Oral Biology
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Tokushima University
Lecture - 18
Molecular mechanism in oral cancer

Hello, my name is Yasusei Kudo. I am a Professor in department of oral science Tokushima University Graduate School of Biomedical Sciences. I am happy to give a lecture to you I will talk about Molecular mechanism of oral cancer progression.

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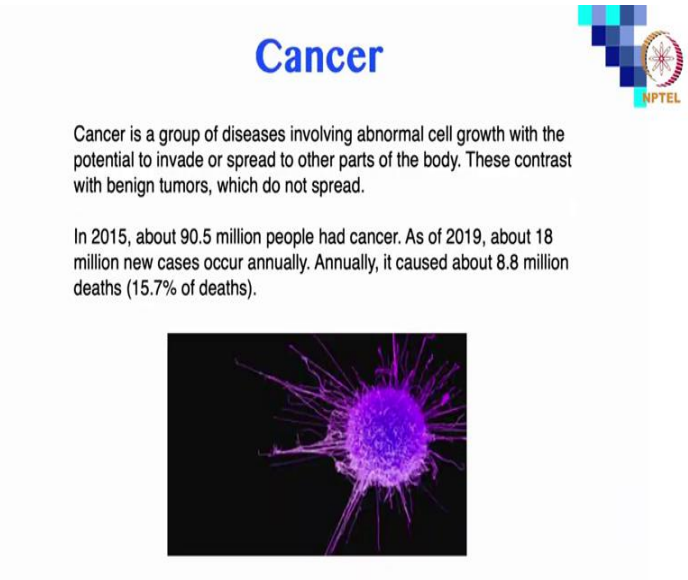

Today I will focus on oral cancer progression before talking about oral cancer I will tell you the general knowledge of cancer. As you know cancer is a leading cause of this worldwide. Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. These contrast with benign tumors, which do not spread.

In 2015, about 90.5 million people had a cancer. As of 2019, about 18 million new cases occur annually. Annually it caused about 8.8 million deaths. The most common types of cancer in males are lung cancer, prostate cancer, colorectal cancer and stomach cancer. In females the most common types are breast cancer, colorectal cancer, lung cancer and cervical cancer.

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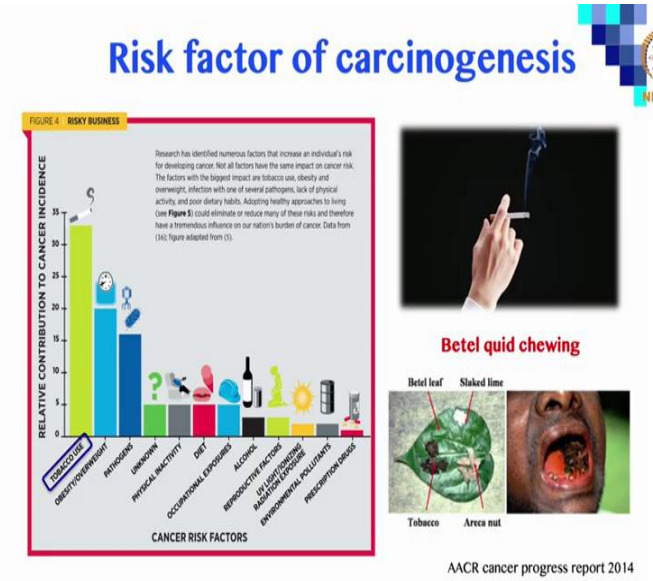

Slide shows risk factors of carcinogenesis, tobacco use is a cause of about over 30 percent of cancer. Obesity pathogen physical inactivity diet occupational exposures alcohol reproductive factors UV radiation and prescription drugs causes cancer. Tobacco use is known as a major risk factor for cancer including oral cancer. Tobacco is responsible for about 1 in 5 cancer diseases worldwide and about 1 in 3 in the developed world.

In West Asian countries including India people have a habit of chewing tobacco. Chewing tobacco can cause oral cancer in the background cause gingiva and lips. Cancer caused by smokeless tobacco often begins as leukoplakia with a whitish patch that develops inside say mouth or throat. Or the cancer may erythroplakia with this condition a led laser the patch develops inside say mouth.

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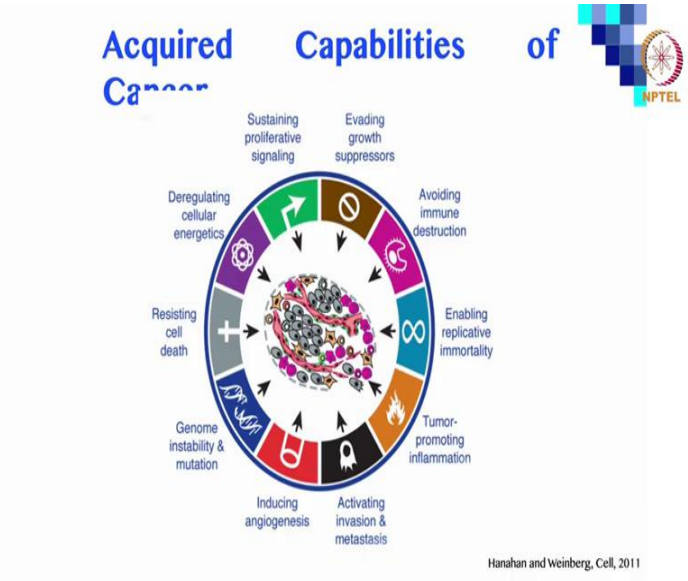

This slide shows acquired capability of cancer. Cancer cells have several features, such as evading growth suppressors, avoiding immune destruction, enabling replicative immortality, tumor promoting inflammation, activation activating invasion and metastasis, inducing angiogenesis, genome instability and mutation, resisting cell death, deregulating cellular energetic, sustaining proliferative signaling. Thus, cancer cells have a special feature like that.

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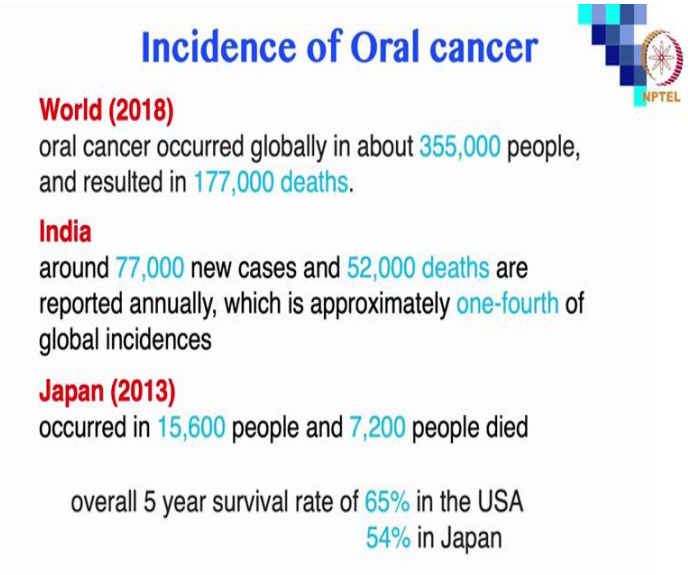

Now, I will talk about oral cancer, all over the world oral cancer occurred globally in about 355,000 people, and resulted in 177,000 deaths. In India around 77,000 new cases and 52,000 deaths are reported annually, which is approximately one-fourth of global incidence. In Japan oral cancer occurred 15,600 people and 7,200 people died or died.

Overall, 5 years survival rate is 65 percent in the USA and 54 percent in Japan. The QOL of oral cancer patients have been graduate gradually improving due to the progress of treatment, such as surgery, chemotherapy and radiotherapy that the survival rate has not been significantly improved. Most of the causes of deaths are local ligands cervical lymph nodes and distant metastases.

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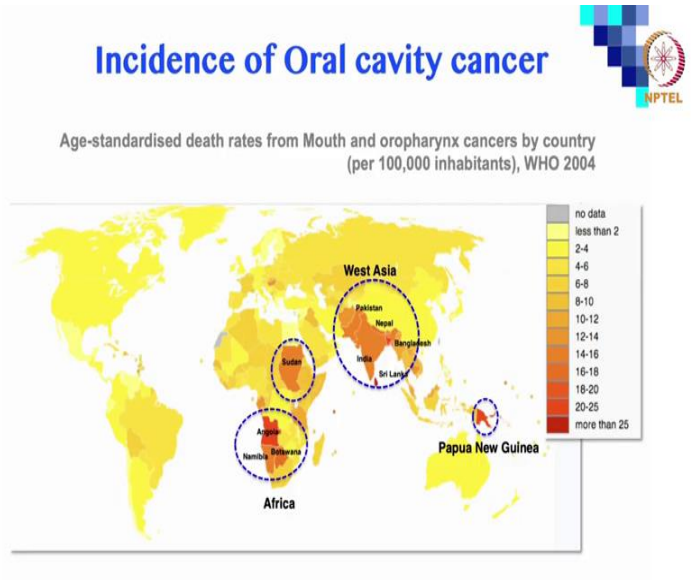

This slide shows age standard death rate from mouths and oropharynx cancers by country. There are many oral cancer patients in West Asian countries, Africa countries and Papua New Guinea.

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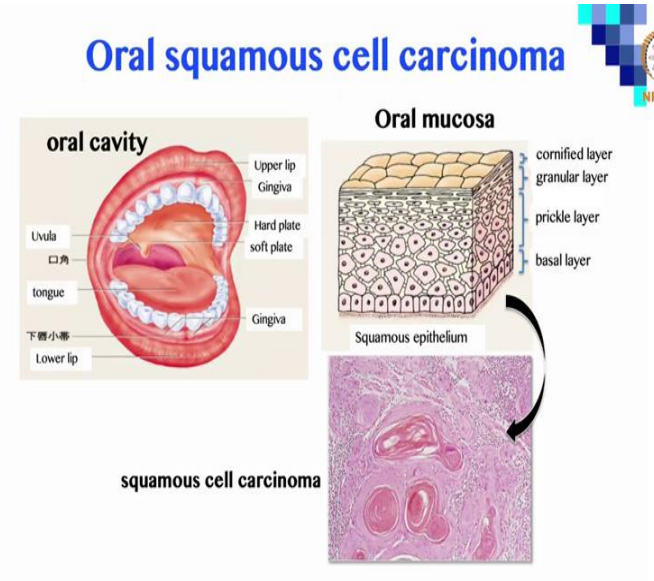

Oral cancer arises in oral epithelium histologically oral mucosa is squamous epithelium therefore; most of oral cancer is squamous cell carcinoma.

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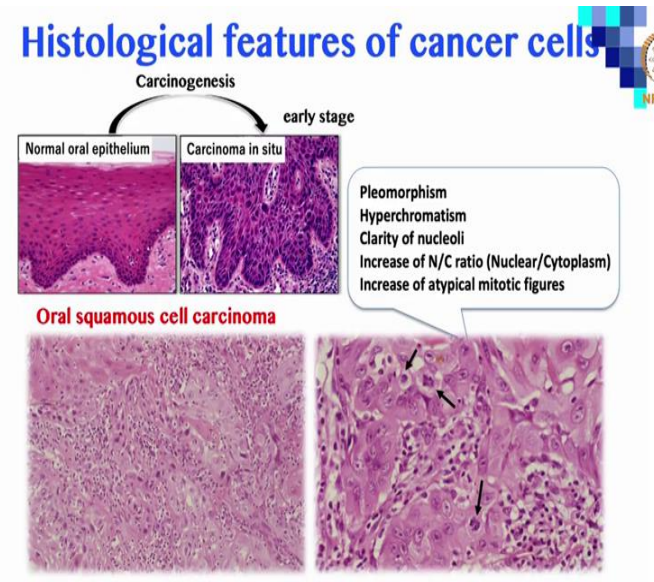

Normal oral epithelium cells transform and become cancer, in early stage oral cancer cells do not destroy basement membrane. In this stage we say carcinoma in situ, carcinoma in situ is an early stage of oral cancer. After destroying basement membrane cancer cells embed deeply. Oral cancer cells show pleomorphism, hyperchromatism, clarity of nucleoli, increase of NC ratio and increase of atypical mitotic figures, under the

microscope. Increase of atypical mitotic figures is the most important findings for diagnosis by pathologists.

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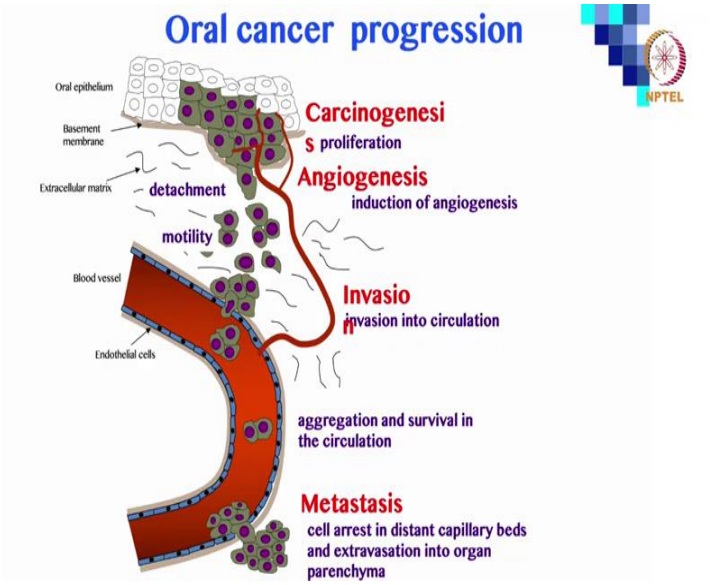

As I said before most of causes of death by oral cancer are loco ligands, cervica or cervical lymph nodes and distant metastasis. During the development of oral cancer, cancer cells arise in oral epithelium and grow. As cancer cells grow very fast cancer cells require much more nutrition, cancer cells generate new blood vessels called angiogenesis for taking the nutrition.

Cancer cells lose cell-cell contact and detached from primary side via destroying basement membrane. Cancer cells embed deeply via degrading extracellular matrix and go into the blood vessels or (Refer Time: 09:45) vessels. Some cancer cells can survive within the circulation and move to distant area, then cancer cells arrest in distant capillary beds and extravasation into organ parenchyma. Cancer cells are heterogeneous in primary side, only cancer cells with excellent ability can metastasize.

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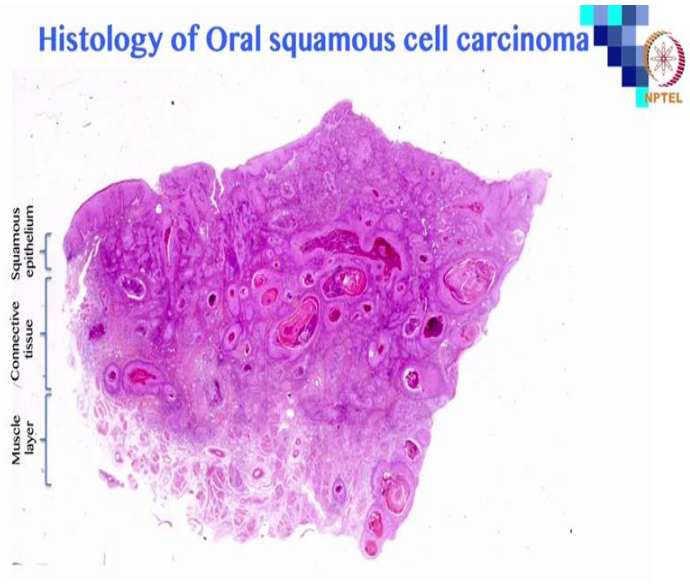

This slide shows the histology of oral cancer. Cancer occurs in the normal oral epithelium, cancer cells invade deeply and frequently metastasize to cervical lymph node and sometimes to lung.

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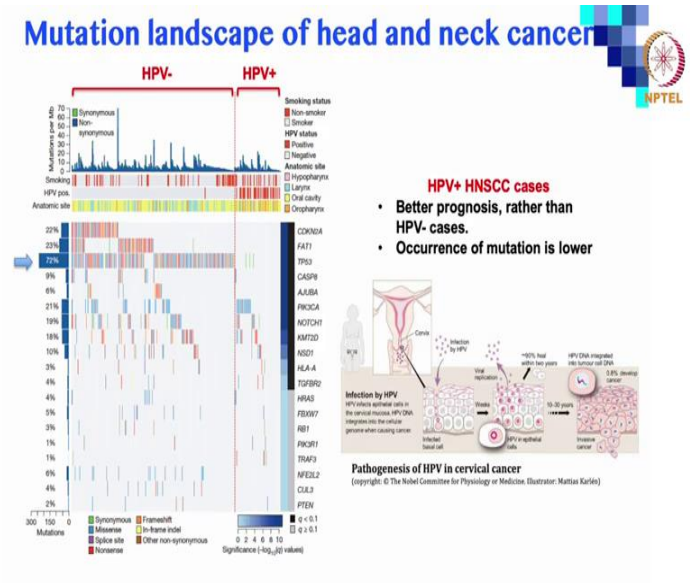

The majority of cancers some 90 to 90 percent of cases are due to genetic mutations from environmental and lifestyle factors. This slide shows the mutation landscape of head and neck cancer recently published in nature. Around 20 percent of head and neck cancer cases are HPV positive interestingly occurrence of mutation is lower in HPV positive

head and neck cancer cases. Therefore, HPV positive head and neck cancer cases show better prognosis rather than HPV negative cases.

HPV infection is well known causes in cervical cancer therefore, young women get HPV vaccination, HPV vaccination can prevent over 90 percent of cancers caused by HPV. HPV vaccines work best when given at age 11 to 12 years before contact with the HPV virus. On the other hand, around 80 percent of head and neck cancer cases are HPV negative.

In HPV negative cases TP53 is most frequently mutated. The TP53 gene is the most commonly mutated genes in human cancers and has many important biological functions including the control of the cell cycle checkpoint. Frequency of other gene mutations is not high the cell cycle regulation pathway is the most significantly altered pathway from this analysis.

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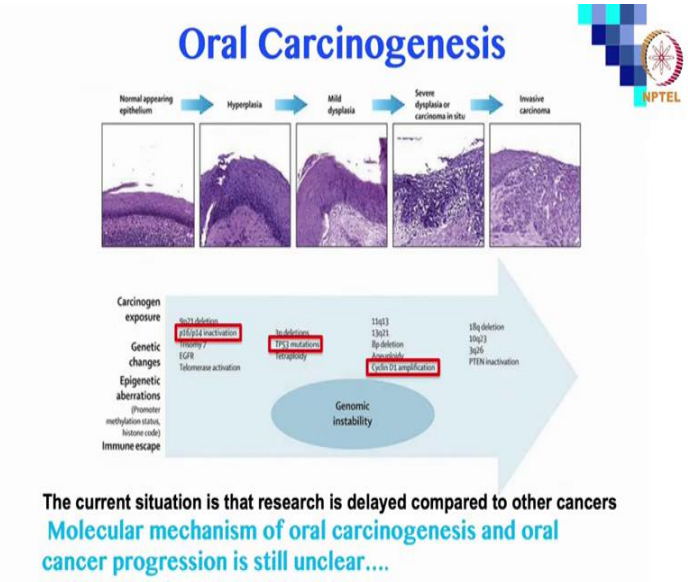

Multi stage carcinogenesis can be divided conceptually into four steps tumor initiation, tumor promotion, malignant conversion and tumor progression. Carcinogenesis requires the malignant conversion of benign hyperplastic cells to a migrant state and invasion and metastasis and manifestations of further genetic and epigenetic changes. During oral cancer progression from normal epithelium hyperplasia, mild dysplasia and severe dysplasia or carcinoma in situ exists.

During oral cancer development or deletions that have been studied to date include genetic and epigenetic changes. This slide show it is the molecular alterations during oral cancer development. Molecular alterations in epithelium cells generally precede phenotypic, histologic changes and accumulate throughout malignant transformation from the benign to premalignant and invasive states.

Among molecular alterations p16 p14 in activation TP53 mutation and cyclin D1 amplification are involved with in dislocation of cell cycle. The current situation is that oral cancer research is delayed compared to other cancers therefore, molecular mechanisms of oral cancers and oral cancer progression is still unclear. We have to clarify this mechanism in the future.

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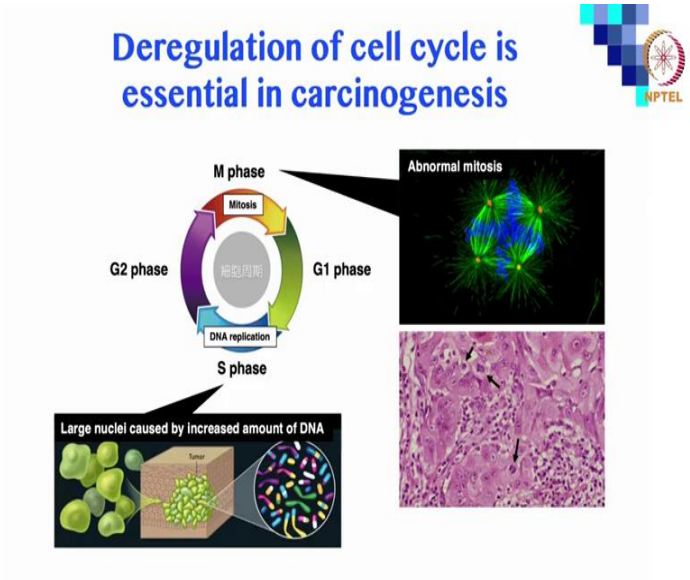

In general deregulation of cell cycle is essential in carcinogenesis, cell cycle is a series of events that take place in a cell that cause it to divide into two daughter cells. These events include the DNA replication and cell division. The cell cycle consists of four distinct phases G1 S G2 and M.

S phase is DNA replication, M phase is mitosis. Histologically cancer cells show large nuclei this is caused by increased amount of DNA via abnormal DNA synthesis at S phase. Moreover, typical mitotic figures are frequently observed in cancer tissues this is caused by abnormal mitosis at M phase.

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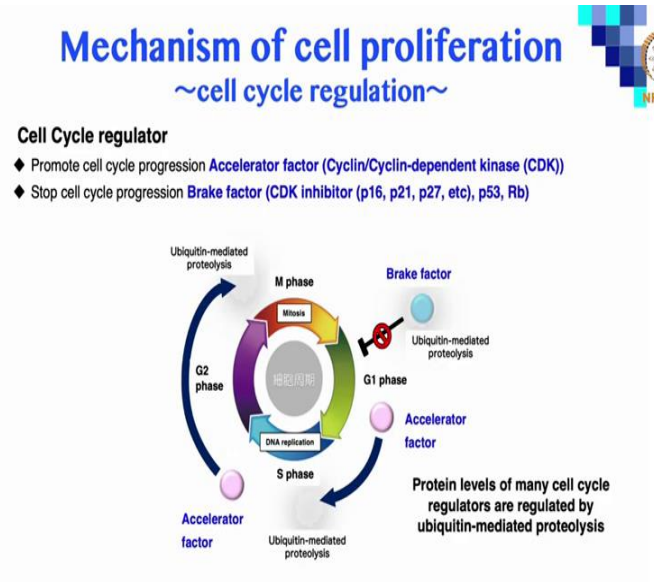

Cell cycle is regulated by many molecules cell cycle is driven by cyclin and cyclin dependent kinase CDK. Cyclin and CDK activates accelerator of cell cycle via proliferation. Moreover, cell cycle can be arrested by brake factors, cell cycle is precisely controlled by many accelerators and brake factors. Most of cell cycle regulators are controlled by their protein levels by ubiquitin mediated proteolysis.

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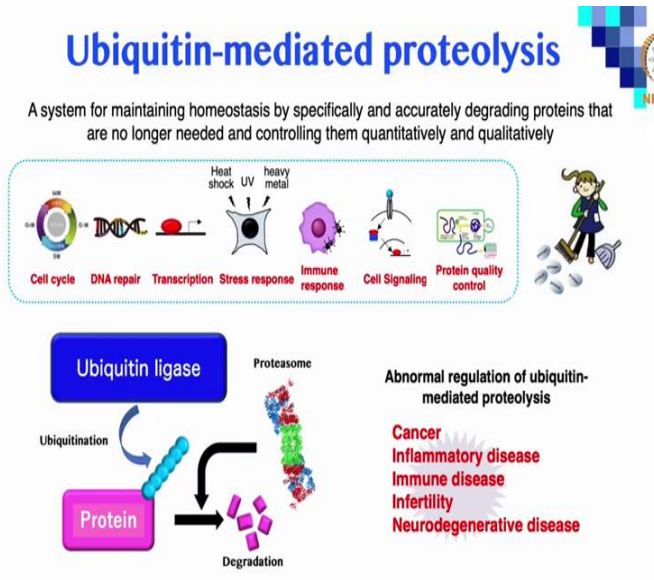

Ubiquitin mediated proteolysis is a system for maintaining homeostasis by specifically and accurately degrading proteins that are no longer needed and controlling them

quantitatively and qualitatively. Ubiquitin ligase conjugate ubiquitin to target protein specifically and accurately.

Ubiquitin conjugated protein is recognized by 26S proteasome and then degraded quickly. Now, it is known that abnormal regulation of ubiquitin mediated proteolysis causes several diseases including cancer inflammatory disease, immune disease infertility and neurodegenerative diseases.

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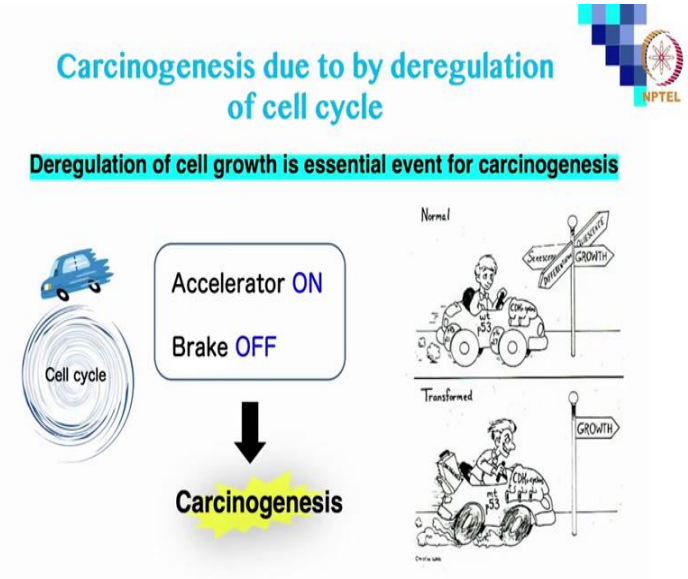

Carcinogenesis is due to by this deregulation of cell cycle. In other words, deregulation of cells growth is essential event for carcinogenesis. Deregulation of cell cycle is caused by accelerator on and brake off. Cartoon shows the normal and cancer cells normal cells can drive to growth senescence differentiation and queer essence, but cancer cells have bigger engine and do not have a brake. Therefore, cancer cells can drive to only growth.

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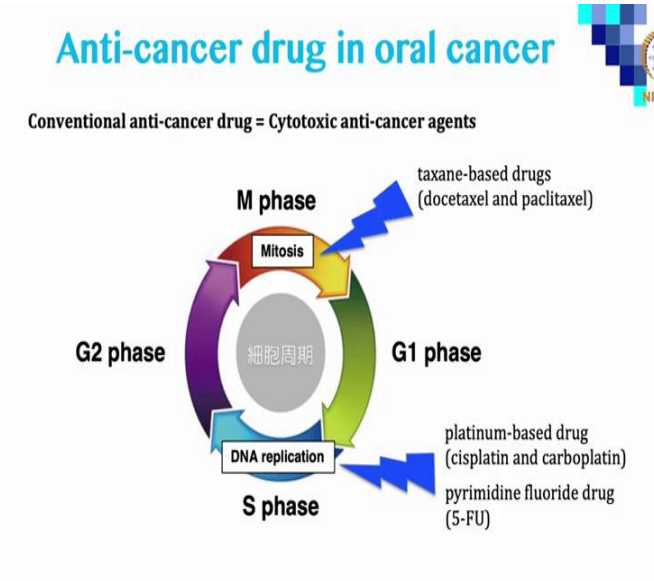

To know that deregulation of cell cycle in cancer cells is important because conventional anti cancer drugs target cell cycle. In oral cancer platinum-based drug including cisplatin and carboplatin pyrimidine fluoride drug including 5 FU type taxane based drugs including docetaxel and paclitaxel are often used. Platinum based drugs and pyrimidine fluoride drug supplies DNA synthesis, taxane based drugs disrupt microtubule function via preventing the (Refer Time: 20:08) in mitosis.

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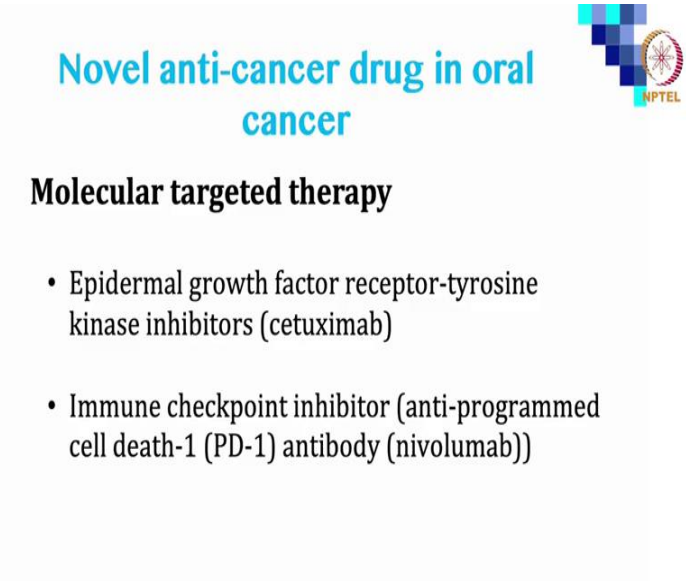

Now, molecular target therapies are revolutionized therapeutics, which interfere with specific molecules to block cancer growth progression and metastasis. Many molecular targeted drugs are approved; however, in oral cancer only two drugs are approved in Japan. One is epidermal growth factor receptor EGFR, tyrosine kinase inhibitors cetuximab. Another is immune checkpoint inhibitor anti PD-1 antibody nivolumab.

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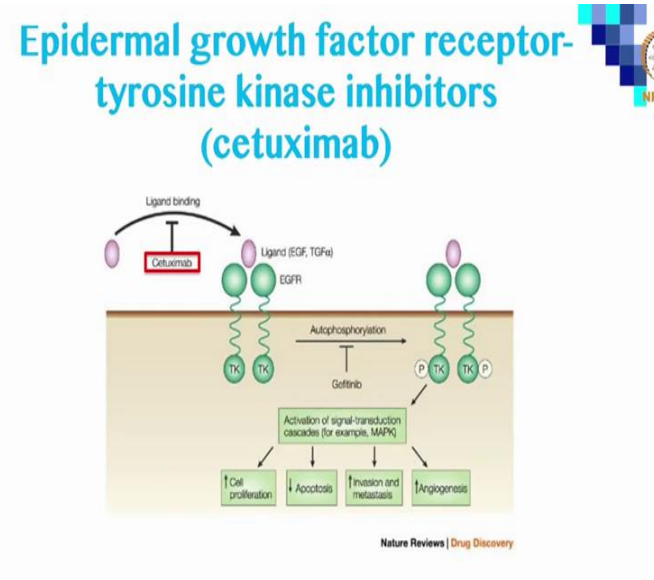

I will explain EGFR receptor tyrosine kinase inhibitor cetuximab. After ligand binding to EGFR; EGFR auto phosphorylated and activate signal transduction cascade for cells proliferation inhibition apoptosis invasion and metastasis and angiogenesis, cetuximab inhibits ligand binding to EGFR.

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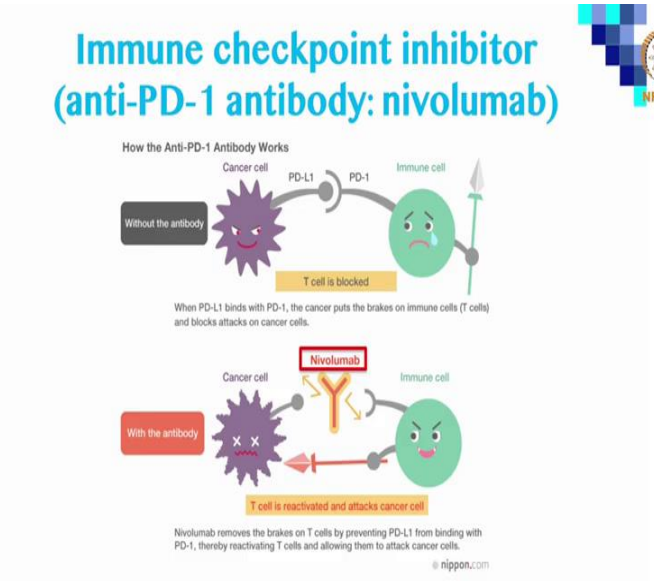

I will explain immune checkpoint inhibitor nivolumab PD-L1 is a ligand of PD-1 PD-L1 is expressed in cancer cells. When PD-L1 binds with PD-1 the cancer puts the brakes on immune cells and blocks attacks on cancer cells. Nivolumab is an anti PD-1 monoclonal antibody and removes the brakes on T cell by preventing PD-L1 from binding with PD-1. Thereby reactivating T cells allowing to attack cancer cells, as I said only these molecular targeted drugs are approved I expect that nivolumab molecular targeted drugs are developed and will be used in oral cancer in the near future.

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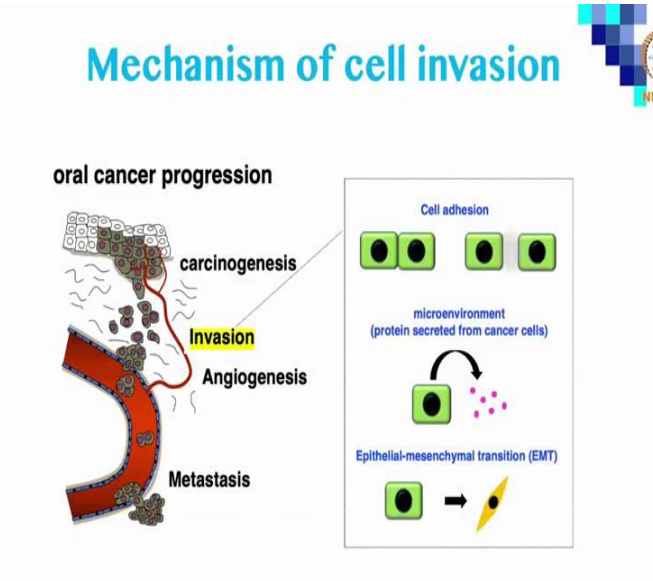

Finally, I will talk about mechanism of invasion during oral cancer progression, invasion is important step for metastasis. Metastasis is the leading causes of death therefore we have to suppress the metastasis. Loss of cell adhesion tumor microenvironment and epithelial mesenchymal transition EMT are involved in promoting invasion.

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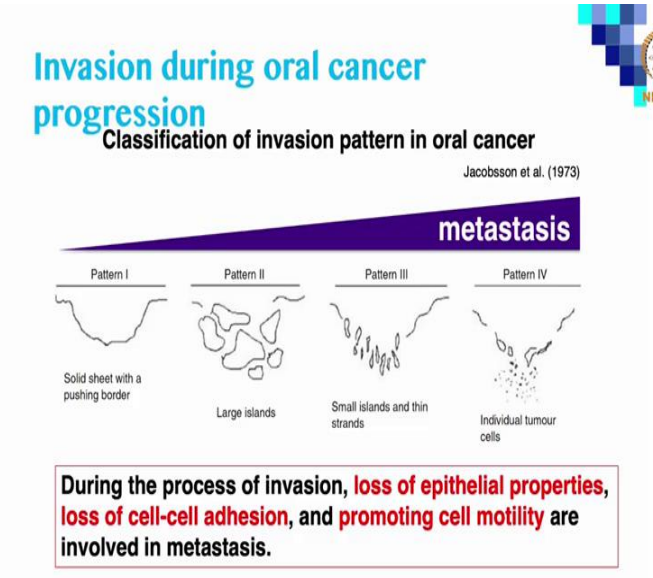

Slide shows the classification of invasion pattern in oral cancer by Jacobsson et al in 1973 this classification is widely used for predicting of oral cancer metastasis. Pattern 1

shows solid sheet with a pushing border, pattern 2 shows large island, pattern 3 shows small islands with thin strands, pattern 4 shows individual tumor cells.

Cancer cells showing pattern 4 easily metastasis, during the process of invasion loss of epithelial properties, loss of cell-cell adhesion, and promoting cell motility are involved in metastasis. Pattern 4 cancer cells show spindle shape these cells may have EMT features.

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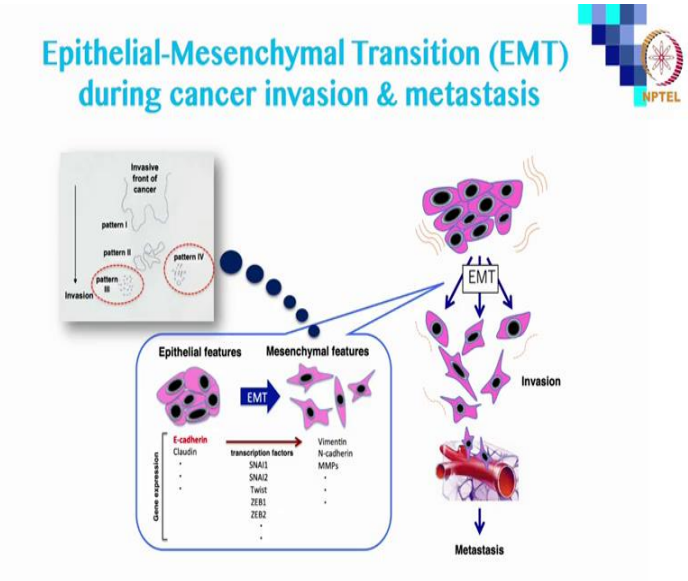

The ability to metastasize is a key hallmark of cancer progression and this ability can be achieved by acquiring the EMT features, EMT is a biological process that epithelial cells lose their epithelial features and gain mesenchymal features. In this transition transcription factors, such as SNAI 1 SNAI 2 twists ZEB 1 and ZEB 2 are involved.

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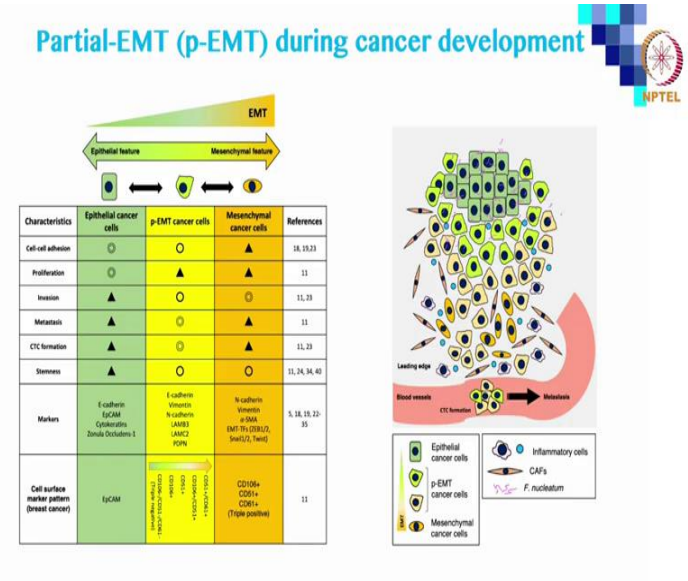

Recent evidence reveals that the intermediate state of EMT process partial EMT shows more aggressive phenotype than completely EMT phenotype. Left figure shows the EMT spectrum and characteristics of each state. EMT is not binary, but gradual proceeding problem partial EMT cancer cells have intermediate.

Features both epithelial and the mesenchymal cells and they contribute on the tumor progression due to their invasive and tough characteristics. Right figure shows that EMT problem is regulated by tumor microenvironment. Partial EMT cancer cells are co-localized with cancer associated fibroblasts blood vessels and inflammatory cells including macrophages on the leading edge of tumor.

Signals from tumor environment component cells may regulate partial EMT problem in oral cancer cells. Recently we found who is a bacterium nucleotide, which is a periodontal periodontopathic bacterium is involved in conversion from epithelial to partial EMT. So, in oral cancer tissues fusobacterium nucleatum is also involved in partial EMT induction. As most of the causes of death are local liquids cervical lymph nodes and distant metastasis.

The key to treatment is how to control the invasion and metastasis of oral cancer. The involvement of partial EMT problem is one of the important factors in the process of cancer invasion and metastasis. The control of invasion and metastasis is important and partial EMT can be a no were target for oral cancer therapy.

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Thank you for your attention I am attaching the address of my lab. If you are interested in my lab, please have a look our website.

Thank you very much.