Slide 1

I would like to start my lecture on Chapter 1 Genomic Abnormalities and Cancer in this course on the Basics of Genomic Medicine and Cancer Genomes.

Slide 2

In this chapter, I will give teach you the basics of “What is cancer?” and “What is a genome” and I will explain about Genomic Abnormalities and Cancer.

Slide 3

To start off with, “What is cancer?”

Slide 4

In Japan today, the average lifespan for men and women is over 80 years. One out of every 2 people is diagnosed with “cancer” and 1 out of every 3 people dies from “cancer.” Therefore, “cancer” is a national affliction affecting modern Japan.

Slide 5

So why is the number of cancer patients continuing to increase? This graph is from a study on the incidence of colon cancer per 100,000 women in the UK, and it shows the incidence of colon cancer by age group. As you can see, the incidence of colon cancer rises sharply over the age of 60 と the incidence of colon cancer. The accumulation of genetic abnormalities or mutations with age is passed on at the cellular level. As a result, the risk of developing cancer increases.

Slide 6

Cancer is a malignancy that haphazardly grows, invades, and metastasizes inside the body, leading to the death of the individual. Cancer invades and metastasizes to surrounding tissue. This is the predominant characteristic of cancer.

Slide 7

Why does cancer grow chaotically and haphazardly? In normal cells, signaling relays are induced pursuant to an order to proliferate issued by other cells, and cells proliferate. Expression of a gene and its translation into a protein is strictly controlled by the number of receptors on the surface of a cell receiving an order to proliferate. The number or size of cells in tissue is strictly managed via this control.

Slide 8

Cancer cells, however, issue their own order to proliferate and then proliferate when that order is received, or the number of the number of receptors receiving an order to proliferate increases, or cells proliferate as a result of the production of a mutated receptor that is constantly activated independent of any order to proliferate. In addition, a genetic mutation can cause a signaling molecule downstream of a receptor to remain activated independent of any order to proliferate. This is because abnormalities in signaling pathways occur in cancer cells, and those cells proliferate continuously and faster than normal cells. Thus, cancer cells proliferate autonomously, chaotically, and excessively.

Slide 9

Unlike a benign tumor, the predominant characteristic of cancer is that it invades surrounding tissue and often metastasizes to other organs. If invasion by or metastasis of cancer could be inhibited, then outcomes of cancer treatment should improve.

Slide 10

In addition, cancer cells have various characteristics unlike those of normal cells. These include the acquisition of autonomous growth signaling, avoidance of growth-inhibiting signaling, avoidance of apoptosis (programmed cell death), acquisition of the capacity for unrestricted growth, induction of angiogenesis, acquisition of the ability to invade cells and metastasize, induction of genomic instability, mutations, and tumor-promoting inflammation, avoidance of destruction by the immune system, and reconfiguration of energy metabolism.

Slide 11

You've recently heard the term "genome," but what does it mean?

Slide 12

A genome is a combination of the German word for gene, which is also gene, and the Greek suffix -ome, meaning body, to refer to a body (or set) of genes. A genome is all of the genetic information for an organism included in its chromosomal DNA.

Slide 13

Each of the 37 trillion cells that make up our bodies contains the human genome, which is made up of 3.2 billion letters (base pairs) of DNA.

Slide 14

And what exactly is deoxyribonucleic acid, or DNA?

Slide 15

DNA is genetic information found in a cell nucleus. DNA comprises all of the genetic information that makes up humans and other organisms. It has a double helix structure as a result of complementary base pairing. The double helix structure of DNA is known to facilitate the accurate replication of DNA. The base adenine forms a hydrogen bond with the base thymine, and the base cytosine forms a hydrogen bond with the base guanine. These complementary base pairs create a double helix structure.

Slide 16

The nucleus of human cells contains DNA that is about 2 meters in length. DNA is tightly wound around histone proteins and tightly folded into chromosomes.

Slide 17

Typically, human diploid cells have 22 pairs of homologous chromosomes and 1 pair of sex chromosomes, for 46 chromosomes in total. Genomic information is found in those chromosomes.

Slide 18

DNA is information to produce proteins that serve various function and facilitate biological activity, and that information is written in genes. There are around 24,000 genes in the human genome.

Slide 19

When genetic information from DNA in the cell nucleus is transcribed into messenger RNA, the double helix structure of DNA unwinds. Genetic information from DNA is transcribed into messenger RNA by RNA synthase, using a single strand of DNA in the nucleus of cells as a template. The letters (base pairs) used to do this are not A, G, C, and T but A, G, C, and U; U stands for the base uracil.

Slide 20

Messenger RNA that is transcribed in the cell nucleus migrates to the cytoplasm via nuclear pores, and it is translated into proteins, which are one or more chains of amino acids, by ribosomes.

Slide 21

In ribosomes, each 3-base sequence of messenger RNA, known as a codon, is translated into an amino acid.

Slide 22

The genetic information written in DNA is transcribed into messenger RNA. Information from messenger is translated into proteins, which are one or more chains of amino acids. This is known as the central dogma of gene expression, and it a basic rule for organisms, though there are exceptions like retroviruses.

Slide 23

Results of analyzing the human genome were reported in 2004. There are 22,000 human genes, which is less than the anticipated 100,000. Humans have about the same number of genes as sea urchins but fewer genes than rice. Accordingly, the expectation that humans surely had significantly more genes than other organisms was clearly wrong. Over 90% of the human genome consists of non-coding DNA, and its biochemical activity is actively being analyzed. Mapping the human genome took 13 years and cost a massive 3 billion dollars. Now, however, it can be analyzed in about 1 week at a cost of 500,000 yen.

Slide 24

What made this possible was scientific and technological advancement brought about by a dramatic improvement in the speed of DNA analysis. Technology for DNA analysis is advancing every day.

Slide 25

Next, I will explain the association between Genomic Abnormalities and Cancer.

Slide 26

Biological activity depends on cell activity. Cell activity depends on protein functioning. Protein functioning depends on amino acid sequences. And amino acid sequences depend on base sequences in genetic DNA. DNA is a blueprint. Thus, if the code of DNA changes, then cell activity can also change.

Slide 27

DNA sequences, gene locations, and the number of chromosomes are stringently controlled to maintain the stability of genomic information. Over 100 genes help to maintain genomic stability by controlling mechanisms of DNA repair, the mechanism of chromosome segregation, and the functioning of cell cycle checkpoints.

Slide 28

So, does one’s genome never change during one’s life?

Slide 29

A large amount of DNA located in chromosomes is accurately replicated when cells follow precise steps and processes known as the cell cycle. A cell divides into 2 daughter cells that are genetically the same. The cell cycle always proceeds in 4 stages — G1, S, G2, and M, and there are cell cycle checkpoints after each stage.

Slide 30

However, gene mutations can occur as a result of an error in DNA replication during cell division, damage to DNA or an error in replication as a result of exposure to radioactivity or a chemical substance, and chromosomal damage. Genetic mutations constantly occur in various cells of the body, but normally those mutations are corrected before they are passed on to future generations of cells. However, the cellular mechanisms for repairing damaged DNA can be disrupted and the capacity for repair diminishes with age. As a result, mutations accumulate.

Slide 31

A mutation in DNA can cause a base to change, thus causing an amino acid to change, translation to stop, or causing an abnormality in an amino acid sequence. If, for example, cytosine changes to thymine and the codon still codes for glycine, then the amino acid sequence will not be affected, resulting in what is known as a silent mutation. If, however, guanine changes to adenine, then the encoded amino acid will change from glycine to serine. Such a mutation is referred to as a missense mutation. In addition, adenine can change to thymine, creating a stop codon. Such a mutation is known as a nonsense mutation. Deletion or insertion of a base can cause a missense mutation or a nonsense mutation.

Slide 32

Thus, a mutation in DNA can cause a base to change, thus producing an abnormality in an amino acid sequence. In such an event, a change in an amino acid sequence will cause the structure or function of a protein to change, which is certain to affect cell activity and the individual.

Slide 33

So how are gene mutations linked to the development of cancer?
Does this apply to all 24,000 genes?

Slide 34

We now know that abnormal cell proliferation is induced by the activation of cancer genes known as

oncogenes that serve to accelerate cell growth and by the inactivation of tumor suppressor genes that slow down cell growth.

Slide 35

Moreover, we know that tumor suppressor genes responsible for apoptosis, mechanisms of DNA repair, the mechanism of chromosome segregation, and the functioning of cell cycle checkpoints are inactivated, inducing genomic instability. This is closely related to the malignant transformation and progression of cancer.

Slide 36

The instability of a cancer genome as a result of the accumulation of gene abnormalities leads to chromosomal instability.

Normal cells, like those in the photo on the left, have 46 chromosomes. However, colon cancer cells, like those in the photo on the right, have 70 chromosomes and various abnormalities in parts of those chromosomes, such as deletions and translocations. We now know that genomic abnormalities cause the development and malignant transformation of cancer.

True or false?

・Genetic information in every cell is processed in the following order: DNA→RNA→protein. This basic principle is known as the central dogma. (Answer: True)

・Genes consist of a regulatory region and coding region. Mutations in the former after the gene's products and mutations in the latter alter the gene's expression. (Answer: False)

・Cancer is a disease of the genome at the cellular level. (Answer: True)

・Patients can be expected to develop increased sensitivity to chemotherapy targeting DNA repair pathways. (Answer: True)

・Most cancer cells have variants of normal genes. (Answer: True)

・Abnormal regulation of the cell cycle is unrelated to the transformation of normal cells into cancerous cells. (Answer: False)

・The human genome does not change over one's life. (Answer: False)