is again very important on controlling the regulation mechanism (I think this is what he meant).

So these viral antigens they mimic normal structural proteins and then you will have abnormalities as you can see.

*Slide # 21*

If we look to the papilloma virus (same as the slides). Antigens, there is a lot of antigens which can be formed by this virus.

*Slide #22*

Same as the slides but add to it “ integrated copies of DNA they can also cause premalignant lesions in the urogenital areas.

*Slide # 23*

The types as in the slides.

18 and 16 mainly can cause cervix cancer.

*Slide#24*

Progression of this virus, in most cases there will be clearance of the virus but if there is no clearance the clinical picture type 1 or type 2 generally there will be regression nothing will happen again it will be cleared with time, if it goes to stage 3 then an invasive type of tumor and it can cause an invasive cancer in the body.

Other co-factors which increase the transformation from stage 2 to stage 3 are viral integration, smoking, hormones, immune status, infections and again genetic changes which we can see in the patient. So these are factors that would increase the tumorgenecity of this virus.

*Slide#25*

Herpes virus is a little larger than the other one (around 200 nm in diameter) and it is enveloped. All of us have been infected with herpes, whether it was simplex, CMV, or EBV. If we tested the population, we will find antibodies in around 95% of the population. Any one of us can have a fever and ulcers, which are due to herpes. It is a DNA virus that causes an acute infection followed by latency. EBV causes infectious mononucleosis. Immunocompromised patients end up with burkitt lymphoma, nasopharyngeal carcinoma, or hodgkin’s disease. These are associated with herpes simplex virus.

*Slide#26*

**EBV can immortalize B-cells by encoding a normal functional oncoprotein (LMP1) that mimics CD-40.**

The oncogene seen here is c-myc (cellular-myc), this gene is found on chromosome 14, very close to the immunoglobulin genes (IgG / IgM etc.).

Human herpes virus 8 (HHV-8) is associated with Kaposi’s sarcoma.

Everyone has EBV, it is also known as “kissing infection”.

*Slide#27*

EBV is focused on the lymph cells and its receptor is CD21 (found on B-lymphocyte (CD 19,20,21) and epithelial cells of the oro- and nasopharynx )

African burkitt’s lymphoma affects the jaw.

Infectious mononucleosis will activate B-lymphocytes, which in turn will produce IgM against the IgG.

*Slide#28*

Endemic in Africa

Poorly differentiated monoclonal B-cell lymphoma.

*Slide#29*

The oncogenes are myc / mos / abl / fes / myb. **There are many different translocations from 8 to 14 but at different loci.**

*Slide#30*

The virus usually enters a latent cycle.

Heterophile antibodies: antibodies generated to different antigens of different origins. (React with more than one antigen from different species.)

The virus can be reactivated by many different ways.

*Slide#32*

Antigens which can initiate the infection in EBV are EBNA2, LMP1, and LMP2A. To differentiate whether the virus is in the latent stage or not, we look for these antigens.

*Slide#34*

HHV8’s manifestations appear on the skin. It causes hematologic malignancies.

*Slide#35*

Hepatitis B is mainly a public health problem, vaccination now a day is mandatory.

10% of the population in under-developed countries is chronic carriers.

Strong correlation between HBV and hepato-cellular carcinoma.

One of the most important viruses in the far east.

*Slide#36*

Integrates to the host’s cells then produces tumors.

*Slide#37*

No indications that adenoviruses cause a disease in humans, but we can see the transplantation antigens 1 & 2, as well as oncogenes. Meanwhile they produce diseases in animals.

*Slide#39*

RNA tumor viruses are retroviruses and therefore have reverse transcriptase, they will generate DNA from the RNA of the virus, they will use the host’s enzyme, and they will integrate their DNA to the host’s DNA. If they work normally, at the end we will have a normal virus. Here as well we have latency.

*Slide#41*

The oncogenes we spoke about previously are of two types:-

1- *Cellular oncogenes*: proteins already found in the cell which will undergo mutations.

2- *Viral oncogenes*: viral genomes which are integrated in the human’s genome. Those are called proto-oncogenes and they are viral oncogenes which can be found in the body. They are unrelated to the strategy of viral replication.

Generally, all RNA viruses can cause tumor-genesis especially in animals.

*Slide#42*

Retroviral transduction and activation of the oncogene: Activation and insertion of the viral genome which will then result in a tumor. They will be either found in proteins (trans-activating) or non-transducing which will have a long latency period.

*Slide#43*

Here we see a normal cellular-onc in a host, if they are activated by one way or another, these proto-oncogenes will change into v-onc and the cell will produce a tumor.

We have many types of v-onc such as src or mos.

*Slide#44*

External signal molecules or growth factors will activate the gene.

Cellular receptors can also activate the proto-oncogene if they are mutated.

Second messengers in signaling cascade (kinases) can activate proto-oncogenes if they are mutated. We may also have a problem in transcription factors.

*Slide#45*

Growth factors act on their specific receptors, which in turn will send a signal to the cytoplasm. In the cytoplasm, there will be production of a protein which will be transported to the nucleus and results in its activation. The mutation can occur in any of the previous steps.

A “single hit” carcinogenesis results from a single mutation. (Dominant)

Retinoblastoma requires two hits since it is recessive. (Mutation is in the tumor suppressing gene)

**DNA tumors are mainly monoclonal.**

Polyclonal tumors are more aggressive.

*Slide#48*

**Human T-cell Leukemia Virus type I (HTLV-I) is the only tumor which can be found in humans**. It is associated with 2 fatal human diseases:

1- Adult T-cell leukemia (ATL) (clonal malignancy of infected mature CD4+ T cells)

2- Tropical spastic paraparesis/HTLV-1 associated myelopathy (neurodegenerative disease)

Endemic in parts of Japan, South America, Africa, and the Caribbean.

These areas have started screening programs for this tumor.

**Infects primarily CD4+ T cells.**

*Slide#49*

Breastfeeding (20%) results in much higher transmission than sexual contact (1%)

*Slide#52*

This is a summary.

*Slide#53*

He is not going to talk about this because he already said all this when he explained retroviruses.