Chapter

Molecular Mechanisms of Distinct Diseases

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Abstract

Molecular medicine describes molecular structures and mechanisms and this chapter focuses on molecular and genetics errors of diseases. Diseases can be classified into deficiency diseases, hereditary diseases, infectious diseases and physiological diseases and to get a glimpse of the mechanisms the chapter covers the most common disease of each class.

Keywords: chromosomal diseases, cancer, neurodegenerative diseases, pulmonary diseases, obesity-induced insulin resistance, lymphoblastic leukemia, viral immunology and infectious diseases

1. Introduction

Distinct diseases have different etiology pattern and this chapter covers the chromosomal diseases, cancer, neurodegenerative diseases, pulmonary diseases, obesity-induced insulin resistance, lymphoblastic leukemia, viral immunology and infectious diseases. These communicable and non-communicable diseases negatively affect structure-function of the organism and specific symptoms are associated with these conditions. Pathogens or internal dysfunctions may lead these diseases. The chapter provides pathology of selected diseases from each class along with the molecular mechanisms.

1.1 Chromosomal diseases

1.1.1 Down syndrome

Down syndrome (DS) is the most common chromosomal genetic disorder. The disease is caused by the trisomy of human chromosome 21 (HSA21) and is also the most genetic mental disability [1]. The HSA21 mosaic can also lead to DS. Maternity age is an important aspect in the formation of an individual with DS [2]. The main cause of this disease is the absence of normal chromosome separation during meiosis and the production of gametes with two copies of chromosome copies instead of a single copy. As a result, DS individuals have trisomy 21 in some body cells, and a normal number of chromosomes in others. This is called mosaicism and is seen in approximately 4% of DS individuals. The term mosaicism was first reported in 1961

[3] and can occur in two ways: either a normal zygote is exposed to an early mitotic error following fertilization, which results in trisomy 21 in some cells, or an early mitotic error in some cells allows it to return to normal karyotype [4].

HSA21 is the most studied human chromosome, and since the long arm of chromosome 21 has been fully sequenced, a significant progress has been made in understanding its functional genomic units. HSA21 is the smallest chromosome and the overall gene density per megabase is about 15 genes per Mb (for the human genome) [5]. HSA21 is also very rich in long encoding RNA (lncRNA) genes, and, one of the poorest for genes encoding microRNA (miRNA). Also, the gene density is average for pseudogenes encoding the protein per Mb [6]. HSA21 is a weak chromosome in non-encoding RNAs (ncRNAs) and long nuclear elements (LINE). Interestingly, HSA21 shows significant enrichment for proteins found in cytoskeleton structures. These cytoskeletal proteins are known to play a role in neurological disorders, especially Alzheimer's neuropathology [7].

Individuals with DS occasionally develop the myeloproliferative disorder (TMD), a disease that is mostly unique to DS. Almost all TMD cases were found to contain somatic mutations on the X chromosome, in the GATA1 transcription factor [8]. Certain features of DS contain genes on other chromosomes causing gene and trisomy mutations and working together to reveal the disorder in HSA21. Studies have shown that the formation of Trisomy 21 precedes the formation of GATA1 mutations [1]. This may indicate that Trisomy 21 either increases genomic discrepancy leading to GATA1 mutations, or it supplies a selected medium for hematopoietic cells containing GATA1 mutations.

1.1.2 Molecular mechanism

Many hypotheses have been proposed to explain the genotype–phenotype relationship in DS. One of these is the 'gene dosage effect' hypothesis putting forward that the phenotypes arise directly from the dosage imbalance of the genes. Overlapping this hypothesis, the 'DS Critical Region' (DSCR) was announced in the 1990s. [9, 10]. Many of the DS features can be called into a subset of the critical genes in the DSCR region, suggesting that DS phenotypes are mainly caused by the dosage imbalance of only a few genes on HSA21. Genomic regions affecting the presence of certain DS phenotypes have been identified and high-resolution genetic maps of DS features have been created [11]. Olson et al. studied the DSCR regions in mice to test its hypothesis. They concluded that dosage imbalance of some individual genes on HSA21 directly affects certain phenotypes, but they stated that more studies are needed [12].

The "amplified developmental instability" hypothesis suggests that dosage imbalance of the HSA21 gene leads to a non-specific impairment of cellular homeostasis [10]. Extra chromosome materials may also contribute to phenotypes by disrupting chromosomal regions. Some data on monozygotic twins for TS21 suggest that differential expression between normal and trisomic twins can be regulated across chromosome domains. This study shows that some DS phenotypes can be enlightened by the modification of the chromatin structure in the nucleus [13]. Monozygotic twins affected by DS but showing incompatible phenotypes have been reported in some cases, suggesting the role of epigenetics in the phenotypic variability of DS. For example, DNA methylation (controlling gen expression) has been shown to change in Trizomy of chromosome 21 (TS21) samples [14].

1.1.3 Turner syndrome

Turner syndrome (TS) is a disorder in mosaic karyotypes associated with complete or partial loss of the X chromosome. Seen especially in women, TS is

associated with short stature, delayed puberty, ovarian dysgenesis, infertility, congenital malformations of the heart, type 1 and type 2 diabetes mellitus, osteoporosis, and autoimmune disorders. It occurs in almost every 2500 live female births. Fetuses affected by TS are 99% estimated to result in fetal death. Approximately half have monosomy X (45, X) and 10% have a repeat (isochromosome) of the long arm of the X chromosome. Most of the rest has a mosaic in more cell lines for 45X. TS, which is associated with a missing X chromosome, was first identified about 100 years ago [15].

Related genes: Shox gene (short length homeobox protein-coding) located on X and Y chromosomes, it is a gene responsible for TS phenotype. This gene does not undergo X inactivation, and a decrease in the expression of SHOX explains some of the TS-related growth deficits. The gene product controls the expression of natriuretic peptide B (NPBB) and FGFR3 (fibroblast growth factor receptor 3) and regulates the proliferation and of chondrocytes, and also cooperates with SOX5, SOX6 and SOX9 and some other genes [16].

The TS genome is hypo-methylated with less hypermethylation sites and there are RNA expression changes that affect the X chromosome genes and autosomal genes compared to women who are 46 XX. Known escape genes are expressed differently in individuals with TS and other X chromosome genes such as RPS4X and JPX (CD40LG and KDM5C) in particularly, KDM5C (encoding lysine-specific demethylase 5C) can participate in the transcriptional profile of neuronal genes and play role in different neurocognitive profiles [17]. 40S ribosomal protein S_4 (RPS_4X) also plays an important role in TS, bringing together multiple protein complexes. In addition, the Y paralog of RPS4X (RPS4Y) may also have a role since it is normally expressed as duplicates [18].

Many different studies show that women with TS have increased mortality compared to the pool of a wide variety of related diseases [19]. The most obvious increase in morbidity is caused by autoimmunities like diabetes mellitus or thyroiditis, osteoporosis, cardiovascular diseases, hypertension, congenital malformations, especially endocrine diseases including heart diseases, digestive system and anemia [20].

1.1.4 Genotype-phenotype

It is still unclear which chromosomal regions or genes make up the phenotypical properties of TS. The physical symptoms of TS were thought to be due to the absence of normal sex chromosomes before inactivation of the X chromosome, or the haplo-insensitivity of the genes in the pseudo-autosomal regions of the aneuploidy [21]. It is thought that a complete phenotype results in the loss of short arm (Xp) in the X chromosome. Aneuploidy itself can cause growth failure. Loss of a region in Xp22.3 was found to be related to neurocognitive problems in TS [22]. Loss of the SRY gene locus in the short arm of the Y chromosome leads to the phenotype of TS, even if it does not cause a population of 45 X cells. It has also been suggested that an area in Xp11.4 is important for the development of lymphedema [23].

1.2 Cellular proliferation: cancer

Cancer can be defined as the uncontrolled cell growth with the most basic explanation. Cell stacks that grow uncontrollably are called tumors. Benign tumors grow much slower and usually do not metastasize, while malignant tumors can spread to other organs through metastasis, and lead to multiple organ damage and eventually death. Tumor cells acquire characteristic features such as sustaining growth signals in the process of cancer, avoiding growth suppressors, resisting cell death,

ensuring replicative immortality, initiating angiogenesis, and activating invasion and metastasis [24].

Cancer cells acquire these abilities in the process due to genetic instability and inflammation caused by environmental and hereditary effects. Many studies show that viruses, in addition to many environmental factors such as radiation and chemicals, induce cancer. Chronic inflammation has been shown to trigger oncogenic mutations, genetic instability, tumor growth, and angiogenesis through angiogenesis and cause local immunosuppression [25].

Two types of gene groups involved in cancer are oncogenes, which trigger cellular growth and uncontrolled proliferation, causing increased genetic instability with increased expression and tumor suppressor genes that cause cancer as a result of decreased control of their expression, cell division, and growth. Proto-oncogenes include RAS, WNT, MYC, ERK, and TRK genes. A mutation that may occur on a proto-oncogene or a regulatory region of the gene (e.g., promoter region) can cause an increase in the amount of protein with the change in protein structure [26]. Expressions of oncogenes can also be regulated with miRNAs [27]. Mutations occurring in these regulatory miRNAs can cause activation of oncogenes [28]. Cancer cells increase cell growth-division by activation of oncogenes, as well as suppress preventive control mechanisms of tumor suppressor genes that control this process.

Mutations in tumor suppressor genes cause loss of function. Therefore, they occur in both alleles. To inactivate the gene and its protein, wide-ranging effects, such as deletions, frame-shift mutations, insertions, should be seen rather than point mutations [29]. Tumor suppressor genes include retinoblastoma (RB) [30], TP53, BRCA1, BRCA2, APC, and PTEN. Many side factors such as transcription complexes, changes in cellular metabolism, microenvironment can guide the course of cancer [31].

The development of cancer is a multi-stage process consisting of initiation, promotion, and progression. Cancer-inducing events are usually caused by genetic mutations. Mutant cell proliferates rapidly in the promotion stage and acquires features that allow malignant behavior in the progression stage. Production of telomerase and expression of p53 are examples of malignant behavior [32]. Then, the process proceeds in the form of dysplasia formation, where new blood vessels are formed (angiogenesis) with cellular transformation. Angiogenesis facilitates the intravasation of cancer cells after undergoing an epithelial-mesenchymal transition (EMT) [33]. EMT gives an invasive phenotype to cancer cells and is managed by various transcription factors (such as SNAI, SLUG, ZEB2, ETS1, TWIST) [34]. These transcription factors also regulate each other for the protection of EMT [35].

1.2.1 Cancer cell metabolism

Normal cells only use anaerobic glycolysis when oxygen is absent or limited, while cancer cells can convert glucose to lactate in the presence of oxygen. Otto Warburg discovered that cancer cells exhibit a differentiated metabolism ability [36]. Warburg effect is biochemical properties that help identify cancer cells. On the other side, cancer cells are generally highly glucose-dependent. Glucose intake of cells is enabled by overexpression of different isoforms of membrane glucose transporters in cancer cells [37]. It has been shown that the benefit of the Warburg effect for cancer cells is not just the formation of glycolytic ATP, but also the production of many glycolytic intermediates before anabolic processes such as NADPH and amino acids [38]. Cancer cells are also able to metabolize glutamine to synthesize some amino acids they need, use it as a nitrogen source and for fatty acid synthesis in hypoxic conditions [39]. Therefore, blood glutamine levels increase

in some cancer cases [40]. Lactic acid is used to produce citric acid and maintain cancer progression in neighboring cancer cells. This is called the "Reverse Warburg effect" [41].

Tumor micro-environment, consisting of fibroblasts, adipocytes, endothelial cells, and macrophages, is a good source for tumor growth. Tumors "steal" energy-rich metabolites from their micro-environment [42]. Monocarboxylate carriers (MCTs) are used for L-lactate transfer between cancer cells and their microenvironment [43]. Tumors have heterogeneous structures with hypoxic and aerobic regions. A "metabolic symbiosis" behavior has recently been found between the two regions [44]. Lactate is produced by glycolysis in hypoxic tumor cells. This product is obtained by aerobic cancer cells by MCT1. Aerobic cells convert lactate to pyruvate with lactate dehydrogenase isoform B (LDH-B) enzyme.

When glucose consumption is not enough to meet the energy need of cancer cells, they begin the fatty acid oxidation (FAO) [45]. For example, prostate cancer, leukemia, and large B-cell lymphoma, increasing palmitate and FAO uptake in cells are among the most commonly used bioenergetic pathways [46–48]. Normal cells usually receive fatty acids by diet, while tumors show an increase in de novo fatty acid synthesis [45].

Pyruvate plays a pivotal role in the regulation of metabolic reprogramming, especially in tumors [49]. Pyruvate dehydrogenase (PDH) converts cytosolic pyruvate into mitochondrial acetyl-CoA, which is the first substrate of the Krebs cycle. Pyruvate dehydrogenase kinase (PDK) negatively regulates PDH. This reaction slides glucose from oxidative to glycolytic metabolism [50]. Lactate dehydrogenase (LDH) is the primary metabolic enzyme converting pyruvate into lactate. LDH plays an important role in arranging food interchange between stroma and tumor. Studies have shown that inhibition of LDH is important for treating advanced carcinomas [51]. Mitochondrial hyperpolarization is a mutual property of several tumor cells [52]. Tumor cells, which have more negative mitochondrial structures, are more selective targets in drug therapies [53].

1.2.2 Brain cancer

Brain tumors are cancer tissues that grow abnormally and prevent the brain or central spinal system from performing its normal functions. Primary brain tumors originating from brain tissue can usually spread only to other parts of the brain, and occasionally to other organs. Tumors that form in another tissue in the body migrate to the brain are called metastatic or secondary brain tumors. These types of tumors occur more frequently than primary brain tumors. They are termed after their tissue of origin [54].

The most prevalent primary tumor types in adults are glioma, astrocytomas, oligodendroglioma, meningioma, schwannoma, pituitary tumors, and central nervous system (CNS) lymphoma.

1.2.3 Genetic background of brain cancer

Retinoblastoma mutations are found in almost 75% of brain tumors and are mostly associated with glioblastoma, and Tp53 mutations are found in more than 80% of advanced gliomas [55]. Primary glioblastomas have EGFR tyrosine kinase mutations, tumor suppressor PTEN gene mutations, DNA repair protein O6-methylguanine-DNA methyltransferase (MGMT) protein abnormalities [56, 57]. While IDH1 mutations in the control mechanism of the citric acid cycle are seen in advanced glioblastomas, IDH2 mutations are usually shown in oligodendroglioma [58]. Mutations in the BRAF oncogene are common in pilocytic

astrocytomas, pleomorphic xanthoastrocytomas, and gangliogliomas [55]. In some glioblastoma tumors, telomere length is maintained by mutations in the TERT promoter and ATRX gene [59].

WHO groups glioma patients based on the presence of two genetic changes; first, mutations [60] in the family of genes encoding isocitrate dehydrogenase (IDH), and second, loss of two specific parts of the genome (1p and 19q co-deletion) [61]. The presence or absence of these changes gives a clue about the patient's prognosis and appropriateness of various kinds of treatments.

Approximately 40% of people with astrocytoma, oligodendroglioma, or IDH mutation bear a hereditary variation. This variation is a single nucleotide polymorphism (SNP) in the 8q24 region of the genome [62]. There is another SNP in the 11q23 region, which enhances the risk of IDH-mutant brain cancer. Approximately 5–8% of gliomas are familial, POT1 gene mutations have been found in 6 of 300 families with glioma [63].

Non-coding RNAs (ncRNAs) play important roles in regulating tumor malignancy in glioma [64–66]. According to healthy brain tissue, mir-21 expression increases in glioma and mir-21 acts as an oncogene [67, 68]. It has been reported that mir-124 and mir-137 act as tumor suppressors in glioblastoma multiform cells [69]. Hotair, SOX2ot, CRNDE, Malat1, H19, GAS are lncRNAs that have been recently shown to regulate glioma [70, 71]. Glioma cells also express the circRNAs, for example, circBRAF, bircFBXW7, circSMARCA5. These regulate proliferation, migration, and invasion of glioma cells [72–74]. The exosomal ncRNAs, mir-21, mir-148a, lncRNA PU03F3, lncRNACCAT2 can be used as circulating biomarkers of glioma patients [75–78]. circRNAs and the exosomal ncRNAs were also reported as potential biomarkers for the diagnosis and prognosis of glioma patients.

1.3 Molecular pathology of neurodegenerative diseases with Alzheimer's disease in focus

As a characteristic of almost all neurodegenerative diseases, abnormal protein assembly gathers these diseases under the prion concept [79]. Prion protein, known as PrP, was introduced to define protein pathogens and distinguish them from viruses and was identified as a proteinaceous infectious particle known to resist inactivation. Even back at that time, its importance was foreseen in terms of shedding light on the etiologies of chronic degenerative diseases [80]. Self-propagation is an important characteristic of prions that is also observed in abnormal protein assembly in Alzheimer's Disease (AD) [81, 82]. Aggregation of proteins in neurodegenerative diseases was believed to occur spontaneously in autonomous cells, however, it was later understood that this aggregation begins in a particular region and propagates across other regions developing the disease further. Transmission of these prion proteins across neuronal cells takes place trans-synaptically [82].

As described more than a 100 years ago, abnormal protein assembly forms the basis of neurodegeneration with AD being one of the most common neurodegenerative diseases. The pathology of abnormal protein assembly starts with misfolding of native proteins that gather to form seeds which eventually lead to aggregation and development of protein fibrils. The pathophysiology of AD involves amyloid plaque inclusions of β-amyloid (Aβ) peptides and neurofibrillary lesions of tau protein. Tau inclusions may also be characteristics of other neurodegenerative diseases, which do not necessarily show the same implications. Altering the native forms of this protein may contribute to its pathology and cause damage to its host cell.

Most cases of this disease are sporadic, while dominantly inherited mutations are also seen to a lesser extent. Back in the 1990s, missense mutations of APP, encoding amyloid precursor, were shown to cause AD [83–87]. Mutations in this

gene also increase the aggregation tendency of encoded proteins. Many studies have demonstrated phenotypes associated with neurodegeneration when this protein is overexpressed.

There are six isoforms of microtubule-associated protein tau ranging from 352 to 441 amino acids, encoded by the MAPT gene as a result of alternative mRNA splicing. One half has three repeats and the other has four repeats, altogether establishing the microtubule-binding domain and also the core of tau filaments in case of pathology [88]. All isoforms have been observed in the brains of AD patients. Diseases that have isoforms with only three or four repeats, but not both, lack the Aβ peptides seen in AD and therefore do not carry the symptoms specific to the disease [70]. Tau inclusions may be of a variety of conformations, which can also be caused by different mutations on the MAPT gene, explaining the existence of numerous tauopathies [89–93].

Aβ peptides are encoded by the amyloid precursor protein gene, APP, and are widely expressed as type 1 transmembrane glycoproteins. As a result of alternative mRNA splicing, there are three major transcripts named APP695, APP751, and APP770 [94, 95]. β- and γ-secretase enzymes take part in the production of Aβ peptides in sequential endoproteolytic cleavage. β-secretase is responsible for cleaving the N-terminus of the peptide thus removing the portion that remains on the extracellular side. This cleaved peptide is endocytosed and intracellular aggregation builds up which is later released into the extracellular space [79]. γ-Secretase is a membrane-embedded enzyme that is able to cleave many transmembrane proteins including C-terminus of the Aβ peptide. It a complex enzyme of four proteins; presenilin (PS) forming the catalytic core, presenilin enhancer-2 (Pen-2) enabling maturation of PS, anterior pharynx-defective (Aph-1) stabilizing the complex, and nicastrin possibly being the receptor for the enzyme's substrate [96, 97]. PS and Aph-1 each have two variants resulting in at least four different enzyme complexes, which give rise to various cleaved Aβ peptides. Additionally, γ-secretases cleave the peptide in three different sites. Different protein variants and cleavage sites produce Aβ peptides of different profiles, some of which may be more susceptible to aggregation [98].

Overall, it is important to target the pathways leading to abnormal protein assembly and only then treatments may be proposed based on these mechanisms. Once the first protein inclusion is formed, it is essential to keep an eye on the time frame until the disease symptoms come forth. When techniques sensitive enough to catch the first protein inclusion are developed, then tracking its transformation into filaments can be helpful in designing novel preventive approaches. Understanding this cascade will also contribute to planning more efficient therapeutic methods.

1.4 Cellular and molecular mechanisms of asthma and COPD

Asthma and chronic obstructive pulmonary disease (COPD) are common disorders characterized by progressive chronic inflammation in the lungs. They have unique characteristics with dissimilarly involved cells, mediators, and inflammation. They also have distinct responses to corticosteroid treatment. Roughly 15% of COPD patients have characteristics of asthma [99]. Also, a comparable ratio of asthma patients has traits of COPD that is currently the fifth leading cause of death worldwide [100]. Many risk factors are linked to COPD including smoking tobacco, air pollution, indoor cooking while tobacco smoking (including passive smoking) making up around 80% of the cases [101]. There are many types of cells and mediators that have a significant effect during the pathogenesis of asthma and COPD.

Macrophages have a crucial role in coordinating the inflammatory response activated by cigarette smoke extract in COPD cases [102]. They discharge inflammatory

mediators including tumor necrosis factor (TNF)-α, IL-8, other CXC chemokines, monocyte chemotactic peptide (MCP)-1, LTB4 and reactive oxygen species (ROS) [103]. However, the role of macrophages in asthma is not certain. Allergens via low-affinity IgE receptors may activate macrophages causing an inflammatory response through the discharge of a definite arrangement of cytokines. On the other hand, macrophages also excrete anti-inflammatory mediators, such as IL-10 that is thought to decrease in subjects with intense asthma [104].

Activated neutrophils were shown to be enhanced in some subjects with severe asthma and COPD in their sputum and airways [105]. Among the serine proteases secreted by neutrophils are neutrophil elastase (NE), cathepsin G, proteinase-3, matrix metalloproteinase (MMP)-8 and MMP-9, leading to alveolar destruction [103]. The mechanisms of neutrophilic inflammation in asthma and COPD are not clear. Demonstration of priming in COPD occurs at neutrophils in the peripheral circulation. Many chemotactic signals exhibit the capacity for neutrophil recruitment in COPD. These include LTB4, IL-8 and related CXC chemokines, comprising GRO-α (growth-related oncoprotein) and ENA-78 (epithelial neutrophil activating protein of 78 kDa) which are enhanced in COPD airways [106]. Although the mentioned mediators might be sourced from alveolar macrophages and epithelial cells, neutrophils have the capacity of being a vital source of IL-8 [107].

Airway and alveolar epithelial cells in COPD can be a vital point of source of inflammatory mediators and proteases 5. Cigarette smoke activates epithelial cells which produce inflammatory mediators, including TNF-α, IL-1β, GM-CSF and IL-8 [108]. Epithelial cells play an important role in airways defense and tissue repair processes. Goblet cells, a type of epithelial cell, in mucus catch bacteria and inhaled particulates [109]. Epithelial cells release antioxidants and antiproteases. Immunoglobulin A is carried by epithelial cells, hence involved in adaptive immunity [110]. On a side note, native and adaptive immune reactions of the airway epithelium are triggered by cigarette smoke and damage by other harmful agents, increasing sensitivity to infection.

The main role of dendritic cells is to introduce innate and adaptive immune reaction by activating macrophages, neutrophils, T and B lymphocytes among others [103].

Lymphocytes are directly involved in the pathogenesis of both asthma and COPD. Both airway and parenchymal inflammation exist in asthma and COPD patients [111]. Most lung lymphocytes are T cells which are in the respiratory tract of ordinary humans. Activated T lymphocytes are characteristic in both asthma and COPD, but CD4+ type-2 T lymphocytes are the major player in asthma whereas CD8+ type-1 lymphocytes are specific to COPD [111]. CD4+ T lymphocytes can generate many cytokines involved in mediating cell functions and cell–cell communications. This is done through impressing physiologic cell properties such as proliferation, differentiation and activation of other immunocompetent cells, chemotaxis, and connective tissue metabolism [112]. On the other hand, CD8+ T lymphocytes exist in the respiratory mucosa and are activated in response to foreign antigens [111]. Specifically, the cells in the respiratory mucosa have an important role in anti-viral immunity. Another lymphocyte type is B cells which are the minority (<5%) lymphocytes. The main function of B cells located in the lungs is the production of immunoglobulins for local defense mechanisms [113].

Apart from these mentioned cells, there are crucial molecular mediators in the pathogenesis of asthma and COPD. The first family of mediators is transforming growth factor (TGF) family. The TGF-β subfamily is composed of five parts that exhibits plenty of effects pertaining to asthma and COPD. A recent study shows that overexpression of TGF-β1 in mice causes Smad3-dependent pulmonary expression of procollagen, antiproteases and fibrosis [114]. TGF-β exhibits

chemotactic signatures for monocytes, macrophages and mast cells. Research shows an abnormal pulmonary expression of TGF-β1 in subjects suffering from COPD. Protein and mRNA expression of TGF- β1 are abundant in the lung tissue, including airway epithelial cells, of mild to moderate COPD patients. TGF-β1 has the role in pathogenesis of COPD because of its increased expression in parallel to the number of macrophages [115].

Another mediator family is the fibroblast growth factor (FGF) family with 23 members in humans. Their functional receptors are named from FGFR1 to FGFR5 [116]. FGFs have many functions such as development, tissue homeostasis, and repair. In addition to further growth factors, FGF-1, FGF-2, and FGF-7 and their receptors FGFR1 and FGFR2, are located abundantly in the lungs [101]. Research shows that increased expression degrees of FGF-1, FGF-2, and FGFR1 were detected in vascular and epithelial areas in the lungs of COPD patients. FGF-1 causes higher collagenase expression and lower collagen I expression in lung fibroblasts which prompt tissue remodeling.

Another family of mediators is the vascular endothelial growth factor (VEGF) family. There are seven units in this family capable of attaching to related cellular receptors. VEGFs have many functions including paracrine acting, angiogenic factors, prompting mitogenesis, emigration, and permeabilization of the vascular endothelium [101]. VEGF and its receptors assist in tissue remodeling as well as disease intensity in incessant lung diseases such as asthma [117]. COPD patients have increased pulmonary VEGF expression in bronchial and alveolar epithelial located around the vascular smooth muscle and alveolar macrophages. Additionally, unlike healthy subjects, COPD patients exhibit elevated levels of VEGFR-1 and VEGFR-2 expression inside the endothelium [118]. Furthermore, VEGFR-2 and VEGF expressions are decreased in COPD patients. Compared to VEGFR-2, VEGFR-1 has a higher affinity for VEGF which leads to VEGFR-1 scavenging VEGF from VEGFR-2. This phenomenon culminates VEGFR-1 activation and in the case of endothelial apoptosis, increased MMP activity as well as vascular and alveolar decimation [101]. This suggests the importance of harmony among VEGF, VEGFR-1, and VEGFR-2 during the pathogenesis of COPD subordinary types.

Finally, cytokines and chemokines are mediators supplying a chemotactic gradient which has the potential to activate macrophages, CD8+ T cells and neutrophils for COPD patients. It is known that inflammatory cells of both native and gained immune systems are significant in the COPD pathophysiology. This is where cytokines and chemokines are the key drivers [103, 119]. Different types of cytokines arrange chronic inflammation in asthma and COPD. T2 cytokines which are IL-4, IL-5, IL-9 and IL-13 interfere with allergic inflammation. Other types of cytokines including TNF-α and IL-1β accelerate the inflammatory response [120]. In asthma and COPD patients, chemokines are instrumental in drawing inflammatory cells from the circulation into the lungs [121].

1.5 The endocrine system

1.5.1 Molecular mechanism of obesity and obesity-induced insulin resistance

Obesity is a serious health problem that has become epidemic all over the world, especially in developed countries. It is characterized by hypertrophied adipocytes that secrete various adipokines and hormones, chronic inflammation in all tissues, and systemic insulin resistance resulting in type 2 diabetes, hypertension, and hyperlipidemia. In addition to these metabolic diseases, it can cause diseases such as cancer, atherosclerosis, obstructive sleep apnea syndrome, steatohepatitis, and musculoskeletal problems [122]. The obesity rate is 20% in women and 18% in men

in developed countries [123]. It affects complex metabolic pathways in all tissues as a result of chronic and progressive inflammation, leads to insulin resistance, endothelial dysfunction and lipotoxicity.

The pathophysiology of obesity includes complex interactions of numerous adipokines, hormones and pro-inflammatory cytokines with the central nervous system and metabolic organs (such as liver, pancreas, and muscle) as a result of genetic-environmental interactions.

Genetic etiology: Obesity is generally present in a polygenic etiology. Many studies have investigated the genetic background of body mass index (BMI) and waist/hip ratio (WHR), which are the best measurements of obesity. The results of these studies have been presented collectively in genome-wide association studies (GWAS) [124]. Although, single gene defects (monogenic) are rare in obesity, including especially melanocortin-4 receptor, leptin and leptin receptor genes [125].

Dysregulation in hypothalamic control: The center of food intake and energy regulation in the central nervous system is the arcuate nucleus (ARC) in the hypothalamus besides the autonomic nervous system and brain stem. The balance between the opposing effects of orexigenic and anorexigenic neurons is important. Agouti-related protein (AgRP) and neuropeptide Y (NPY) (AgRP/NPY) neurons are orexigenic that promotes appetite and eating. Pro-opiomelanocortin–producing (POMC) peptide and cocaine-and-amphetamine–regulated transcript (CART), collectively known as POMC/CART neurons are anorexigenic that suppress appetite and eating. Oxygenic pathways that increase energy balance become more effective in obesity [126].

Adipose tissue dysfunction and systemic inflammation; The most important pathophysiological mechanisms of obesity and obesity-related insulin resistance are adipocyte dysfunction (visceral adipose tissue; VAT) and low-grade chronic systemic inflammation. In particular, white adipocyte tissue in obese subjects contributes to the regulation of food intake, energy metabolism and other functions by secreting adipokines from adipose tissue, which provide the necessary signals to the central nervous system, hypothalamus, liver, pancreas, muscle tissue, and other systems to regulate appetite, food intake, and energy balance [125]. Leptin is the most important adipokine that stimulates anorexigenic POMC/CART neurons and induces production of pro-inflammatory cytokines (TNF-alpha and IL-6) by macrophages and monocytes. In the case of hyperleptinemia, leptin resistance develops by the inhibition of the JAK2/STAT3 signaling pathway, which later increases oxidative stress and inflammation, causing insulin resistance, hyperlipidemia and hypertension [127]. Resistin is a pro-inflammatory adipokine produced by the resistin gene (RETN), which activates SOCS3, causing the insulin signaling pathway to be inhibited and consequently induces insulin resistance [128]. Other adipokines like Retinol binding protein 4 (RBP4), Angiopoietin-like protein 2 (ANGPTL2), Visfantin, Adiponectin, Lipocalin 2, Serum Amyloid A, Angiotensinogen, Renin, Angiotensin-Converting Enzyme, Acylation-Stimulating Protein, and Vaspin, are increased, and adiponectin, and Apelin are decreased in obesity, altogether stimulating inflammation, lipolysis, releasing free fatty acid (FFA) and causing insulin resistance as a result [129].

Gastrointestinal hormones and microbiota: Gastrointestinal hormones and gut microbiota play a significant role in the complex pathophysiology of obesity. Ghrelin produced in the stomach induces starvation and food intake by stimulating orexigenic AgPR/NPY neurons in the hypothalamus. Although the effect of ghrelin cannot be fully explained, it is thought to increase in obesity, stimulate growth hormone release (GH), increase gastrointestinal motility and insulin secretion [130]. Decreased GLP-1, Peptide YY, pancreatic polypeptide, and increased amylin and cholecystokinin cause appetite inhibition and gastric emptying delay, resulting in excess energy [129]. Besides hormones in the gastrointestinal tract, changes in

microbiota-gut-brain axis and their effects on metabolic organs are also important. Occurring as a result of nutrition and gene–environment interactions; chronic systemic inflammation resulting from intestinal microbiota dysbiosis (increase in Firmicutes-Bacteroides ratio), microbial fermentation products, increase in short-chain fatty acid formation and intestinal permeability, decrease in butyrate-producing bacteria rate, leads to an increase in proinflammatory response in metabolic organs, impaired fat metabolism and glucose metabolism [131, 132].

İmpaired insulin sensitivity and oxidative stress; The beginning of insulin resistance is the first step in the pathophysiology of T2D. Anabolic effects such as glycogen and protein synthesis, glucose transport, adipogenesis are formed by phosphatidylinositol-3-kinase (PI3K)/Akt pathway activation as a result of insulin binding to its receptor (INSR) synthesized in the pancreas [133]. On the other hand, insulin shows mitogenic effects with mitogen-activated protein kinases/Ras pathway (MAPK/Ras).

Adipokines, FFA's, pro-inflammatory cytokines (TNF-a, IL-18, IL-1β, IL-6), synthesized as a result of inflammation in adipose tissue in obesity, also cause systemic inflammation in metabolic tissues such as liver and muscle. As a result, decreased GLUT-4 expression, activation of Ser/Thr kinases with insulin receptor substrate (IRS) phosphorylation, production of ceramides and proinflammatory cytokines, suppressing of cytokine signaling-3 (SOCS-3) expression, insulin pathways and effects. On the other hand, increased production of reactive oxygen radicals and production of toxic doses NO with inducible nitric oxide synthase (iNOS) activation, affect mitochondrial and endoplasmic reticulum functions. Activation of pro-inflammatory pathways increased oxidative stress, mitochondrial dysfunction, ER stress affects lipid metabolism, insulin mechanisms of action and other metabolic pathways, causing insulin resistance, Type 2 diabetes, hypertension, and hyperlipidemia [134].

Beta-cell dysfunction: In addition to peripheral insulin resistance in obesity, serious reductions in beta cell function are also observed. An increase in fat accumulation in islet cells due to chronic lipotoxicity disrupts the function of beta cells by blocking calcium channels. Chronic hyperglycemia due to disruption in glucose metabolism and systemic inflammation due to an increase in oxidative damage and lipotoxicity, disrupt insulin secretion pathways and cause changes in apoptosis gene expression. Hyperinsulinemia in obesity, impaired insulin signaling pathway, oxidative stress, lipotoxicity in islet cells, loss of beta-cell function and apoptosis may lead to the formation of type 2 diabetes [122, 135].

Obesity has become a pandemic all over the world as a result of rapidly changing lifestyles and genetic heritage in the last century. Despite the findings in recent studies on the development and complications of obesity, it is difficult to say that the subject of etiology and pathophysiology is still not fully understood. Especially omics technologies, big data on environmental gene interactions, neuroendocrinology, and neuropsychological studies will reveal findings that open up different horizons. However, due to its complications from deadly metabolic diseases to cancer, rapid preventive measures should be taken, and effective treatment models should be developed.

1.6 Alterations of blood cells: lymphoblastic leukemia

Acute lymphoblastic leukemia (ALL) is a heterogeneous malignancy emerging from lymphoid precursors. It is characterized by the proliferation of immature lymphoid cells with somatic mutations including chromosomal rearrangements, and aneuploidy [136]. ALL has two peak points; first point occurs at ~5 years of age (80%), and the second point occurs at the age of ~50 (20%) [137]. The basic mechanism underlying the development of ALL is similar in children and adults,

while they have the frequency of different genetic subtypes. Molecular analysis of genetic changes in leukemia disease provides a great advantage in order to understand prognosis and pathogenesis of ALL [138].

The diagnosis of ALL depends on the presence of at least 20% lymphoblast in bone marrow. Immunophenotyping by flow cytometry (FCM) identifies the subtype of ALL that may be B-cell precursor (BCP), mature B-cell types, or T-cell ALL. Chromosomal abnormalities are a characteristic of lymphoblastic leukemia, which are found in B or T cell lineage. The most common abnormality found in adult B precursor ALL is the t(9;22) BCR-ABL translocation, while the t(12;21)(p13;q22) TEL-AML1 translocation is most commonly found in childhood B precursor ALL [139]. On the other hand, the discovery of mutations in the receptor tyrosine kinase FLT3 contributes to the understanding of leukemogenesis mechanism in hyperdiploid ALL (20% of cases). Based on this finding, targeting specific tyrosine kinase inhibition may be useful in the management of leukemia [140].

1.6.1 Treatment in patients with lymphoblastic leukemia

Small-molecule kinase inhibitors have a clear benefit in the treatment of many cancer types including leukemia. Imatinib mesylate, a small-molecule inhibitor of BCR-ABL kinase, is highly effective in the treatment of chronic myelogenous leukemia (CML) [141]. Although the single kinase inhibitor is a remarkable treatment option in a different type of leukemia, it will need to be combined with either other targeted therapy or chemotherapy because of the resistance to small-molecule inhibitor [142]. Unlike ALL, Chronic Lymphocytic Leukemia (CLL) is defined the accumulation of monoclonal B cell with a special immunophenotype in the bone marrow, blood, and other lymphoid organs where B lymphocytes express CD19, CD23, CD5, low-level CD20 and surface immunoglobulins [143]. The standard treatment procedure of ALL and CLL includes consolidation therapy following chemotherapy in pediatric patients. For adult patients, unlike pediatric patients, the allogeneic hematopoietic stem cell transplantation is frequently preferred as consolidation therapy [144]. Because the patients resistant to chemotherapy are not respond to treatment well enough, novel therapy approaches such as Chimeric antigen receptor-modified T cell (CAR-T) therapy have developed in order to overcome chemotherapy resistance and improving the outcome of patients [145]. CAR-T cells, as immunotherapeutic tools, are genetically engineered to express a chimeric antigen receptor recognizing an antigen that is located in the special cells such as a tumor [146]. CD19 antigen on B lymphocytes was considered the initial target for CAR-T cell therapy. However, specific antigen loss might cause the failure of CAR-T cell therapy in CLL. CD19–20 co-targeting CAR-T cells were designed to kill both CD19-positive and CD19-negative CLL and it was shown that these cells were very effective in killing CLL cells. In one of the first reported in pediatric ALL the clinical trials, CAR-T cells targeted the CD19 antigen of B cells are designed with CD3ζ and CD28 costimulatory domain [147].

1.7 Viral immunology and infectious diseases

1.7.1 The differences between HIV-1 and SARS-CoV-2 genome

The origin of a pathogen has a crucial role in developing vaccines and blocking transmission. This may last many years due to its elusiveness as seen in HIV-1, SARS, and MERS [148–150]. According to a recent report, it was emphasized that

SARS-CoV-2 is able to infect T cells, which are targeted by HIV [151]. Another report alleged that the motif insertions of spike glycoprotein, similar to HIV-1, may help increase the range of host cells of SARS-CoV-2. HIV-1 envelope glycoprotein contains mutable insertions and deletions not necessary for biological function. Only 1 and 2 insertions are matched in only a few HIV-1 strains and this reveals that four insertions are scarce. Thus, HIV-1 cannot be assumed as the source for those insertion sequences in the SARS-CoV-2 genome due to their inefficient identities and scarceness in the HIV-1 sequences [152].

1.7.2 The origin of SARS-CoV2

The reported cases showed that there have been 3,162,284 COVID-19 cases in at least 212 countries and approximately 7.1% of which was resulted in death as of April 30, 2020 [153]. It is known that SARS-CoV, MERS-CoV, and SARS-CoV-2 are the members of coronoviridae family of the Nidovirales order, which comprises a relatively positive-sense, single-stranded RNA genome of around 26–32 kb [154]. 5o-methylguanosine cap at the beginning, a 3o-poly-A tail at the end, and a total of 6–10 genes in between exist in their genome [155, 156].

This family has extremely expressive instability and recombination rate, which is similar to RNA viruses, so it is practically unfeasible to prevent their distribution among humans and animals worldwide; nevertheless, the fact that the virus is exceedingly pathogenic to humans is closely related to random genetic recombination in the host. Although there is a strict genetical relation between SARS-CoV-2 and SARS-CoV, it is explicit that SARS-CoV-2 has a unique feature providing rapidly spread worldwide [157].

SARS-CoV-2 genome sequence is much more resembles a SARS-like bat rather than SARS-CoV [158, 159]. Two open reading frames translating the replication- and transcription-related gene into two large non-structural polyproteins [156]. Ribosomal frameshifting contributes to translate two different but overlapping open reading frames. Besides these nonstructural proteins, the subgenomic RNA also encodes the viral genome packaging protein N (nucleocapsid), and the viral coating proteins M (membrane), E (envelope), and S (spike) as the structural proteins. Viral coating proteins, which interact with host surface receptors, is generally preferred as the therapeutic target blocking protein–protein interaction [160, 161]. TMPRSS2, the human serine protease, enables S Protein of both SARS-CoV and SARS-CoV-2 to prime, and these two viruses use the angiotensin-converting enzyme 2 (ACE2) receptor in order to bind the host cell as the first step of the viral entry mechanism. Unlike SARS-CoV and SARS-CoV-2, the cell entry of MERS-CoV depends on the binding of its own spike protein to DPP4 (dipeptidyl peptidase 4). The RT-PCR analysis of the throat swabs is essential to the diagnosis of COVID19 pneumonia, and it takes 3.5 h to provide the results [162].

1.7.3 Current treatment approaches

Clinical management puts emphasis on the importance of supportive care and prevention of complications due to a lack of specific treatment for COVID-19 pneumonia. On the other hand, potential antiviral therapies for the purpose of rapidly dealing with this pandemic are taking place on several clinical trials. These trials focused on three main targets that include enhancing the host immune system, blocking the virus spike protein-host cell surface receptor interaction, and vaccine development [163].

1.7.4 Human Papillomavirus genome and treatment

HPV genome, which is a double-stranded circular DNA, has the early (E) genes that are responsible for replication and transcription, and the late (L) genes that are responsible for viral capsid proteins. In the early stage of HPV infection, the highly expressed E1 and E2 proteins provide the maintaining of viral replication and transcription within the cervical cell [164].

HPVs, unlike SARS coronaviruses, are non-enveloped viruses and don't have a specific host cell receptor that initiates the viral infection. Additionally, HPVs have many different genotypes such as HPV type 16 and type 18 which are known as the reason for cervical cancer. HPV infection may cause low-grade cytological changes on Papanicolaou smears, or low-grade squamous intraepithelial lesions [165]. When malignant conversion considered, viral oncoproteins E6 and E7 attach, respectively, tumor suppressor protein p53 and Rb have a crucial role [166]. Until today, many vaccine developments studies have been carried out to protect HPV malignant type 16 and 18. For example, the clinical vaccine Gardasil 9 provides effective protection against vaginal, cervical, and vulvar diseases caused by HPV type 16,18 and also its 5 other different types [167].

2. Conclusion

The chapter outlined the unique mechanism of each disease. Depending of the origin of the disease; deficiency, hereditary, infectious and physiological diseases may be treated diversely but the perturbation effect can only be eliminated with proper intervention. Current amelioration may be improved by biochemical methods only if the molecular mechanism is clearly understood. Therefore, molecular medicine provides unique solutions to diagnose and treat disease by elucidating macromolecular interaction and abnormalities in cells and tissues. The chapter summarizes current findings and methods to alleviate and cure the diseases.

Acknowledgements

BYK, EK, KUC and ENYT acknowledge YOK100/2000 bursary and thanks to Turkish Council of Higher Education (YOK).

Conflict of interest

None.

Notes/thanks/other declarations

Thanks to Assistant Prof. Dr. Lütfi Tutar for carefully reading the manuscript.

DOI: http://dx.doi.org/10.5772/intechopen.95114

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