Oral Cancer - pathophysiology

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Cell life:

Proliferation

Differentiation

Cell death (apoptosis)
Most cells are in resting state, while a small percent of the cells are in the process of cell division

Regulation:
- **permanent**: S and M
- **variable**: $G_1$ and $G_2$

[Diagram showing cell cycle phases: $G_0$, $G_1$, $S$, $G_2$, $M$. Arrows indicate transitions between phases.]

- Return to cycle
- Out of cycle
Regulation of cell division

G1 decision regulation

Proliferative signals

Antiproliferative signals
Terminology

- Oncology: the study of tumors

- Neoplasia: new growth (indicates autonomy with a loss of response to growth controls)

  - uncontrolled cell division due to multiple mutations of somatic cells
What happens in cancer?

Cancer is a complex multifactorial disorder that leads to the loss of regulated cell proliferation.

- Cancer cells proliferate more frequently
- Cancers cell do not exhibit contact inhibition and produce tumor
- Cancer cells invade other tissues (metastasis)
- Cancer originates from a single cell
Cancer: consequences

• Cancer is a disease in which some of the body’s cells become dysregulated in their normal functions and properties:
  – Increased replication
  – Resistance to apoptosis
  – “Immortality”
  – Destruction/remodeling of extracellular matrix
  – Angiogenesis
  – Metastasis
Cells display widely varied functional phenotypes
Cell response to external stimuli

- Physiologic conditions
- Injury from chemical, biological & physical agents
- Other cells
- Extracellular matrix

Signal transduction → Alteration in protein activity

Regulation of gene expression → Differentiation
Replication
Apoptosis
Metabolism
Motility
Cancer is a genetic disease on an organism level too

• Only a minority of cancer is familial
  – Cancer-susceptibility gene passed through germline DNA transmission (gametes)
  – Study of cancer gene families can be quite informative about how cancer originates
  – Non-familiar cancer is referred to as sporadic
A. 1996 ESTIMATED CANCER INCIDENCE BY SITE AND SEX*

<table>
<thead>
<tr>
<th>Site</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma of skin</td>
<td>3%</td>
</tr>
<tr>
<td>Mouth</td>
<td>3%</td>
</tr>
<tr>
<td>Lung</td>
<td>13%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>2%</td>
</tr>
<tr>
<td>Stomach</td>
<td>2%</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>9%</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>7%</td>
</tr>
<tr>
<td>Prostate</td>
<td>41%</td>
</tr>
<tr>
<td>Leukemia and lymphomas</td>
<td>6%</td>
</tr>
<tr>
<td>All others</td>
<td>14%</td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>3%</td>
</tr>
<tr>
<td>Mouth</td>
<td>2%</td>
</tr>
<tr>
<td>Lung</td>
<td>13%</td>
</tr>
<tr>
<td>Breast</td>
<td>31%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>2%</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>11%</td>
</tr>
<tr>
<td>Ovary</td>
<td>4%</td>
</tr>
<tr>
<td>Uterus</td>
<td>9%</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>4%</td>
</tr>
<tr>
<td>Leukemia and lymphomas</td>
<td>6%</td>
</tr>
<tr>
<td>All others</td>
<td>15%</td>
</tr>
</tbody>
</table>

* Excluding nonmelanoma skin cancer and carcinoma in situ
### 1996 Estimated Cancer Deaths by Site and Sex

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma of skin</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Mouth</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Lung</td>
<td>32%</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>5%</td>
<td>25%</td>
</tr>
<tr>
<td>Stomach</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>9%</td>
<td>17%</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Prostate</td>
<td>14%</td>
<td>10%</td>
</tr>
<tr>
<td>Leukemia and lymphomas</td>
<td>9%</td>
<td>6%</td>
</tr>
<tr>
<td>All others</td>
<td>19%</td>
<td>4%</td>
</tr>
<tr>
<td><em>All others</em></td>
<td></td>
<td>3%</td>
</tr>
</tbody>
</table>

*Note: The percentages for all other sites combined are 20%.*
Oral leukoplakia
Oral cancer
Incidence of cancers in Hungary
<table>
<thead>
<tr>
<th>Tumor incidence in Hungary, 2001 (58 772 tumor, 51 136 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lung</strong></td>
</tr>
<tr>
<td><strong>Colorectal</strong></td>
</tr>
<tr>
<td><strong>Skin</strong></td>
</tr>
<tr>
<td><strong>Breast</strong></td>
</tr>
<tr>
<td><strong>Lymph and blood forming system</strong></td>
</tr>
<tr>
<td><strong>Oral-head-neck cancers</strong></td>
</tr>
<tr>
<td><strong>Prostate</strong></td>
</tr>
<tr>
<td><strong>Stomach</strong></td>
</tr>
<tr>
<td><strong>Bladder</strong></td>
</tr>
<tr>
<td><strong>Kidney</strong></td>
</tr>
<tr>
<td><strong>Pancreas</strong></td>
</tr>
<tr>
<td><strong>Melanoma</strong></td>
</tr>
<tr>
<td>Tumor</td>
</tr>
<tr>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>Lung</td>
</tr>
<tr>
<td>Colorectal</td>
</tr>
<tr>
<td>Breast</td>
</tr>
<tr>
<td>Stomach</td>
</tr>
<tr>
<td>Lymph and blood producing system</td>
</tr>
<tr>
<td><strong>Oral-head-neck</strong></td>
</tr>
<tr>
<td>Pancreas</td>
</tr>
<tr>
<td>Prostate</td>
</tr>
<tr>
<td>Liver</td>
</tr>
<tr>
<td>Esophagus</td>
</tr>
<tr>
<td>Gallbladder</td>
</tr>
<tr>
<td>Bladder</td>
</tr>
<tr>
<td>Brain</td>
</tr>
<tr>
<td><strong>Altogether</strong></td>
</tr>
</tbody>
</table>
Mortality rate in Hungary from 1960 (percent change over 1960)
### Incidence changes of the six different common cancers leading to death in Hungary (1975-1999)

<table>
<thead>
<tr>
<th>Tumor</th>
<th>incidence</th>
<th>1975</th>
<th>1999</th>
<th>Increase %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral-head-neck</td>
<td></td>
<td>462</td>
<td>1618</td>
<td>250</td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td>4169</td>
<td>7883</td>
<td>89</td>
</tr>
<tr>
<td>Colon</td>
<td></td>
<td>3025</td>
<td>4912</td>
<td>62</td>
</tr>
<tr>
<td>Pancreas</td>
<td></td>
<td>1076</td>
<td>1562</td>
<td>45</td>
</tr>
<tr>
<td>Breast</td>
<td></td>
<td>1650</td>
<td>2381</td>
<td>44</td>
</tr>
<tr>
<td>Prostate</td>
<td></td>
<td>1196</td>
<td>1387</td>
<td>16</td>
</tr>
</tbody>
</table>
Onset of malignant transformation

The malignant transformation is not a single step, but it is believed to be a result of 5-10 subsequent somatic mutations (accumulating in the same cell). This is the so called multi-step theory.

Consequences:

• tumors develop more frequently with older ages

• there are inherited malignant tumor syndromes
All malignant tumors are monoclonal

Virtually all malignant tumors are of monoclonal origin.

All descendants of a single cell are called a **clone** in cellular biology. Members of a clone are genetically identical in theory.
Evidence for clonality of neoplastic cells

- Most tumor cells are monoclonal
  - Identical glucose-6-phosphate isoenymes in tumors of female patients (an X-linked enzyme).
  - All tumor cells may possess a specific chromosomal abnormality.
  - Unique rearrangement of immunoglobulin or T-cell receptor genes in lymphoid tumors.

- Tumor cell heterogeneity is common

- Clinical behavior is the best definition of malignancy
The progress of carcinogenesis (months, years)

Genetical instability

Apoptosis avoidance
TERT ↑
Bcl-2 ↑
p53 ↓

CAMs
E-cadherin ↓
integrins +/-

Cell cycle oncogenes
TSGs ↑

First mutation
Second mutation
Third mutation
Fourth mutation
Fifth mutation
Stages of the Development of Colon Cancer: Vogelstein Model

Normal colon epithelial cell (1 working APC copy) → Mutation in 1 copy APC tumor suppressor gene → Colon epithelial cell (1 working APC copy) → Mutation in 2nd APC gene (Loss of APC function) → Hyperproliferative epithelial cell → Early adenoma → Mutation in K-ras proto-oncogene (converts to oncogene) → Intermediate adenoma → Loss of DCC (18q) tumor suppressor gene function → Late adenoma → Loss of p53 tumor suppressor gene function → Carcinoma

A lymphoid metastatic cascade (immun-selection)

1. **PRIMARY TUMOR**
   - Lymphangiogenesis
   - Local Invasion
   - Matrix adhesion degradation
deposition

2. **10^9-11** tumor cell
   - Intravasation (lymphatic)
   - Subendothelial
   - Virtual BM
   - Matrix adhesion degradation
   - migration

3. **10^6** cells
   - Passive/active lymphatic transport
   - Intravasation (lymphatic)
   - Subendothelial
   - Virtual BM
   - Matrix adhesion degradation
   - migration

4. **10^2** cells
   - Cortical arrest /extravasation
   - Interactions with
   - antigen-presenting cells (dendritic)
   - immune-effectors (T cells, NK cells)

5. **LND**
   - Secondary growth
   - matrix adhesion degradation
   - migration

6. **LND**
   - Matrix adhesion degradation
   - migration
Tumor Progression and Heterogeneity

- Tumor progression is defined as the acquisition of permanent changes in characteristics of selected subpopulations of the tumor.
- The mutation rate of malignant tumors is higher than that of the healthy tissues. The original clone will give rise to subclones because of this (heterogeneity).

Why do some cancers appear to ‘accelerate’?
Why are the therapeutical results better:
  - with cases that have been diagnosed early?
  - after the first use of a chemotherapeutical drug, than after subsequent uses?
Cancer progression: Clonal selection due to therapy

neoplasm with heterogeneous cell population

selection pressure

selection of resistant cells, with subsequent expansion
Genes involved in malignant transformation

- Proto-oncogenes

- Tumor suppressor genes

- DNS repair genes

- Genes involved in apoptotic cell death
Oncogenes

Normal version is proto-oncogene
Normally induce cell proliferation
Gain of function variants more active
Act in dominant manner

Tumor suppressors

Normally inhibit proliferation, or
Induce apoptosis, or
Guard the stability of the genome
Loss of function variants exist
Act in recessive manner
Proto-onkogenes activated in a way that is not controlled

- increased expression in a new genomic region

- formation of fusion proteins that exhibit new function
Types of Normal Cellular Genes that are Homologous to Oncogenes

• Growth Factors
• Growth Factor Receptors
• G Proteins
• Kinases
• Gene Regulatory Phosphoproteins
Activation of proto-oncogenes

- **Point Mutations**
  - The ras gene is an oncogene that becomes activated by a point mutation.

- **Chromosomal Translocations**
  - Translocation of chromosome 9 and 22 in CML creating a fusion gene that produces an activated tyrosine kinase.

- **Gene Amplification**
  - Specific oncogenes such as N-myc and C-neu are amplified in neuroblastoma and breast cancer respectively.

- **Epigenetic mechanisms**
  - A gene control mechanism which is not coded in the DNA sequence. Such is eg. parental imprinting (gene expression depending on the parent’s sex).
  - The mechanism of imprinting is selective methylation of genes. (Methylated genes are not expressed.) Most malignant tumors seem to have less methylated genes, than healthy cells.
Activation of proto-oncogenes

- Proto-oncogenes are normal genes with required normal functions in development and/or homeostasis, that serve as precursors of genes that can gain the ability to be dominant-acting oncogenes

- Change in genetic coding sequence leads to new or accelerated biochemical activity
Activation of proto-oncogenes: mutation of small GTPases

Example: RAS

- Normal functions as a GTPase involved in signal transduction from cell surface receptors to the MAP kinase pathway
- Two variants H, K, commonly mutated in tumors
- Mutated in many kinds of cancers, particularly carcinomas
- Mutation results in inactive GTPase, GTP bound RAS protein stays in its active form
- Mutations are found in only a few codons, especially codon 12
Point mutations in \textit{K-RAS}

- Missense mutations in codons 12, 13 and 61 alter gene product activity

<table>
<thead>
<tr>
<th>codon number</th>
<th>DNA</th>
<th>amino acids</th>
</tr>
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<tbody>
<tr>
<td>9</td>
<td>GTT GGA GCT GGT GGC GTA-</td>
<td>val gly ala gly gly val-</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
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<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\text{mutation}

<table>
<thead>
<tr>
<th>9</th>
<th>GTT GGA GCT GAT GGC GTA-</th>
<th>val gly ala asp gly val-</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td></td>
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<tr>
<td>12</td>
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<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Activation of proto-oncogenes: 

**K-RAS** mutation

**Normal RAS**

\[
\text{RAS-GDP} \xrightarrow{\text{P}_i} \text{RAS-GTP} \xrightarrow{\text{GTP}} \text{GTP} \xrightarrow{\text{GDP}} \text{RAS-GDP}
\]

Regulated MAP kinase cascade

**Mutant RAS**

\[
\text{RAS-GDP} \xrightarrow{\text{GTP}} \text{RAS-GTP} \xrightarrow{\text{GDP}} \text{GTP} \xrightarrow{\text{GDP}} \text{RAS-GDP}
\]

Unregulated MAP kinase cascade

Increased cell proliferation
Activation of proto-oncogenes: activation of protein kinases

- **Example:** c-src
  - Normal function is tyrosine kinase that passes growth stimulatory signals
  - Mutation of C-terminal tyrosine removes inhibitory regulation resulting in highly active kinase in oncogenic viruses (v-src) and occasionally in tumors

- **Protein kinases are particularly important in growth signal transduction**
  - Receptor tyrosine kinases particularly important in cancer
Protein kinases and cancer

• About 500 distinct kinases in genome
• Many have altered expression in growing or malignant cells
• Many scientific careers have been made studying kinases
• Very few kinases have been found mutated in human cancers (MET, b-RAF)
• Several receptor tyrosine kinases are amplified in specific tumors (EGFR, ERBB2)
Targeted cancer therapy is focusing on protein kinases

- Kinases are inherently ‘druggable’
  - Drugs usually mimic ATP.
    Modified for specific kinases
- While uncommonly mutated in cancer, many oncogenic signals pass through signaling kinases such as AKT or ERK/MAPK
A krónikus mieloid leukémiás betegekben található „Philadelphia” kromoszómáról egy olyan fúziós fehérje képződik, amit eredetileg a 9. és 22. kromoszómákon elhelyezkedő gének kódolnak.
A c-Myc proto-onkogén átrendeződése a 8. kromoszómáról egy, a 14. kromoszómán elhelyezkedő nagyon aktív gén közelébe okozza a kórt.
DNA viral oncogenes

- True, viral encoded oncogenes
- Not analogues of mammalian genes
- Responsible for a few subtypes of human cancer
- Example: Human papillomavirus (HPV) in cervical and oral carcinoma
  - E6: Inactivates p53 tumor suppressor gene
  - E7: Inactivates RB tumor suppressor gene
- Also, SV40, JC, polyoma, EBV
HPV and cervical (and also ORAL) tumorigenesis

HPV virus infects normal squamous mucosa.

Condyloma/low grade dysplasia results.

Additional genetic hits cause high grade dysplasia to develop.

Additional genetic hits cause invasive carcinoma to develop.

Anti-HPV immunization may prevent 70-95% of cervical carcinoma in next two decades.
HPV is teaching us about tumor suppressor proteins p53 and pRb

Adenovirus and SV40 oncogenes also inactivate both p53 and pRb
Tumor Suppressor Genes

- A class of genes that normally suppress cell proliferation. Examples are p53 and Rb.
- Mutations that inactivate the tumor suppressor gene products can release cells from growth suppression and lead to hyperproliferation.
- Both alleles of the tumor suppressor gene must be inactivated by mutation for hyperproliferation to occur.
Inactivation of genes that inhibit cell proliferation (examples):

Cell cycle control by normal retinoblastoma (Rb) gene keeping cells in G1 phase. p53 gene induces apoptosis following DNA damage. Its mutation is frequent in cancers.

BRCA1 gene is important in tumor suppression and DNA repair, its mutation may lead to breast cancer.
Features of Retinoblastoma

• 1 in 20,000 children
• Most common eye tumor in children
• Occurs in heritable and nonheritable forms
• Identifying at-risk infants substantially reduces morbidity and mortality
The role of Rb protein in cell cycle regulation

- RB Dephosphorylation
- RB Phosphorylation
- G0
- Programed cell death

Diagram:
- Cyclin B/A + CDC2
- Cyclin A + CDK2
- Cyclin D1s + CDK2 CDK4
- RB Dephosphorylation
- RB Phosphorylation

Cell cycle phases:
- G1
- S
- G2
- M
# Nonheritable vs Heritable Retinoblastoma

<table>
<thead>
<tr>
<th>Feature</th>
<th>Nonheritable</th>
<th>Heritable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor</td>
<td>Unilateral</td>
<td>Usually bilateral</td>
</tr>
<tr>
<td>Family history</td>
<td>None</td>
<td>20% of cases</td>
</tr>
<tr>
<td>Average age at dx</td>
<td>~2 years</td>
<td>&lt;1 year</td>
</tr>
<tr>
<td>Increased risk of second</td>
<td>No</td>
<td>Osteosarcoma, other sarcomas, melanoma,</td>
</tr>
<tr>
<td>primaries</td>
<td></td>
<td>others</td>
</tr>
</tbody>
</table>
Knudson’s “Two-Hit” Model for Retinoblastoma

Normal
2 intact copies

Predisposed
1 intact copy
1 mutation

Affected
Loss of both copies

Modified from *Time*, Oct. 27, 1986
p53 tumor suppressor gene

• Perhaps the most commonly mutated gene in human cancer
• A nuclear phosphoprotein with transcriptional regulatory function
Normal p53 pathway for control of cell apoptosis in breast cancer

- DNA damage
- Increased p53
- G1 arrest for DNA repair
  - Apoptosis if DNA not repairable
  - Cell cycle continues if DNA repaired
Mutant p53 pathway leading to prevention of cell apoptosis in breast cancer
p53 protein paradox

• Wild type p53 protein does not have high levels of expression and has a short half life
  – Not usually detected by immunohistochemistry

• Mutant p53 protein, while inactive, has a longer half life
  – Increased cellular accumulation allows detection by immunohistochemistry

In other words: when p53 is visible, p53 function is absent!
Normal p53 function

Normal p53 dimers
(unstable, present at very low level in cell)
Activated p53 function

Stimulated normal p53 dimers make tetramers, bind DNA, and induce gene expression that results in apoptosis and cell cycle blockade (Stabilized p53 present at high level in cell transiently)
Mutant p53 Function

Mutated p53 dimers make tetramers with normal p53. These do not bind DNA or transcribe the ‘usual’ p53 promoters. (Mixed p53 tetramers are present at high level in cell permanently)
p53 immunohistochemistry
**p53 gene function**

- **Oxidative stress (Hypoxia)**
- **Genotoxic stress (DNA damage)**
- **Pro-replication stimuli**
- **Transcription factor**
- **Induction of redox genes**
- **Apoptosis (induction of pro-apoptotic genes)**
- **Inhibition of cell cycle (induction of \textit{p21(cip1/waf1)} genes)**
- **DNA repair (induction of repair genes)**
- **Inhibition of cell cycle (induction of repair genes)**
- **Direct role in DNA repair mechanisms**
- **Direct role in chromosome segregation**

- **Induction of repair genes**

- **Apoptosis**
  - (-) inhibition
  - (+) induction

- **Induction of redox genes**
  - (-) inhibition
  - (+) induction

- **DNA repair**
  - (-) inhibition
  - (+) induction
p53: guardian of the genome

DNA damage (radiation, chemotherapy) sensor

- High DNA damage: Die by apoptosis
- Low DNA Damage: Repair damage and survive

Cell cycle

- S phase
- M phase
- G1 phase

Cell Death

Wild type p53
Programmed cell death, apoptosis inhibited (ie blc-2 gene) and induced (ie bax, p53 genes) by a number of genes. Their functional amplification or ablation significantly affect cell survival or death.
microRNAs

• Rapidly emerging field
• Certain, but complex mechanisms of gene expression control
• Some miRNAs (e.g. miR15) have associations with cancer
Steroid hormone receptors in cancers

• Cancers arising in hormonally-responsive tissues often retain a hormone-responsive proliferation drive
  – “normal”
  – increased hormone sensitivity
• Hormone receptors tend not to be mutated as oncogenes in early tumor progression
• Anti-hormone therapy is however effective in treating hormonally-responsive tumors
  – Anti-estrogen therapy in breast cancer
  – Anti-androgen therapy in prostate cancer
Steroid hormone receptors in cancers

- Abnormal levels of hormones may predispose to cancer due to increased cell replication
  - Breast cancer, endometrial cancer
  - Hormone drive may be endogenous or exogenous
Steroid hormone mechanism

Steroid hormone binds to the cytoplasmic steroid hormone receptor. The hormone/receptor complex translocates to the nucleus. In the nucleus, the complex binds DNA and regulates transcription.
Oral cancer

Genetic determination

Environmental factors

Life style

Smoking

Alcohol
Genetic types or oral cancer - four distinct categories
HNC=head and neck cancer

<table>
<thead>
<tr>
<th>Genetic marker</th>
<th>HNC1</th>
<th>HNC2</th>
<th>HNC3</th>
<th>HNC4</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P53 mutation</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9.chromosome deletion</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>(ARF/INK4A/B)</td>
<td>(+)</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>EGFR</td>
<td></td>
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</tr>
</tbody>
</table>
P16 tumor suppressor gene inactivation in oral cancer

Methylation
(epigenetic)

Methylation frequency:
- **65%**

Mutation
(genetic)

Mutation frequency:
- **5%**

LOH
(loss of heterozygocity)

LOH frequency:
- **30%**
Therapeutical approaches

Classical methods
- surgery
- chemotherapy
- irradiation

New methods
- immunotherapy
- inhibition of angiogenesis
- gene therapy
Cellular and biochemical processes of successful angiogenesis
Angiogenic stimuli for tumor neovascularization in breast cancer
Angiogenesis

• Cells require blood vessels to carry oxygen and nutrients

• Cancers must either grow along existing vessels or create new ones
Angiogenesis

- Many cancers secrete angiogenic cytokines
  - Vascular endothelial growth factor (VEGF)
  - Basic fibroblast growth factor (bFGF)
  - Platelet derived endothelial cell growth factor (PD-ECGF)

- Stimulate endothelial cell proliferation, migration, vessel formation and vessel maintenance

- Anti-angiogenesis therapy may be a useful way of controlling cancer
Angiogenesis

- Tumors can grow to a **maximum size of 1 mm** without their own blood supply (in situ carcinoma)
- Several tumors produce materials stimulating or inhibiting angiogenesis. The primary tumor can inhibit the growth of metastases or the growth of other tumors
- Inhibition of angiogenesis, and therefore tumor growth can be achieved by inhibition of endogenous angiogenesis promoters (ie. VEGF), or stimulation of endogenous angiogenesis inhibitors (ie. angiostatin, endostatin).
Gene therapy 1

Proteins to change the target cell activity

Target cell

nucleus

Target nucle

adenovirus

adeno-associated virus

retrovirus/lentivirus

naked DNS
Gene therapy 2

adeno-associated virus

adenovirus

retrovirus/lentivirus

naked DNS

nucleus

Target cell

Proteins to affect other cells
Examples of using gene therapy to treat malignant tumors

- Reintroduction of the normal copy of an inactivated tumor suppressor gene (would need 100% efficacy)
- Introduction of genes coding for antigens, cytokines to enhance the immune response
- Introduction of a gene causing toxicity (thymidine kinase gene + gancyclovir treatment)
- Treatment with artificial virus (cytopathogenic adenovirus, that can infect only cells deficient of p53 or Rb)
Treatment of oral-head-neck cancers by application of Onyx-015

- p53 + cancer cell
- No virus replication → sensitivity to chemotherapy
- Cell lysis
- Virus replication
- p53 - or mutated cancer cell
- Onyx-015, no E1b gene
- Chemotherapy
Treatment of neck cancer by use of Onyx-015
Cancer therapy – future perspectives?

Targeted oncolytic virus

+ Anti-angiogenesis transgene