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Introductory Chapter: Insight into the OMICS Technologies and Molecular Medicine

Sinem Nalbantoglu and Abdullah Karadag

1. Introduction

Molecular medicine aims to reveal molecules, such as genes, transcripts, proteins, and metabolites, to underlie the mechanism behind the physiological processes as well as alterations during the pathological conditions at the cellular level. Furthermore, molecular medicine intends to improve public healthcare and disease management through development of biomarker-based screening, diagnostic, and monitoring systems as well as target- and mechanism-based treatment strategies. Human Genome Project has been completed in 2003, exactly 50 years after Watson and Crick invented DNA structure. Based on this valuable breakthrough, the twenty-first century's molecular medicine approaches have been attributed to identify and understand functions and interactions of human genes to shed further light on health and disease mechanisms at the basic molecular and cellular level.

Published by James Watson in the first edition of “The Molecular Biology of the Gene” (1965), the central dogma of molecular biology was a complete demonstration of the flow of genetic information basically described as DNA makes RNA, which in turn makes proteins: DNA → RNA → protein [1]. However, later on the 1980s–1990s by applying improved molecular biology methods, the single gene and inheritance concept has changed to multiple genes and inheritance with interactions of genes, RNAs, proteins, and environment in a particular cell. Extinction of central dogma has led to proper and critical understanding of diseases and generation of molecular medicine. By this way, a new concept called phenome, as the total phenotypic characteristics of an organism, has emerged, which implies interaction of the whole genome with the environment [2].

Primary objectives of molecular medicine includes predicting potential future pathologies, identifying disease state through effective screening and early diagnosis systems, decision on effective treatment strategies, monitoring the prognosis and health care, and predicting recurrence earlier to apply alternative treatments. In this regard, molecular medicine aims to obtain decreased under/over/mis-diagnosis and generate effective targeted therapies without side effects. Here, we provide an overview of the latest headings of molecular medicine including promising research strategies and their emerging roles in biomedical research.

2. OMICS technology

The terms “Ome” derived from a Greek word and “Omics” are derivations of the suffix -ome which means “whole,” “all,” or “complete.” With the addition of -ome to

cellular molecules, such as gene, transcript, protein, metabolite, it can be referred as genome, transcriptome, proteome, metabolome, respectively [3, 4].

Omics technologies and systems biology are the emerging concept of molecular medicine (**Figure 1**). Omics refers to collective and high-throughput analyses including genomics, transcriptomics, proteomics, and metabolomics/lipidomics that integrated through robust systems biology, bioinformatics, and computational tools to study the mechanism, interaction, and function of cell populations' tissues, organs, and the whole organism at the molecular level in a non-targeted and non-biased manner [5].

Genomics is the systematic study of an organism's entire genome [6]. The human genome is made up of DNA (deoxyribonucleic acid) comprising approximately 3 billion base pairs of four chemical structures (adenine, guanine, cytosine, and thymine), also called nucleotides. DNA contains genetic information required to build and maintain cells. A gene denotes a specific unit of DNA that hold information to make a specific functional unit named protein. It is estimated that the entire human genome contains approximately 21,500 genes. The order of the nucleotides reveals the meaning of the information encoded in DNA. Emergence of high-throughput sequencing technologies, such as next-generation sequencing, enables analysis of variations between individuals at the genomics level.

Transcriptomics is the study of transcriptome that comprises the entire collection of RNA (ribonucleic acid) sequences, called transcripts, in a cell. It is estimated that a human cell contains about 25,000 transcripts. RNAs are classified into two groups: (1) mRNA is the coding RNA that is translated into protein sequences. (2) Non-coding RNAs are also classified into two subgroups; short non-coding RNAs such as microRNA (miRNA) and long non-coding RNAs (lncRNA). Non-coding RNAs are involved in gene regulation. Next-generation RNA sequencing technologies allow deeply understanding of variations and gene expression on various types of RNA molecules including miRNA, mRNA, and lncRNA [2].

Proteomics is the study of proteome, which is defined as the set of all expressed proteins and interacting protein family networks, and biochemical pathways in a cell, tissue, or organism. Although, the exact number of proteins/peptides is still unclear, it is estimated to be around a few hundred thousand.

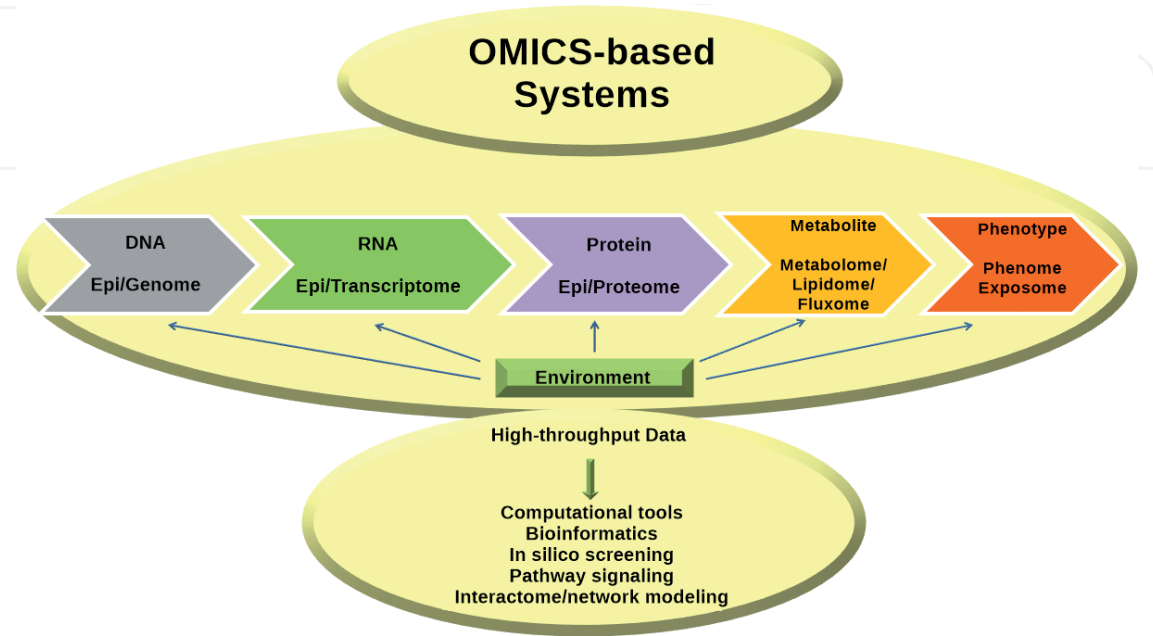


Figure 1.
Building blocks of OMICS approach and systems biology in molecular medicine.

Metabolomics is the study of metabolome within cells, biofluids, tissues, or organisms. Metabolome can be defined as the small molecules and their interactions within a biological system under a given genetic, nutritional, and environmental condition. Since the metabolome is the final downstream product, changes and interactions between gene expression, protein expression, and the environment are directly reflected in metabolome making it more physically and chemically complex than the other “omes.” The metabolome is the closest to the phenotype among other omics approaches. Metabolomics best modulates and represents the molecular phenotype of health and disease [7]. In this regard, metabolomics is a brilliant source for disease-associated biomarkers. Mass spectrometry-based metabolomics/lipidomics provides a useful approach for both identification of disease-related metabolites in biofluids or tissue, and also encompasses classification and/or characterization of disease- or treatment-associated molecular patterns generated from metabolites [8, 9]. Metabolomics analysis identifies different metabotypes of disease severity and makes successful clinical and molecular phenotyping and patient stratification.

3. Application field of OMICS technology in molecular medicine

Omics-based approaches have been significantly improved recently with the addition of novel concepts such as exposome/exposomics, the study of the environmental exposure, to unravel the role of the environment in human diseases. Furthermore, the addition of adductomics, the study of compounds that bind DNA and cause damage and mutations, and volatilomics, the study of volatile organic compounds to the metabolomics/lipidomics analysis for comprehensive research of the metabolome have been newly emerging [2, 10, 11]. Exposome is a person's total lifestyle and environmental exposures, which is not well understood yet. Researchers from NIH, Dr. Chao Jiang and his colleagues, have developed a method to capture and map an individual's “exposome”—under the concept “exposing the human exposome—every breath you take, exposome tells where you have been and when.” Furthermore, they have designed a portable, battery-powered device comprising sensors, a collection container with filter, and a pump that simulates human breathing to be able to track and quantify personal environmental exposures. The sensors can detect different particles such as biologicals (biotics), chemicals (abiotics), tobacco smoke, and automobile fumes. They have detected more than 2500 species, including bacteria, fungi, plants, metazoa, and more than 200 viruses. One of them was remarkably called “brochosome” which look like viral particles, in a sense, but it is actually some sort of hydrophobic protein/lipid mixture made by insects as a waterproof mechanism on their body.

Systems biology, can be defined as the integration of omics-based systems, is a hypothesis-generating approach, while classical biology is hypothesis-driven [6, 12–14]. Bioinformatics is the application of computational tools and analysis used to capture, store, and interpret biological data. Focusing on large-scale data/information obtained from a comprehensive, or global, assessment of a set of molecules, bioinformatics tools are then used to analyze the multi-dimensional amount of data to reveal metabotype, proteotype, and DNA-RNA panel biosignatures.

Analysis of multi-omics-based technologies through systems biology, bioinformatics, and computational power allows us to understand diversity of diseases, molecular heterogeneity of complex pathologies, mechanism involved in disease progression, and drug resistance. Subsequently, improvement has been made in the development of molecular-based screening, early detection, and monitoring systems as well as personalized treatment strategies [15, 16]. Omics-based integrative

identification and characterization of biomarker targets and their clinical translations are essential to develop comprehensive profiling, risk stratification, future cell-targeted early interventional and therapeutic strategies. First established, a decade ago, “multi-omics” approach to disease by integrative analysis of “single omics platforms” have been a paradigm shift attributed to personalized medicine [4, 15, 17, 18]. In this manner, Chakraborty and colleagues successfully documented “onco-multi-omics” approach in cancer research [17]. Systems biology integrated high-throughput multi-omics approach has been dedicated to understand complete molecular biosignature of health and disease.

Accurate determination and validation of disease-related biomarkers necessitates the development of biorepository systems with a large collection and storage of patient biospecimens such as tissue, blood, and other bodily fluids, and well annotated clinical and pathological data [19–21]. By this way, biorepository systems enable integration of basic, translational, and clinical research to lead the discovery of hindered relevant biomarkers and emerging personalized diagnostic/therapeutic strategies on reliable big sample sizes associated with specific diseases [19, 20]. In another aspect, a recent Nature editorial (2019) critically highlights focusing on to study healthy individuals biobanking rather than people with diseases to better understand the exact definition of health with all its manifestations [22]. Projects such as “100K Wellness Project” and “The All of Us Research Program” have been producing next-generation sequencing data through specimens from healthy individuals to obtain molecular, lifestyle, and environmental measurements (<http://allofus.nih.gov/>), in particular for future drug discovery studies.

Genomic diversity and molecular heterogeneity of complex diseases obscure the discovery of theranostic, prognostic, and predictive biomarkers as well as their translation into personalized medicine at the single-cell level. In this aspect, promising single-cell studies formed another emerging concept in the field of the molecular medicine. Single-cell level analysis has been suggested to be crucial for a better and precise enrichment of biomarkers related to complex heterogeneous nature of diseases [23]. Omics-based analysis at the single-cell level comprises epi/genomics, epi/transcriptomics, epi/proteomics, and metabolomics/lipidomics approaches. These technologies facilitated our understanding of variations, interactions, biological functions, and disease heterogeneity at the single-cell level which paves the way for a personalized medicine-based smart healthcare system [24, 25]. Lately, one of the hottest research fields emerged as molecular characterization of circulating biomarkers composed of circulating tumor cells (CTCs), cell free DNA (cfDNA) and/or exosomes as liquid biopsies to assess disease management and evolution in real time [26]. Exosomes have been described as microvesicles (50–150 nm) released into the extracellular region by a variety of cells. Exosomes contain intact oligonucleotides, protein, and metabolites and have been identified in a vast range of biofluids including serum, urine, plasma, breast milk, saliva, pleural effusions, bronchoalveolar lavage fluid, ocular samples, tears, nasal lavage fluid, semen, synovial fluid, amniotic fluid, and pregnancy-associated serum [27]. With the development of high-throughput omics technologies, liquid biopsy has settled in the center of non-invasive or minimally invasive applications of easily accessible biofluids to detect disease-associated CTCs for diagnostic, monitoring, and therapeutic approaches. Isolation, detection, and molecular characterization of CTCs have been performed in a variety of diseases mostly in cancers. Due to high heterogeneity and resistance to treatment observed in tumor biology, single-cell CTC characterization allows clinical profiling and targeted treatment strategies and monitoring.

Molecular medicine applications not only improved the basic understanding of disease mechanism, but also contributed to the understanding of mechanism

of drug action, identification of theranostic targets, and hence a paradigm shift in drug discovery [28]. Molecular theranostics can be defined as integration of disease diagnosis and treatment with the same molecular target. Promising oligonucleotide-based (DNA or RNA) therapeutics and vaccines such as gene therapy, DNA vaccines, and RNA pharmaceuticals have been successfully developed in the last 2 decades using antibodies and aptamers. Regarding DNA, viral or bacterial vectors are used and polymeric materials such as poly lactic-co-glycolic acid (PLGA), chitosan, and polyethylenimine (PEI) have been applied for efficient delivery [29]. Aptamers or antibodies can be conjugated to theranostic biomarkers and nanomaterials for specific targeting [30]. Aptamer-based applications include imaging, targeted drug delivery, and treatment such as targeted phototherapy, gene therapy, and chemotherapy [31]. Limitations in non-toxic specific targeting and delivery encouraged researchers to use drug carriers such as liposomes and nanoparticles for encapsulation of oligonucleotide therapeutics [32]. Studies on some tumor types including lung, pancreas, and breast have demonstrated successful results with encapsulated antisense oligonucleotides [33, 34]. RNA oligonucleotides using the antisense gene silencing technology has given promising results to inhibit disease-related mRNA gene expression. RNA therapeutics including antisense RNA, small interfering RNA (siRNA), and anti-miRNA (anti-miR) are promising for the treatment of a number of diseases including chronic complex diseases. Furthermore, their impact has been evaluated in the different stages of development from preclinical to Phase III clinical trials [35–39]. Major challenges dealing with efficient delivery include biocompatibility, protection from nucleases, distribution location, and persistence. Peter and colleagues have identified suicide/killer RNA molecules (siRNA, shRNA, miRNA, siRNA+miRNA complex) on numerous cancer types. In addition, they have shown that specific toxic RNAi-active sequences present in the genome can kill cancer cells [40–44]. Rozowsky and colleagues have generated a comprehensive analytic platform for extracellular RNA profiling called “exceRpt” [45].

Murillo and colleagues have created exRNA Atlas Analysis, and explored how RNA transmits information through cell-to-cell communication, known as extracellular RNA or exRNA [46]. Moreover, they have identified complexity in steps of transport exRNA molecules, types, carriers between cells, target cells, and functions, and found that even the type of carrier affected how exRNA messages were sent and received which may suggest potential novel disease-associated biomarkers and therapeutic targets. To date, exRNA-originated potential biomarkers have been identified in 13 biofluids like plasma, saliva, and urine in over 50,000 samples from over 2000 donors for nearly 30 diseases including cardiovascular diseases, diseases of the brain and central nervous system, pregnancy complications, glaucoma, diabetes, autoimmune diseases, and multiple types of cancer. Thus, exRNA profiles could be an individualized source and for personalized treatment of various diseases.

Examples of current and future applications in molecular medicine may also include DNA/RNA chips, peptide/antibody arrays, aptamer/antikor-based immunoassays, and/or sensor systems for disease screening, diagnosis, and monitoring. Molecular tools/devices such as lab-on-chips combined with sensors using microarray techniques have been developed which are able to perform patient stratification based on specified clinical and molecular features [47]. Those tools are assessed to capture very low concentrations of biochemical substances at the early disease phase, and result in effective/sensitive treatment and eradicate and/or reduce over-/undertreatment, and side effects [48–50].

4. Conclusions


In contrast to one single gene disease concept of Mendelian inheritance, chronic complex diseases are result of alterations in multiple genes and signaling pathways. Furthermore, these diseases are generally characterized with heterogeneity at the cellular/tissue level. Therefore, identification and omics-based profiling of multiple biomarker profiles rather than one single gene/biomarker possess greater statistical power and reliability for future screening/diagnosis/monitoring/treatment strategies. In this aspect, molecular medicine applications have brought novel and significant outputs to the research as well as challenges that require further preclinical and clinical studies. Development of omics-based discriminatory biomarkers for early detection, as well as novel targeted interventional and therapeutic strategies are crucial for a personalized healthy life as well as disease management.

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