MEDICAL GENETICS

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MEDICAL GENETICS

ONCOGENESIS

What is oncogenesis?

It is a complex of mechanisms by which normal hemopoietic cells become malignant.

This is a process in which there is increased cell proliferation and survival **without differentiation.**

Chromosomal abnormalities play a very important role in oncogenesis, i.e. numerical or structural

This process of oncogenesis may be induced by some factors such as;

1. **Gene activation**: transformation of pro oncogenes to oncogenes
   Two types of gens play a role in oncogenesis; oncogenes and tumor suppressor genes. So as a result of activation they become oncogenes and thus increase cell proliferation and survival
2. **Tumor suppressor genes:** these control cell growth and regulate cell cycle. If they are mutated, the result is no control.
3. **Activation of anti-apoptosis**:
4. **Replication:** acquire ability to keep dividing: in normal cells, the ends of chromosomes becomes weak, but the enzyme telomerase make the ends of these chromosomal ends stronger. Thus cancer cells become immortal because the action of telomerase continues.
5. **Intra cellular signaling**: the role of signaling within cells is very important in tumor growth and development. That is there is no proper communication within the cells

CLASSIFICATION OF ONCOGENES

ONCOGENES ARE SUBDIVIDED INTO 3 GROUPS

a) Proliferation enhancers (these a substances that enhance, increase or eliminate. In our case they increase cell proliferation

b) Cell survival enhancers
c) Cell death suppressors

CELL PROLIFERATION ENHANCERS

1. GROWTH FACTORS: such as proteins, hormones and oligo-peptides. These stimulate growth of cells, e.g. erythropoietin.
2. GROWTH FACTORS RECEPTORS
3. CYTOPLASMIC SIGNAL TRANSDUCERS (they connect the receptors to the nuclear factors
4. NUCLEAR SIGNAL TRANSDUCERS

BIOLOGY OF LUEKEMIA

The leukemic process can begin in a single normal cell of any lineage or origin and at any stage of the cells differentiation. This defect or mutation can be intrinsic (inside the cell) and it's inheritable by its progeny.

Leukemia's have two important characteristics

1. Hematological malignancies are clonal, i.e. arise from one single cell
2. Leukemia develop by a multi-step process. The mechanism of for the cause of leukemia is still not known.

Factors that are involved in the development of leukemia's

1. **Genes**: they play a very important role in the development of malignant transformation of cells.
2. **Mutagenic chemicals**: the % of cancer increases with exposure.
3. **Radiation:** this can be from the sun or from radioactive materials. The % of development increases with the type of skin an individual has.
   Two types of radiation: UV light and x-rays. X-rays produce free radicals which damage DNA
4. **Infective agents:** these can be bacterial or viral infections. These are severe infections.

DIFFERENCES BETWEEN CANCER CELLS AND NORMAL CELLS

1. **Cancers are immortal**: unlimited cell division unlike human cells which have a limited life span.
2. **Cancers cells are transformed:** they are capable of growing and survive in physical and chemical environment where normal cells cannot survive. They acquire new properties.
3. They progressively lose their biochemical and genetic similarity to their normal ancestors.

GENETICS AND CANCER

According to statistics, some forms of cancers affect more than 30% of human populations. It causes 20% of human deaths and in developed countries is responsible for more than 10% of the total cost of medical care.

THE GENETIC BASIS OF CANCERS

I. Cancer is truly a genetic disease

(Remember that this is not hereditary or congenital but the genes are involved)

II. Different genes in cancer process and these are genes encoding some proteins.

What kind of proteins;

I. Proteins involved in cell proliferation
II. Proteins involved in the regulation of mitotic cycle.
III. Components of programmed cell death mechanism e.g. apoptosis or anti apoptosis
IV. Proteins responsible for detecting and repairing mutations.

DIFFERENT TYPES OF MUTATIONS ARE RESPONSIBLE FOR CUASING CANCER

1. Mutations can activate proto oncogenes to oncogenes. Proto oncogenes are cellular progenitors of oncogenes.
2. These mutations can inactivate tumor suppressor genes. TSG control and regulate cell cycle. If inactivated, they can't control cell growth and regulate cell cycle.
3. Some certain mutations have chromosomal translocation cause confusion of genes or create genes with new functional properties.

HOW CANCER DEVELOPS

Cancer develops by accumulating additional genetic damage due to mutations or by silencing the genes which detect and repairing mutations.

Difference between spontaneous mutations and cancer causing mutations

1. Strong and aggressive increase and survival proliferation and survival of cells
   This is phenotypic and characteristics of cancer cells, uncontrolled and excessive proliferation of cell.

TUMOR SUPRESSOR GENES

They regulate cell growth and block tumor development. If there are mutations in TSGs there is:

i. Uncontrolled cell division
ii. Abnormal cell growth
iii. Defective apoptosis

TSGs and their products are by nature protective against cancer.

CHARACTERISTIC OF ONCOGENES

These are genes responsible for cell proliferation, survival and differentiation. They constitute the normal genetic makeup of cells.

PROTO ONCOGENES

The basic model, cell proliferation, cell differentiation and cell death have some rules

1. Cell proliferation must be strictly controlled
2. Balance must be achieved between cell loss and cell replacement.
3. This basic model: is under the control of genes which regulate cell proliferation, cell differentiation and cell death.
4. Genes which control cell growth may increase cell proliferation suppress cell proliferation and they can increase cell death.
5. These genes are part of the normal genetic makeup of cells

There is a connection between **activation of oncogenes** or **inactivation of TSG** and the disturbed balance between proliferation and differentiation and this is characteristic of malignancy.

Inactivation of TSG leads to increase cell proliferation but the cells do not differentiation. i.e. the cells remain in the same state that they were during their

Multiple or few alteration in one oncogene or changes in two or more oncogenes or TSG leads to fully malignant phenotype.

The activation of proto oncogenes in human leukemia's can result from process or factors

1. Mutations can lead to some consequences
    I. Production of proteins with new biochemical properties
    II. Productions of proteins which increase existing pro
    III. Some mutations can lead to the loss of function of proteins
2. Point mutations
3. Gene amplification which is the production of additional copies of a particular DNA sequences which maybe extrasomal.
4. Chromosomal translocation which can cause confusion of genes or the production of wrong proteins.

TUMOR SUPPRESOR GENES ARE DIVIDED INTO TWO GROUPS

1. Gate keepers which regulate cell cycle and growth.
2. Care takers: they are responsible DNA damage repair

IDENTIFICATION OF TSG'S

The 1st research of activity of TSG's was done by **Henry Hairs In 1969**. They concluded that some genes derived from the normal cells maybe TSG's. The 1st TSG discovered was Rb (retinoblastoma gene) this is a very rare childhood eye tumor. If it is discovered in early stages has good prognosis. If parents are affected by Rb 50% of the children will have it. It is inherited as a dominant gene. In 1971, Alfred k. they discovered that the development of Rb tumor caused by two mutations and these mutations lead to the loss of activation of TSG's. There is two types of Rb: inherited and non-inherited

Non-inherited Rb

This is rare because it need two mutations that are not inherited, Rb will need two independent somatic mutations which cause Rb.

Inherited Rb

Inherited Rb, the Rb affected allele that is one, genetically transmitted and the second allele must have a somatic mutation.

Tumor development results from loss of normal Rb alleles in the tumor cells.

Gene experiments also demonstrated that insertion of normal Rb gene in Rb cells which are affected changes its characteristic to the better and this the evidence of activity of Rb gene as a TSG. The study also show that Rb TSG's gets inactivated or mutated in many cancers such as breast cancers.

P53

Is inactivated or mutated in many cancers such as; leukemia's, lymphomas, sarcomas and carcinomas and in many types of brain tumors. 50% of cancers which develop involve the inactivation of p53.

Other TSG's include INK 4, APC and DCC

FUNCTIONS OF TSG

The proteins encoded by TGs inhibit cell proliferation. The products of Rb and INK 4 TSG's inhibit cell proliferation. But the products of p53 TSG's regulate both cell cycle and apoptosis. Because of these two functions, p53 is a very powerful TSG's.

Loss of p53 activity leads to the increase of number or frequency of mutations and leads to general instability in the cell genome and such genetic instability is a common characteristic of

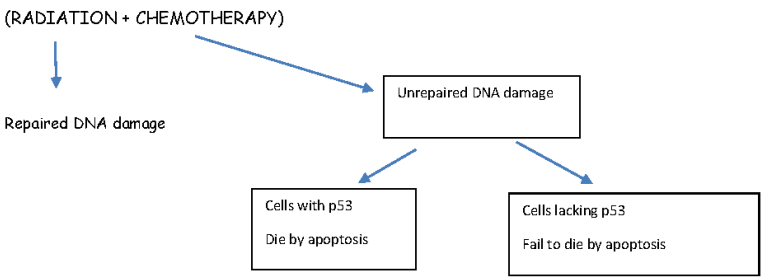
cancer cells and it may contribute to further alteration and changes in oncogenes and TSG's during tumor progression.

DNA DAMAGE

If the DNA damage is not repaired the cells containing the unrepaired DNA are eliminated through apoptosis because these cells have a potential to produce cancer.

Cells which lack in p53 fail to die in apoptosis because p53 helps to induce apoptosis. Usually cells which lack p53 and fail to die in apoptosis are due to the effects of radiation, drugs such as chemotherapy. This apoptosis failure in response to DNA damage contributes to the resistance of many tumors to chemotherapy.

AGENTS WHICH DAMAGE DNA



The development of cancer is a multi-step process in which normal cells transform into malignant cells

Two genes are involved. Oncogene activation or inactivation or mutations in TSG's.

Multiple damage to the genes final leads to increased proliferation of cells and this is characteristic of phenotype of cancer cells.

The role of multiple genetic damage or defects is best demonstrated in the case of colon carcinoma which have been studied by Bert Vogelstein. He found out that there are 3 TSG which are involved in the development of colon carcinoma which are, APC dcc and TSG.

I. mutation or inactivation of APC

II. there is mutation in the RASK and this causes early adenoma

III. mutations in the dcc which causes late adenoma

IV. The last TSG to be mutated is p53

Accumulated damage to both TSG and oncogenes appear to be responsible for the development of other types of cancers including breast and lung carcinomas. The progressive of growth control is characteristic of cancer cells and is the result of abnormalities of multiple genes that normally regulate cell proliferation, cell differentiation and cell survival.

THE HUMAN GENOME PROJECT HGP & GENE THERAPY

Application of human genome project in health and the consequences of the HGP and research

CONSEQUENCES OF THE HUMAN GENOME PROJECT

The 1st researcher who come up with the ideal of HGP was Renato Dulbecco. The end of 20th century and the beginning of 21st century was the time for completion of the human genome project and it was an international effort to determine the complete content of the human genome.

The ideal of HGP was born in 1977 but the HGP started in 1990 and it took 15 years. The main goals for HGP

I. to find from 80,000-100,000 of human genes
II. To determine the sequence of 3 billion chemical bases of human DNA.

The HGP was directed by Ari Patrinos. He was the head of office of biological of environmental

In 2003, the HGP was almost finished but some research was still on going. In May 2006 researchers completed DNA sequences for the last of the 23 pairs of human chromosomes. After this, the final papers of the HGP were published.

In this final paper it was published that human beings are in the process of some situations

I. we are in the process of taking control of life
II. shaping our future
III. receiving the power to predict and plan of our human lives in ways which never before happened
IV. we will produce new species
V. diagnose illness long before it happens
VI. Manipulate our reproductive process and change us (embryo cloning)

THE MAJOR GOALS OF THE HUMAN GENOME PROJECT

I. To identify 80 -100 thousand human genes in human DNA and determining the sequence of 3 billion base pairs

II. Store this information in data bases

III. Transfer related technologies to private sector

IV. Address the ethical, illegal and social issues (ELSI) which arise from the HGP.

V. Construction of genetic maps of the HG

VI. The production of variety of physical maps of selective organisms

THE TECHNICAL ASPECTS OF HGP

The process of determining the HG INCLUDE two steps

I. **Physical map:** this includes the characteristics of chromosomes

The chromosomes are divided into different fragments and they then characterize and analyse these different fragments. Then after this is done, they send the fragments into the previous chromosomal location

II. Genetic maps: This is determination of the DNA bases on the chromosomes

GENETIC MARKERS

These are any inherited physical or molecular characteristics that are different among individuals in the population.

It's very important in solving crime cases with blood sample or semen (CSI)

Are genetic mark in this cases shows a relative locations of these specific markers on chromosomes.

APPLICATION OF HGP TO PHYSICAL MAPS AND GENETICS MAPS

Scientist found out that chromosomes in the human population differ at about 0.1%.this % is small but helps understand the discovery and difference genetic disorders.

1. The cloning of genes responsible for muscular dystrophy, and retinoblastoma, CF and SCD.
2. Details of some genomic mas gives chance to find the genes associated with fragile x syndrome, the types of inherited colon cancer and familial breast cancers.
3. Also if scientist can isolate other diseases related genes, there is a possibility to understand very important few genetic disorders such as; cancer, cardiovascular and diabetes. This can lead to better medical care and medical management of these diseases and also pharmaceutical discoveries.

The human genome project improve human and medical genetics by understanding of many diseases and improving the diagnosis of such diseases in the future.

Human genome project made it possible to:

1. **To get the complete sequence of all human DNA**
2. **To identify and characterize all human genes**
3. **To determine how variations in these genes contribute in health and disease.**

Medical and human genetics play an important role in diagnosis, treatment and management of many hereditary disorders, that is why it is important to understand the principles of human and medical genetics.

PRINCIPLE OF HUMAN AND MEDICAL GENETICS

1. The importance of interconnection between genes and environment during disease.
2. The role of somatic mutations in cancer and aging.
3. The possibility of pre-natal diagnosis and population screening
4. The promise of powerful gene therapies
5. Preventing of a big group of disorders such as; Parkinson disease, diabetes, haemophilia etc.

One aspect of medical genetics does not only focus on the single patient but also on the family of this individual or patient because familial history is important

BENEFITS AND IMLICATIONS OF HGP

Some potential aspects of genome research include;

i. **Molecular medicine:**
   a. improve diagnosis of disease
   b. early detection of predisposition to dx
   c. drug design
   d. gene therapy and control systems for drugs

ii. **Energy sources and environmental aspects**
   a. Use of microbial genomics research to create new energy sources i.e. bio-fuel
   b. Use microbial genomics research to develop environmental techniques to detect pollutants.
   c. Use microbial genomic research for safe environmental correction

iii. **Risk assessment**
   a. Asses health damage and risk caused by radiation, including low dosage radiation

b. Assess health damage and risks caused by mutagenic chemicals and cancer causing toxins.
c. Reduce the possibility of negative mutations

iv. **Bio archaeology, anthropology, evolution and human migration.**
a. Study evolution through germline mutations
b. Study evolution of the X chromosomes and migration of females
c. Study evolution of Y chromosome and migration of males
d. Compare aspects in the evolution of mutations with ages of populations

v. **DNA forensic or identification.**
a. Identify potential suspects whose DNA may match evidence left at crime scenes.
b. To prove the innocence of people wrongly accused of crimes.
c. Identify crime and catastrophic victims
d. Establish paternity and other family relationships.
e. Identify and protect the species in the wildlife
f. Detect bacteria and other organisms that may pollute, water, soil and food
g. Match organ donors with recipient's in organ transplantation services.

vi. **Agriculture livestock and breeding…**
a. Produce disease resistant crops
b. Healthier and productive dx resistant animals
c. Bio-pesticides
d. Vaccines induced into food products

To achieve these goals of the hgp, researchers study genetic makeup of several non-human organisms which include bacteria such as E.coli. Others include fruit flies, mice and rats

- Up to today the exact number of human genes is not known. In April 2003, about 26,000 genes were identified
- 150,000 human genes. E.g. Y chromosomes which is present only in mails was identified in 2003, X chromosomes was identified in March 2005.
- Chromosome 4 and 2 were identified in April 205
- In January 2006, they identified chromosome 8 and then in March they identified chromosome 11, 12 and 15 and then in April 2006, they identified chromosome 3 and 17.

LIST OF SOME RESULTS EXPECTED ACCORDING TO HGP 2020.

I. More effective pharmaceuticals.

The complete list of human genome products will give scientists a possibility to create new drugs for the human beings. In 2000, there were about 500 new drugs created. In 2020, 3000 new drugs will be created to enable disease treatment. In 2020, our medical report will include our complete genome and this complete genome will predict our response to certain drugs, and response to the environmental substances. In 2020 more effective drugs will be developed with individual genetic profile, because according to the statistics 100,000 people die due to side effects of drugs e.g. heart abnormalities and hormone regulatory drugs such HRT because they cause muscle damage in certain individual. Anti-depressants can cause nervous system damage in certain individuals.

THE AIMS OF BETTER PHAMACUETICALS

- To create new drugs, to treat different diseases
- To eliminate dangerous side effects of certain drugs
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II. SOCIAL AMPIFICATION

- Your medical info will be maybe available for the people
- Some people are in danger of developing diseases in the future- this has an implication on people in such a way that some people may not be employed because of the disease that the person will develop.
- Family relationships maybe affected – some people would not want to marry someone with a disorder.
- Insurance policy cannot be given to people with certain genetic disease

III. GENETIC TESTING THERAPY

- Gene therapy for single gene disorders will be successful after 2020. E.g. CF and SCA
- Certain disease associated genes will be replaced with normally functioning genes and several 100 diseases will be curable because of the genes.
- Neonatal genetic testing for some conditions will be an ordinary procedure.
- Scientists are going to grow simple organs or parts of more complicated organs for transplantation (tissue engineering). This is because organ donating is complicated and expensive- as for an organ to be donated the

person has to die, get permission from the relatives and the organ should also match etc.

In 2020, the cloning of certain organs and tissues will be possible.

CLONING

There are 3 types of cloning

i. Recombinant DNA technology or DNA cloning or molecular cloning
   It is the transfer of DNA fragments from one organism to a self-replicating genetic element such as bacterial plasmid. This technology is very old and very popular in molecular biology laboratory

ii. Reproductive cloning: this is a technology which is used to generate or create an animal which has the same nuclear DNA as another previously existing animal. Farmers used in animals and plants

iii. Therapeutic cloning or embryo cloning: the aim was the production of a human embryo for research. Not to create human beings but to get stem cells and use them in research and disease treatment.

SUICIDE GENES (GENE THERAPY)

- In genetics suicide genes will cause a cell to kill itself through apoptosis.
- The presence of suicide gene is good because it is a potential way of treating cancer and proliferative disorders
- Making cancer cells to chemical therapy.
- The goal of cancer therapy with the use of suicide genes is complete elimination of all cancer cells and leaving non cancer cells unharmed.
- In 2020, the HGP thy have promised to build a functioning cell with free living existence

HGP CONSQUENCES

- The ethical issues which are raised by the hgp can be divided into two
  1. Genetic engineering
  2. Genetic information

GENETIC ENGINEERING

- The difference between somatic cells and germline intervention- meaning passing or not passing to the future generation.
- The difference between therapeutic and improving gene engineering. These can case an imbalance in the natural functioning of the body.
- In case of screening for diseases, ethical questions such, personal privacy.
- New born genetic testing. What kind of test are going to the new born baby. If the test is expensive some people can afford while others cannot. If the diagnosed disease is untreatable how will parents live with that? What kind of people will have access to these test?

ETHICAL, LEGAL AND SOCILA ISSUES OF THE HGP

- In 2001, the embryo survived this process, and after divided sex cell, the embryo died.
- Another potential application of cloning to organ transplantations the creation of genetically modified pigs, from these pigs, organs or tissue can be harvested for use in human beings.
- Xenotransplantation's the transplantation of organ or tissue from animals to humans
- Reproductive cloning is extremely expensive and difficult. More than 90% of cloning fails to produce offspring because more than 100 nuclear transfer produce will be required to produce on clone. Cloned animals have very weak immune system and a susceptible to infections. They do not live for a long time since they die very young, scientist are not able to see how they age die.
- Cloned animas die mysteriously. E.g. first cloned sheep died mysteriously in the first few weeks after being cloned.
- In 2002, scientist showed that 4% of genes in cloned mice had different functional abnormalities and this did not come from mutations but they came from changes in the normal activation of genes.