Functional Genomics and Human Diseases

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Abstract

Functional genomics is a rapidly advancing field of research that aims to understand the functions and interactions of genes in the context of disease biology. Epigenomics, metabolomics, and whole-genome sequencing are employed to detect and analyze genes, genetic modifications, mutations, and the corresponding molecular signals involved in the development and progression of different diseases. Moreover, through the utilization of techniques such as gene knockdown or deletion using RNA interference and CRISPR-Cas9, researchers can get insight into the impact of certain gene mutations on cellular processes and establish connections between genetic variants and human diseases. The incorporation of functional genomics with proteomics and clinical data can enhance the assessment of disease treatment response and drug resistance concerns. In this chapter, we discuss the diverse uses of functional genomics, including the identification of genetic markers for common diseases like cancer, cardiovascular diseases, autoimmune disorders, and dementia. It also highlights the discovery of new targets for therapy and biomarkers and the role of functional genomics in the development of new drugs and targeted treatments. Ultimately, these advancements contribute to the field of personalized medicine and enhance the quality of individual patient care.

Keywords

Functional genomics · Diseases · Therapeutic targets · Biomarkers · Personalized medicine

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Abbreviations

CVD	Cardiovascular disease
DNA	Deoxyribonucleic acid
GWAS	Genome-wide association studies
NGS	Next-generation sequencing
RNAi	RNA interference technology
SNV	Single-nucleotide variant
siRNA	Small interfering RNA
shRNA	Short hairpin RNA
WGS	Whole-genome sequencing
WHO	World Health Organization

7.1 Introduction

Functional genomics is a branch of genomics that focuses on uncovering the functions of genes and the gene products of an organism. It aims to understand the relationship between genes, their resulting phenotypes, and the regulatory mechanisms that control gene expression and activity. In the past, genome sequencing has provided the complete sequence of an organism's DNA (Cooper 2000). The advent of high-throughput DNA sequencing technologies in the early 2000s revolutionized the field, allowing for a comprehensive analysis of the entire genome and transcriptome. However, functional genomics goes beyond that for its ability to investigate how the genes within that sequence work. Genome-wide association studies (GWAS) have identified thousands of disease-linked polymorphisms in the human population (Raizen and Wu 2011). Functional genomics encompasses a variety of experimental and computational approaches and particularly includes contributions of omics-based approaches involving other key branches in elucidating gene functions, gene expression identification of biomarkers, functional annotation, etc. (Zhou et al. 2016). In recent years, the various technologies of functional genomics, including gene profiling and gene editing, have enabled the generation of large-scale datasets and their analysis to unravel complex gene regulatory networks and identify novel gene functions (Gudmunds et al. 2022). The applications of functional genomics are broad and span various fields of biology, especially disease and medicine, as they can help comprehend the associated molecular pathways and in the discovery of therapeutic targets and the development of personalized medicine approaches. This chapter provides the dynamic approach of functional genomics and its aspects on human diseases.

7.2 Functional Genomics with Multi-Omics Approach

One of the key essences of functional genomics is gene expression profiling, which involves measuring gene expression levels in different cells or tissues under different conditions. This allows researchers to identify genes that are active in specific biological processes or disease states. However, functional genomics encompasses an integrative omics approach for studying gene regulation at different levels like DNA, RNA, etc. This particularly valuable approach helps reveal the complex regulatory system at the molecular level (Storz and Cheviron 2016). An important component of functional genomics is transcriptomics, which focuses on studying the complete set of cellular RNA transcripts including miRNA, lncRNA, and small RNAs. The study of the transcriptome is widely useful for interpreting the functional elements of the genome and molecular constituents of cells and tissues and unraveling biological pathways associated with development and disease (Raghavachari and Garcia-Reyero 2018). Epigenomics is a significant aspect of functional genomics that mainly focuses on the alterations in DNA methylation patterns and histone modifications that control gene expression. Multiple studies have emphasized the ability of epigenomics to clarify the causes of diseases, direct the development of diagnostic and prognostic tools, and offer in-depth knowledge for translational research (Moosavi and Ardekani 2016). The collective studies in the field of epigenomics highlight its crucial role and relation with functional genomics. In addition to examining DNAs and RNAs, the analysis of cellular metabolites was found to be very crucial for comprehending disrupted metabolic pathways that play a pivotal role in several diseases including glucose metabolism disorders and cancer. Metabolomics has also played a significant role in cancer research by identifying metabolic malfunctioning, elucidating the processes of drugs, and investigating the impact of dietary changes (Z. Li et al. 2021). Functional annotation is an essential aspect of functional genomics that enables researchers to gain knowledge about the functions of different genes in particular cell signaling pathways or cellular processes. The process entails attributing the biological functionalities to genes by utilizing many sources of information, such as sequence homology, protein domains, and gene ontology (GO) concepts (Ejigu and Jung 2020). In addition, proteomics is a distinct and advanced discipline that investigates the functional aspects and interactions of all the proteins produced by particular cell types. Proteomics complements functional genomic studies by providing information on protein end products under specific conditions (Mathesius et al. 2003) and revealing novel protein functionalities (Honoré et al. 2004). Human proteomic databases have helped further enhance the study of functional genomics in human disease (Gromov et al. 2002).

7.3 Techniques of Functional Genomics

Over the years, the advent of several powerful tools and techniques of functional genomics has helped unveil the complexity of gene regulation and expression patterns and underlying molecular mechanisms related to particular disease

development and progression and further develop their targeted therapies. We have discussed some of the major techniques used in functional genomics below:

1. ***Whole-Genome Sequencing (WGS) and Next-Generation Sequencing (NGS) Techniques***: WGS is a powerful tool in functional genomics that aids in the identification of suppressor mutations and other complex genetic interactions. NGS, however, reveals some more details about how individual genomes and individual aspects of their regulation differ from each other (Qin 2019). NGS technologies have not only enabled the sequencing of ancient DNA samples but also immensely helped solve intricate biological problems and develop personalized medicine, thus overall revolutionizing WGS (Morozova and Marra 2008). These technologies are being used to improve the accuracy of reference sequences, identify genomic variations, and predict genetic defects and DNA sequence alterations, such as single-nucleotide variants (SNVs), structural variations, and copy number alterations, thus majorly contributing to the studies in functional genomics.
2. ***Gene Expression Profiling***: Gene expression profiles have become a more feasible and logical alternative to sequence similarity searches in a wide range of experimental conditions. Identification of gene expression profiles at the single-cell or small-cell level is particularly relevant for understanding pathological processes such as tumorigenesis (Saadatpour et al. 2015). DNA microarrays have emerged as a powerful tool for gene expression profiling, and microarray technologies are rapidly attaining a central platform for functional genomics (Carpenter and Conlan 2021). Advancements in gene expression profiling have proven more effective in characterizing diseases and identifying gene expressions.
3. ***RNA Sequencing***: The use of RNA sequencing in transcriptomics has revolutionized the field of functional genomics in the context of gene function analysis. RNA sequencing is a powerful tool for studying the transcriptome of a cell, providing a clear understanding of gene expression dynamics (Kukurba and Montgomery 2015). It is mostly used to detect and characterize gene expression, mutations, and noncoding RNAs (International Journal Of Molecular Sciences Editorial Office 2016). Recent advances in RNA sequencing have expanded its applications to include single-cell gene expression and RNA structure (Stark et al. 2019). RNA interference (RNAi) technology (as discussed in the next point) has been a key tool in RNA sequencing (Scherr et al. 2004).
4. ***RNA Interference (RNAi):*** RNA interference, or RNAi, is a high-end and widely applied technique of functional genomics where small RNA molecules are used to inhibit gene expression and explore gene functions in biological processes and disease pathways. Small interfering RNA (siRNA), double-stranded RNA molecules, or short hairpin RNA (shRNA) molecules are target-specifically delivered into cells to silence the expression of individual genes. High-throughput RNAi approaches like the one based on microarray can be employed in large-scale gene screening to identify genes involved in specific phenotypes (Vanhecke and Janitz 2005). This method enables researchers to systematically "knock

down" individual genes, study the resulting changes in cellular processes or phenotypes, and identify potential therapeutic targets. Therefore, the advantages of RNAi are systematic analysis of gene function on a large scale and help in the comprehensive functional analysis in combination with other high-throughput assays.

5. ***High-Throughput Functional Assays or Screening Methods***: Functional genomics aims to comprehend the function and interactions of genes on a large scale. One commonly used approach in functional genomics is functional genetic screening, which involves systematically perturbing genes or gene pathways and assessing the phenotypic consequences (Ipe et al. 2017). In this regard, high-throughput screening techniques enable simultaneous analysis of thousands of genes or gene products. High-throughput screening has revolutionized the field of genomics, allowing scientists to efficiently identify and characterize gene functions concerning certain conditions like disease.
6. ***Gene Editing***: Techniques of gene editing are used to generate libraries of mutant alleles highlighting the genetic variants in the human populations and aiding in the deciphering of genotype–phenotype relationships on a large scale. The application of gene editing techniques has significantly advanced the field of functional genomics. Gene editing techniques, particularly CRISPR/Cas9, have revolutionized functional genomics by allowing precise modifications and editing of specific DNA sequences (Gaj et al. 2016). By introducing specific alterations in a precise and efficient manner, CRISPR-based screening of gene function on a genome-wide scale facilitates systematic investigation of the functional implications of individual genes (Fig. 7.1). By using pooled CRISPR libraries of large cell populations, and high-throughput CRISPR screening, valuable insights into the associated signaling pathways and cellular responses can be made available. CRISPR/Cas9 has become an indispensable tool in functional genomics as it provides the understanding of key genes and their functional dependencies via regulation on a molecular level and helps identify the drivers for various diseases.

Human embryonic stem cells (hESCs) can be modified to express their features through the CRISPR machinery. CRISPRn could be used for gene knockout, CRISPRi for gene silencing, or CRISPRa for gene activation. These screening strategies can include survival/proliferation-based and FACS/MACS-based screens for simpler phenotypes, single-cell-transcriptomics-based screens and imaging-based screens for more complex phenotypes. The representation of the strategy was published by Li et al. (2023a) and is presented here with due permission from Elsevier.

7.4 Crucial Role of Functional Genomics in Human Disease Biology

Many major diseases like cancer, cardiovascular diseases, autoimmune diseases, and neurological disorders are caused by a dysregulation of a complex interplay of genes. GWAS have genotyped human patient samples and compared genomic

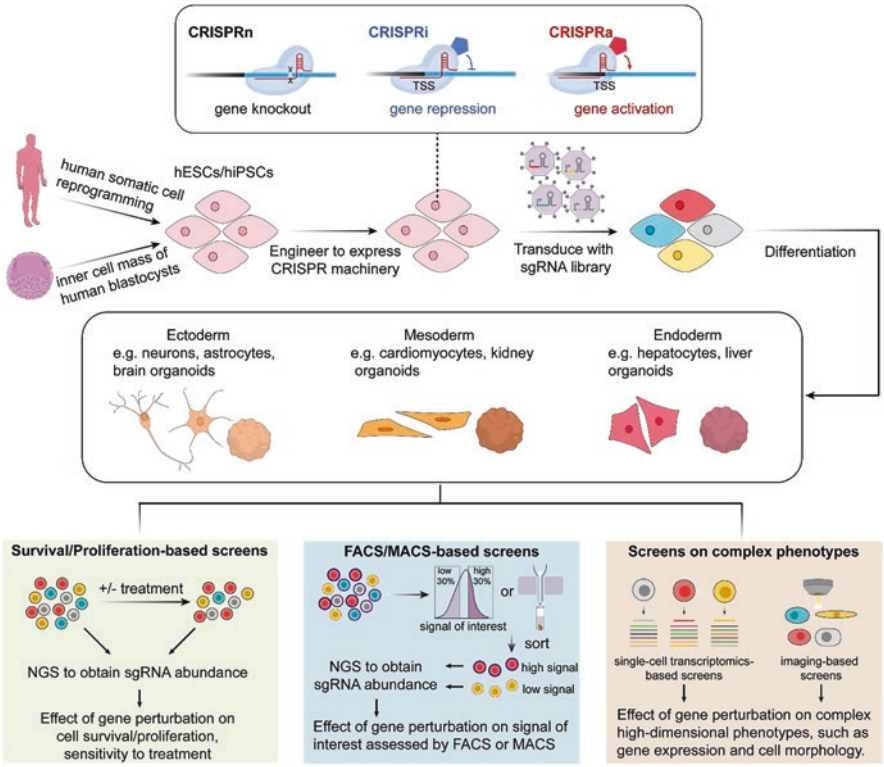

Fig. 7.1 Functional genomics screening of hPSC-derived cells by CRISPR technology

profiles to reveal thousands of disease-linked polymorphisms or genetic variants contributing to specific diseases. However, detailing the causative gene expression or functional changes underlying those associations has been elusive in many cases. Functional genomics aims to deconvolute the link between genotype and phenotype by making use of large-omics datasets and next-generation gene and epigenome editing tools to perturb particular genes of interest. Some crucial roles of functional genomics in the field of human disease biology have been explained hereunder:

1. First, it helps unveil the complex genetic landscape of a certain disease by systematic exploration, screening, and analysis of huge genetic data and results of functional genomic assays (e.g., gene expression profiling). This reveals the set of altered genes, mutations, and deregulated molecular pathways particularly associated with a particular disease and can predict the disease's risks. Furthermore, functional genomics helps decipher the functional consequences of the genetic variations concerning disease biology.
2. Another critical role of functional genomics is the identification of biomarkers and their refinement concerning their types and association with specific diseases. Biomarkers can be simply defined as "*A defined characteristic that is*

measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention" (Califf 2018). Some of the common categories of biomarkers are diagnostic biomarkers (whose presence confirms diagnosis of a disease) and prognostic biomarkers (predict the future progression of an individual's disease and the likelihood of disease recurrence). The need to find novel and specific biomarkers for human diseases is escalating at a rapid pace to know the underlying genetic susceptibility of disease, predict risks of the diseases in advance, and develop diagnostic tools to detect disease at an earlier and treatable stage. Analysis of gene expression levels and gene mutations through gene expression profiling, high-throughput technologies, and DNA sequencing enables researchers to identify disease-associated biomarkers.

3. Functional genomics has immense significance in unraveling the specific nature of drug resistance (Poulton and Rock 2022). Screening altered gene expressions and analyzing molecular pathways through the techniques of functional genomics help clinicians identify genes that confer drug resistance. Functional genomics helps check the response of drug treatment and find out if the development of drug resistance is playing a key role in the case of inefficient responses. Moreover, analysis of gene expression datasets can further aid in dissecting the drug resistance mechanisms to find therapeutic ways to overcome the drug resistance or change to alternative therapies.
4. Functional genomics provides valuable insights into the impact of noncoding regions of the genome on gene expression and regulation (Kuksa et al. 2022). It has been observed that in the context of whole-genome sequencing (WGS) data, noncoding variants are prevalent with a significant influence on disease etiology (Kuksa et al. 2022). For instance, the role of noncoding regions in cancer development is increasingly recognized. However, the identification of such crucial noncoding loss-of-function variants is a challenge that requires the development of new strategies and techniques (Zappala and Montgomery 2016). Strategies and techniques of functional genomics aid in the investigation of the functional impact of noncoding regions (e.g., long noncoding RNAs or enhancer elements) of the genome.
5. The translational role of functional genomics is promising and significant in the medical field. The sophisticated tools of functional genomics help identify the novel molecules associated with a disease that can be used to develop novel targets for drug interventions and preclinical and clinical studies. For instance, targeted therapies like tyrosine kinase inhibitors for lung adenocarcinoma with EGFR mutations demonstrated significantly benefited patient outcomes (Fu et al. 2022). This type of drug development is clear proof of the translational implications of functional genomic studies in clinical applications.
6. Functional genomics plays a crucial role in making tailor-made treatment more successful in today's personalized medicine era. Identification and analysis of disease-specific gene alterations, expression levels of specific mutated genes, and deregulated molecular pathways with the help of functional genomics are guiding clinicians in selecting a particular targeted therapy for a specific patient or similar cases. Therefore, functional genomics techniques like gene expression

profiling and DNA sequencing are aiding in the optimization of treatment based on individual patient genetic signatures and in advancing the field of personalized medicine.

7.5 Major Human Diseases and Implications of Functional Genomics

According to the current health scenario, some diseases are significantly burdening the health sector globally. We have presented some of those diseases below, to describe the role of functional genomics as a major contributor to their drug development and personalized treatment scopes:

7.5.1 Cardiovascular Diseases (CVDs)

CVDs are a group of disorders including coronary heart disease and cerebrovascular disease that are related to the heart and blood vessels. According to the statistical report from the World Health Organization (WHO), CVDs are the leading cause of death worldwide, taking around 17.9 million lives each year (Cardiovascular Diseases n.d.). Functional genomics would help identify the specific genetic variants and transcriptomic signatures for the pathogenesis of CVD. Moreover, it will unveil molecular mechanisms related to CVD pathology. Functional genomics has significantly advanced our understanding of cardiovascular disease biology, particularly through the identification of genes associated with coronary artery disease (CAD) and type 2 diabetes (De Rosa et al. 2018). Functional genomics also plays a crucial role in the diagnosis and therapy of cardiovascular diseases through the identification of genetic variants that have a direct influence on the susceptibility of disease and treatment response (Kathiresan and Srivastava 2012). A majority of the variants associated with CVD and myocardial infarction susceptibility in humans reside in noncoding regions, and with the help of functional genomics, it would be easier to identify major variants to improve the understanding of CVDs. Single nucleotide polymorphisms (SNPs) are common in candidate genes for cardiovascular diseases, and reports indicated that through the high-end techniques of functional genomics, the disease could be diagnosed in time (Sitinjak et al. 2023). Yang et al. observed a specific pattern of expression profile that helped researchers identify biomarkers that can predict the risks of atherosclerosis (B. Yang et al. 2022). The discovery of novel therapeutic targets and biomarkers contributes toward early diagnosis, risk predictions, and advancement of target drug development. The advent of advanced technologies, such as CRISPR/Cas9 and RNA interference, has immensely contributed to the field of cardiovascular diseases regarding comprehensive exploration of gene function and identification of novel drug targets. Such functional genomics-related advancement for personalized intervention will pave the way for more effective management of CVDs in the future.

7.5.2 Cancer Biology

Cancer is a complex and heterogeneous disease whose development and progression are majorly regulated by the pivotal role of genetic alterations. The Human Genome Project and Cancer Genome Atlas (TCGA) project helped sequence and analyze tumors leading to the identification of novel cancer-associated mutations and key molecular pathways (Weinstein et al. 2013). The discovery of oncogenes (e.g., *ras*) and tumor suppressor genes (e.g., *p53*) has made functional genomics fundamental in cancer research. Importantly, functional genomics helps identify the cancer-specific genes, mutated genes, and genetic interactions in the progression of cancer development. Functional genomics has several integrative components, and in-depth analysis of these components could help identify candidate cancer genes that are frequently mutated across multiple cancer types or show co-expressions (Sundara Rajan et al. 2020). With the help of functional genomics, researchers assess the response of cancer cells to various therapies and comprehend the development of drug resistance in different cancer types. In particular, transcriptomics helps analyze tumor heterogeneity-based distinct gene expression signatures to further analyze and dissect the altered molecular pathways and develop relevant therapeutic strategies. Conversely, the identification of novel metabolic biomarkers related to metabolic susceptibility for the growth and survival of tumors is aided by the use of metabolic profiling techniques (W. Yang et al. 2018). Of note, epigenomic techniques unveil the aberrant DNA methylation patterns and histone modifications in human malignancies, which further help find effective solutions that may normalize the dysregulated gene expressions. The rational development of siRNA and shRNA expression libraries has strengthened the application of RNAi in assigning critical functions to cancer genes and understanding their molecular targets (Silva et al. 2004). Systematic perturbation of oncogenes and analysis of their functional consequences will help researchers uncover key genetic drivers in tumorigenesis. It was observed that gene perturbation in cancer cells via RNAi or gene knockout by CRISPR-Cas9 gene editing technologies helped researchers identify major changes in cell proliferation, migration, survival, or drug response patterns in cancer (Katti et al. 2022). Moreover, CRISPR-based screens helped significantly unravel the type of gene editing or targeted therapy that should be developed for the therapeutic interventions for cancer. Functional genomics contributes immensely toward the identification of genomic markers for cancer diagnosis and prognosis in a noninvasive and accurate manner (Mehta et al. 2010) unlike through invasive biopsies and tissue sampling procedures. Thus, early cancer detection and subsequent interventions leading to improved patient outcomes are achievable through novel biomarker identification through the technologies of functional genomics. Therefore, rational approaches to functional genomics, including functional genetic screening, large-scale genome profiling, integrated analysis of epigenomics, transcriptomics, and metabolomics, and in-depth investigation of noncoding regions of the genome have significantly revolutionized cancer research and initiated the development of target-specific therapies that are being used in personalized medicine for improving cancer patient outcomes. In addition to this, functional genomics could be applied to

identify the drug targets for the decoding of cancer cell signaling networks. Systematically, researchers perturbed genes within cancer signaling pathways, which allowed for the delineation of signaling cascades crucial for cancer cell survival and metastasis and can be analyzed by computational tools (Shimada et al. 2021). This approach enables the development of targeted therapies that disturb specific molecules within these networks, offering more precise and effective strategies for therapeutic intervention. Several reports demonstrated how functional genomics has helped unravel the complexity of cancer signaling pathways, providing valuable perceptions for targeted specific drug development (O'Loughlin and Gilbert 2019). Despite these advancements in biomedical research, challenges also persist in applying functional genomics to identify clinically viable drug targets. Several issues including off-target effects and the complicated nature of biological systems require continuous innovation and improvisations. Kabadi et al. discussed the challenges and opportunities in translating functional genomics to drug design and development, emphasizing the need for advanced technologies and rigorous validation processes to harness the full potential of functional genomics for proper drug target identification (Kabadi et al. 2020).

7.5.2.1 Functional Genomics in Cancer Biomarker Discovery

The identification and validation of genetic markers have significant potential for improving cancer diagnostics, prognostics, and therapeutic decision-making processes. This can ultimately result in better patient outcomes, disease prognosis, and a more individualized approach to cancer care (Hammond et al. 2010). For instance, if a genetic cancer marker is associated with a poor prognosis, clinicians may consider administering more aggressive chemotherapeutics or they can enroll the patient in clinical trials for novel treatments (Malone et al. 2020). Conversely, if a genetic marker indicates a better prognosis, it was observed that patients may be exposed to unnecessary side effects of aggressive chemo- and radiotherapy and may instead receive more conservative interventions. Genomic markers can help immensely in identifying specific molecular pathways that are aberrantly activated or downregulated in cancer cells. By targeting these pathways, researchers and clinicians can develop tailored therapeutic approaches, thereby increasing the treatment efficacy and reducing the risk of adverse effects (Collins and Barker 2007). Precision medicine, which involves customizing treatment plans based on a patient's genetic profile, is considered a direct consequence of the identification of genetic biomarkers for cancer (Collins and Varmus 2015). The emergence of single-cell cancer genomics has revolutionized the field of cancer research. This groundbreaking approach, being a new avenue of functional genomics, provides unprecedented insights into the complexity and diversity of tumors at the individual cell level. Unlike traditional bulk sequencing methods that overlook genetic variations and cellular dynamics, single-cell genomics allows for a much deeper understanding of clonal evolution, tumor heterogeneity, and the identification of rare subpopulations with unique molecular profiles. Recent studies have demonstrated the remarkable capabilities of single-cell technologies in unraveling the intricate genomic architecture of different cancer types. Importantly, studies by Navin et al. used single-cell

sequencing to map the evolution of breast cancer, revealing dynamic subclonal populations that contribute to treatment resistance and disease progression (Navin and Hicks 2010). Such an experimental approach demonstrates how single-cell genomics can improve therapeutic strategies by focusing on specific genetic alterations that drive malignancy at the cellular level. Moreover, advancements in single-cell RNA sequencing (scRNA-seq) have enabled researchers to explore the transcriptomes of tumor cells, shedding light on the transcriptional heterogeneity within cancer cell populations. A report by Tirosh et al. showed the employment of scRNA-seq to uncover distinct cellular states associated with drug resistance in melanoma, further highlighting the powerful applications of this technology in cancer biology (Tirosh et al. 2016). The possibilities of using single-cell techniques to customize precision medicine interventions based on the distinct transcriptional profiles of individual cancer cells are highlighted. Single-cell genomics has not only helped us understand the differences within tumors but has also played a crucial role in deciphering the tumor microenvironment. A study by Zheng et al. demonstrated the use of single-cell analysis for investigating the interactions between cancer cells and immune cells in the tumor microenvironment, revealing the molecular mechanisms behind immune evasion and suggesting new targets for immunotherapy (Zheng et al. 2017). Despite these advancements, challenges still exist in the field, including the expensive costs and technical difficulties associated with single-cell sequencing. Furthermore, integrating multi-omics data from single cells remains a daunting task. It is crucial to continue researching and advancing technology to overcome these challenges and fully capitalize on the potential of single-cell genomics in uncovering the complexities of cancer biology.

7.5.2.2 Functional Genomics and Cancer Immunotherapy

Functional genomics has great advantages for understanding the complex interplay between cancer and the immune system. The dynamic nature of this interaction can be elucidated through high-throughput technologies, such as transcriptomics and proteomics, which provide a comprehensive view of changes occurring in both cancer cells and immune cells at the molecular level (Valdes-Mora et al. 2018). Recent studies indicated that transcriptomic profiling of key genes associated with specific cancers identifies major signaling pathways involved in tumor immune evasion (Hong et al. 2024). By integrating both genomic data with clinical outcomes, researchers have discovered the potential of immunotherapies and identified immune function-related signature genes that could predict treatment response and patient survival (Chen et al. 2022). Moreover, functional genomics approaches, especially single-cell isolation and sequencing have also provided valuable insights into the molecular mechanisms underlying immune evasion by cancer cells (Fig. 7.2). Studies suggested that with the integration of genomics and epigenomics data, key genetic and epigenetic alterations in cancer.

Drop-sequencing is an innovative method that employs droplet microfluidics and library preparation for next-generation sequencing. The figure represents the study by Mahgoub et al. (2023) that revealed cell clustering and preparation of functional

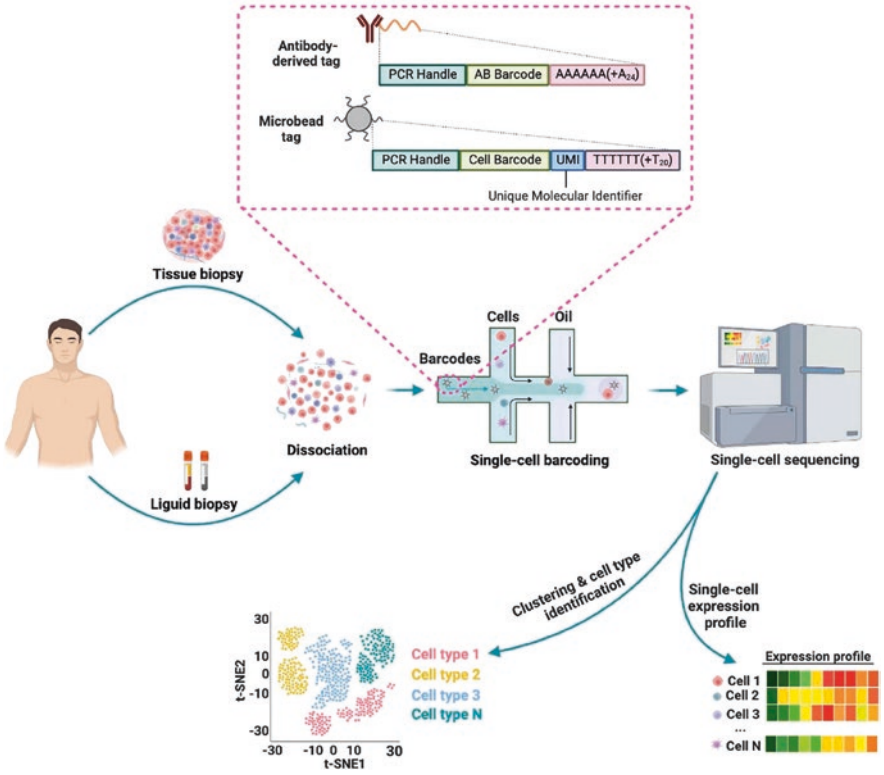

Fig. 7.2 Strategies for single-cell isolation and sequencing in cancer research

mapping with gene expression profiles at the single-cell level. The illustration is presented here with due permission from Elsevier.

Cells were identified by researchers, and these epigenetic modifications in the cancer cells enable them to escape immune surveillance (Cao and Yan 2020). Interestingly, functional genomics analyses have revealed the importance of noncoding RNAs, including microRNAs and long noncoding RNAs, in modulating the immune response and affecting tumor immune evasion (Guo et al. 2022).

7.5.3 Functional Genomics in Neurodegenerative Disease Research

The application of functional genomics in neurodegenerative disease biology is a comparatively new field of research. Undoubtedly, the combination of functional genomics with single-cell profiling of human patient tissues will play a significant role in uncovering disease pathogenesis. Potashkin et al. provided a bioinformatics analysis that specifically investigates the crucial genes and biochemical pathways that have the potential to initiate dementia. In particular, research revealed that

phosphodiesterase 4D-interacting protein plays an important role in inducing frontal brain dementia (Potashkin et al. 2020). Neurodegenerative diseases, such as Alzheimer's, Parkinson's, and Huntington's, present an intimidating challenge because of their intricate etiology and limited therapeutic opportunities. Functional genomics stands as a beacon of hope in this landscape, offering a good perception of the molecular underpinnings of these diseases, and could help in the discovery of neurodegenerative disease biomarkers for early diagnosis and treatments.

7.5.3.1 Genome-Wide Association Studies (GWAS) for Genetic Identification of Neurodegenerative Disease Contributors

Functional genomics, namely using GWAS, is crucial in revealing the genetic factors that cause neurodegenerative disorders. Recent research by Jansen et al. used extensive genomic data to.

To unlock the complete functional understanding of the human genome, it is imperative to integrate and combine personal genetic and phenotypic data obtained from health records worldwide. This comprehensive and innovative approach is crucial to truly harness the potential of precision medicine. The figure was produced by Calame et al. for discussing the role of functional genomics in predicting mitochondrial neurodevelopmental disorders (Calame and Emrick 2024) and is represented here with due permission from Elsevier.

discover new genetic locations linked to Alzheimer's disease. This research served as a basis for comprehending genetic elements that contributed to the chance of developing the disease and for identifying prospective biomarkers (Jansen et al. 2019). GWAS has great potential to delineate the genetic basis of neurodegenerative diseases, but the results sometimes show inconsistency and could be challenging to interpret (Gandhi and Wood 2010). However, these intensive studies have identified specific loci with risk variants for Alzheimer's disease and provided datasets for investigating transcriptional mechanisms related to the disease pathogenesis (Neuner et al. 2020). GWAS was shown to be very helpful in exploring the genetic underpinnings of various neurological disease predictions and potential therapeutic drugs (Tan et al. 2014). As the advancement and the applications of GWAS are highly increasing, GWAS could be an important tool for the diagnosis and treatment of neurological diseases (Cowperthwaite et al. 2010).

7.5.3.2 Functional Annotation: Connecting Genomic Variants and Disease Pathology

After the discovery of genetic variants, functional genomics became more popular in determining their biological significance. The development of CRISPR/Cas9 editing technologies offers a more profound comprehension of these polymorphisms that play a significant role in disease progression (Li et al. 2023b). Such understanding is crucial for identifying prospective neurodegenerative disease biomarkers. The process of functional gene annotation involves the assignment of biological functions to genes and gene variants using the gene ontology (GO) technique. By in-depth analysis of the functions of genes and gene variants, researchers can gain insights into the molecular basis of these diseases (Fig. 7.3). Studies suggested

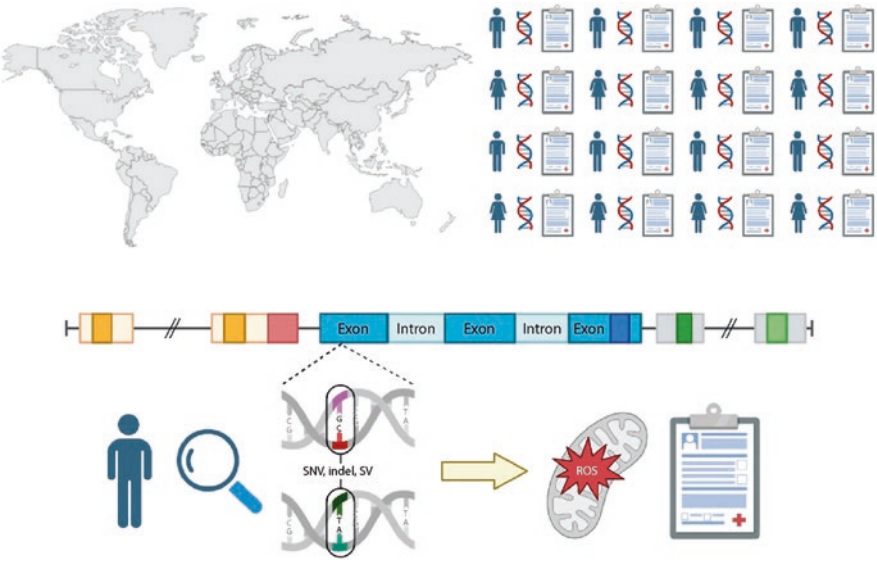

Fig. 7.3 Integration of global data for the functional annotation of the human genome. The figure illustrated here shows the integration of combined genetic and phenotypic data obtained from global health records. The data was produced by Calame & Emrick for discussing the role of functional genomics in predicting mitochondrial neurodevelopmental disorders (Calame & Emrick, 2024) and represented here with due permission from Elsevier

that the use of invertebrate in vivo model systems, such as flies and worms, will help classify the genetic variants and understand their role in neurological disorders. In addition, the "Gene Ontology Consortium" is working on improving the neurological domains of the GO resources all over the world, which will benefit the research community working on dementia and Alzheimer's diseases (Kramarz et al. n.d.).

7.5.3.3 Transcriptomics: Deciphering Modified Gene Expression Patterns

Functional genomics uses transcriptomics to elucidate alterations in gene expression linked to neurodegenerative disorders. The research conducted by Mathys et al. on Alzheimer's disease demonstrates the effectiveness of transcriptome studies in finding unique patterns associated with the disease. This paves the way for the identification of transcriptomic biomarkers that can indicate the beginning and progression of the disease. In current days, transcriptomics studies using single-cell RNA sequencing are being used to identify biomarkers for neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, and vascular/mixed dementia (Shigemizu et al. 2020). These studies provided great insights into the molecular landscape and cellular basis of disease types and severity, revealing cellular heterogeneity and differences in the gene expression patterns. By analyzing the transcriptomic data from individual cells, multiple cell subsets and functional changes during disease progression have been identified, leading to a much deeper understanding of neurodegenerative disease pathology (Courtney et al. 2010). Moreover, transcriptomics analysis

also identified different dysregulated signaling pathways, including immune response and glucose metabolism, in Alzheimer's disease (Bagyinszky et al. 2020). Furthermore, gene expression analysis revealed a big promise in diagnosing neurodegenerative diseases and their biomarker genes such as *apoe*, *psen1*, *abca7*, and *snca* (Martínez-Iglesias et al. 2023). These research findings demonstrated the applications of transcriptomics analysis in identifying biomarkers and understanding the underlying molecular pathology of neurodegenerative diseases.

7.5.3.4 Proteomics: Investigating Protein Biomarkers and Aggregates

Proteomic methods, including mass spectrometry, play a crucial role in identifying biomarkers by revealing alterations in protein profiles and aggregates linked to neurodegenerative disorders. Saez-Atienzar et al. emphasize the capacity of proteomics to identify distinct proteins as biomarkers, providing a significant understanding of disease causes and prospective targets for therapy. Functional genomics has a direct contribution to enabling the analysis of proteins and their interactions, resulting in the detection of important protein biomarkers implicated in neural dysfunction in Alzheimer's disease (Saez-Atienzar et al. 2021). Functional genomics approaches including transcriptomics and proteomics can be employed to investigate axons and synapses related to disease progression. These techniques possess the ability to discern disease-specific proteins, hence facilitating further exploration of novel drug targets for pharmaceutical research. Additionally, functional genomics can help identify certain biomarkers for precise diagnosis, monitor the advancement of diseases, and assess the drug response during treatment in neurodegenerative disorders.

7.5.3.5 Integration of Multi-Omics Data: Comprehensive Biomarker Discovery

Functional genomics is highly proficient in integrating data from many omics levels, such as genomics, transcriptomics, and proteomics. The multi-omics method offers a thorough understanding of the molecular characteristics of neurodegenerative illnesses (Athieniti and Spyrou 2022). This technique facilitates the identification of integrated biomarkers that effectively represent the intricate nature of these ailments. Integration of multi-omics data is being used for the detection of neurodegenerative disorders. Researchers adopted various computational pipelines and techniques to facilitate the process. For example, the joint analysis of different datasets, including gene expression, protein abundances, and drug screening data, was found to be useful in identifying potential therapeutic targets for synucleinopathies like Parkinson's disease (Menon et al. 2022). Moreover, analysis of transcriptomic, proteomic, and metabolomic data was also found to be crucial for the detailed investigation of deregulated pathways associated with Alzheimer's disease. Such a strategy could be applied to comprehend the disease pathology by observing the changes in neurotransmitter synapses, oxidative stress, and inflammatory pathways (Singh et al. 2019). Deep-learning models, particularly those applying transfer learning, have also been employed to accurately identify Alzheimer's disease from clinical data and MRI. In addition, simultaneous integration of multiple high-dimensional multi-omics data modalities through similarity network fusion (SNF) can provide

an in-depth understanding of the heterogeneity of neurodegenerative disease conditions (Wang et al. 2022).

Functional genomics plays a crucial role in identifying biomarkers, which not only enable early detection but also pave the way for precision medicine strategies. The incorporation of genetic, transcriptomic, and proteomic indicators into diagnostic tools and therapeutic techniques has significant potential for alleviating the impact of neurodegenerative illnesses. Functional genomics is an essential tool for alleviating the impact of neurodegenerative illnesses, specifically by identifying biomarkers. Functional genomics enables the identification of genetic, transcriptome, and proteomic complexities associated with these illnesses. This knowledge facilitates early detection, individualized treatment, and a more efficient strategy to combat neurodegenerative diseases.

7.5.3.6 Functional Genomics and Autoimmune Disorders

Understanding the Intricate Nature of Autoimmune Diseases

Autoimmune disorders can be considered as heterogeneous conditions characterized by the immune system's assault on one's own tissues and pose substantial health issues. The complex nature of these illnesses necessitates novel disease diagnostic strategies, and functional genomics has emerged as a pivotal area in comprehending their genetic foundation and identifying biomarkers for prompt detection and focused therapeutic interventions.

GWAS in Autoimmune Disease Genetics

The field of functional genomics, specifically through genome-wide association studies (GWAS), has played a crucial role in uncovering genetic variables linked to autoimmune illnesses. Recent research, shown by the study conducted by Ma et al., has uncovered multiple regions in the genome that make individuals more prone to autoimmune illnesses (Ma et al. 2015). This has helped better understand the complex genetic factors involved in these disorders and has laid the groundwork for identifying biomarkers. These extensive genomic studies not only discover risk locations but also provide an understanding of the possible functional effects of genetic variants. GWAS have revolutionized our understanding of the genetic basis of autoimmune diseases by identifying numerous risk loci shared among different autoimmune disease conditions, suggesting a common genetic basis (Lettre and Rioux 2008). These loci were considered as "expression quantitative trait loci (eQTLs)" that play an important role in regulating gene expression involved in immune cell functions (Nica and Dermitzakis 2013). It was observed that the genetic architecture of autoimmune diseases is complex, but it may share variable genetic effects across different disease symptoms, particularly in the major histocompatibility locus (Goris and Liston 2012). With the help of GWAS, researchers can locate specific genes and related pathways that may be involved in the pathogenesis of autoimmune diseases.

Functional Annotation of Genetic Variants: Linking Genomic Information to Disease Mechanisms

Functional genomics not only identifies genetic variations but also allows for the annotation of their functional effects. The utilization of CRISPR/Cas9 editing and functional tests, as exemplified by several research groups, provided a valuable understanding of the molecular pathways by which genetic variants contribute to autoimmune disorders (Lee et al. 2022). Having a comprehensive analysis is essential for recognizing potential biomarkers that indicate illness pathways and severity. CRISPR/Cas9 technologies enable accurate modification of genes, facilitating the discovery of crucial regulatory elements and the assessment of their influence on autoimmune responses. Several studies have demonstrated that the majority of risk variants related to autoimmune diseases are located in the noncoding region of the genome and are likely to regulate gene expression (Jones et al. 2019). These risk variants may dysregulate splicing and the expression pattern of specific genes, resulting in the development of autoimmune disorders. Moreover, integrative analyses using expression quantitative trait loci (eQTLs) and splicing quantitative trait loci (sQTLs) were employed to understand how functions of noncoding variants are contributing to the risk. Additionally, post-genome-wide association studies (GWAS) were employed to prioritize likely causal genetic variants and identify target genes related to autoimmune diseases (Gerussi et al. 2022). Such strategies involve extensive gene annotation, molecular modeling, and integrative functional genomics and epigenomics analyses.

Transcriptomics: Analyzing Gene Expression Patterns in Autoimmune Diseases

Functional genomics, using transcriptomics, enables researchers to investigate modified gene expression patterns linked to autoimmune disorders. The research conducted by Fang et al. in the field of rheumatoid arthritis serves as a prime example of how transcriptome studies can effectively discover unique patterns associated with the condition (Fang et al. 2021). This creates opportunities for identifying transcriptome biomarkers that can function as indicators for the initiation, advancement, or response to the treatment of a disease. Transcriptomic studies not only identify genes associated with autoimmune disorders but also reveal complex networks and processes involved in the disruption of the immune system. Transcriptomic analysis is very crucial in diagnosing and treating autoimmune diseases by identifying differentially expressed genes and associated molecular pathways. Gene expression patterns can serve as signature biomarkers for early diagnosis and potential therapeutic targets for autoimmune diseases (Chun et al. 2023). Research showed that integrative analysis of immunophenotyping and transcriptomic data could help classify patients into subgroups based on specific immune cell infiltrations and gene expression profiles. Such studies suggested the use of transcriptomic analysis for a better understanding of disease pathogenesis and personalized treatment approaches (Casamassimi et al. 2017). Additionally, rule-based machine learning models and gene networks could be useful tools to identify gene expression patterns and molecular endotypes that distinguish between disease severity levels and predict clinical

outcomes (DiNardo et al. 2022). Of note, categorizing patients into molecular clusters based on their gene expression profiles would be helpful for the clinical characterization of individual patients more effectively and tailoring treatment strategies accordingly.

7.5.3.7 Proteomics: Revealing Protein Biomarkers and Pathogenic Processes for Autoimmune Diseases

Proteomic methods, including mass spectrometry, play a crucial role in identifying biomarkers by revealing alterations in protein patterns linked to autoimmune disorders. The study conducted by Ohlsson et al. demonstrates the capacity of proteomics to identify precise proteins as biomarkers, providing valuable information on disease causes and prospective targets for therapeutic interventions (Ohlsson et al. 2021). Proteomics not only detects protein biomarkers but also uncovers posttranslational changes and protein–protein interactions that are crucial for comprehending the molecular complexities of autoimmune reactions. Proteomics approach allows researchers to establish the connections between the proteins produced by cells or tissues and the development autoimmune diseases. Studying the proteome would be helpful in identifying new protein markers for diagnostics and potential targets for drug development. Such valuable information complements the genetic data obtained through genomics and aims to characterize the functional proteins, analyze the genetic variations to comprehend their expression levels during normal and diseased conditions, study their interactions, etc. In the near future, the fields of proteomics and computational biology will focus on profiling the autoantibodies in autoimmune diseases. Moreover, patients would be classified based on the severity of disease; identification of subsets of patients with a similar set of autoantibodies, studying the spread of autoreactive B-cell epitopes, and identifying new biomarkers could be possible by applying advanced proteomics. Ultimately, proteomics will enhance our understanding of the immunopathogenic mechanisms behind autoimmune disorders as well as early diagnosis, prognosis, and better management of patients. Reports indicated a crucial role of autoantigens such as anti-neutrophil cytoplasmic antibodies (ANCA), myositis-specific antibodies, anti-endothelial cell antibodies (AECA), anti-red cell antibodies, and anti-endomysial antibodies in autoimmune diseases (Kang et al. 2020). Importantly, the use of protein microarrays has proven to be a powerful molecular tool in diagnosing autoimmune diseases including systemic lupus erythematosus, rheumatoid arthritis (RA), polymyositis, and systemic sclerosis. The new advancements in proteomics research revolutionized the identification methods for autoantigens and their corresponding autoantibodies. Currently, researchers combined traditional techniques like 2-DE and Western blotting with cutting-edge mass spectrometric (MS) analysis and bioinformatics tools for protein database retrieval and analysis (Selected Bioinformatic Tools and MS (MALDI-TOF, PMF) Techniques Used in the Strategy for the Identification of Oat Proteins After 2-DE|Springer Nature Experiments n.d.).

7.5.3.8 Utilization of Integrative Multi-Omics Approaches: Comprehensive Identification of Biomarkers

Functional genomics is highly proficient in the integration of data from several omics levels, such as genomics, transcriptomics, and proteomics. The utilization of an integrative multi-omics strategy, as exemplified by the research conducted by Chu et al., offers a thorough understanding of the molecular characteristics of autoimmune illnesses (Chu et al. 2021). This technique facilitates the identification of integrated biomarkers that effectively encompass the intricate nature of these ailments. By adopting a holistic approach, researchers can detect synergistic interactions among several omics layers, leading to a more comprehensive comprehension of the fundamental illness mechanisms. In recent times, omics studies have gained popularity for their ability to develop precise and efficient methods for identifying autoimmune disorders. These studies involve obtaining and analyzing a specific layer of biological information without any prior filtering or targeting of data. The goal of this approach is to gather as much information as possible, without focusing on specific associations or hypotheses. The omics approaches, such as genomics, epigenomics, transcriptomics, proteomics, and metabolomics, are named after the biological layers they cover. In particular, the use of multi-omics approaches shows promise in aiding the understanding of underlying mechanisms and the diagnosis and management of autoimmune conditions. However, despite the thorough research, their applications in autoimmunity is still limited. To successfully apply multi-omics to autoimmune diseases, critical steps such as data collection, data handling, and analysis must be taken into account.

7.5.3.9 Clinical Applications: Transitioning from Biomarkers to Precision Medicine

Functional genomics plays a crucial role in identifying biomarkers, which not only facilitates early detection but also offers the potential for personalized precision medicine strategies for specific patients. The incorporation of genetic, transcriptomic, and proteomic biomarkers into diagnostic tools and therapeutic strategies has the potential to fundamentally transform the treatment of autoimmune disorders, thereby alleviating the overall impact on affected persons (Åkesson et al. 2023). Precision medicine in autoimmune diseases entails customizing treatment approaches according to the distinct molecular characteristics of individuals, hence enabling more efficient and individualized interventions. Functional genomics plays a crucial role in the endeavor to alleviate the impact of autoimmune illnesses, specifically by identifying biomarkers. Functional genomics explores the complex genetic, transcriptomic, and proteomic aspects of these illnesses, providing opportunities for early identification, tailored therapy, and a more efficient strategy to address autoimmune diseases.

7.5.3.10 Ethical and Regulatory Considerations in Functional Genomics Research

At the forefront of biomedical innovation, gene editing and manipulation in cancer research offer promising advancements in our understanding and treatment of

cancer. However, this scientific frontier brings with it a range of ethical considerations that require careful examination to ensure responsible and fair use. One key ethical concern in gene editing for cancer research revolves around the precision and potential unintended effects of these technologies. Despite the impressive specificity of CRISPR/Cas9, off-target effects remain a challenge. Recent studies have emphasized the need for ongoing research to minimize off-target effects and enhance the precision of gene editing tools (Naeem et al. 2020). Ethical frameworks must prioritize thorough preclinical testing and validation to ensure the safety and accuracy of these interventions before they advance to clinical applications. The ethical dimension becomes even more complex when considering germline editing, particularly in the context of hereditary cancer (Rothschild 2020). While the possibility of modifying the germline to eliminate or reduce the risk of inherited cancer predispositions is appealing, it raises profound ethical questions. In the realm of cancer gene editing, ensuring that patients and research participants are fully informed and provide consent is crucial. It is important to clearly and comprehensively communicate the potential risks, benefits, and uncertainties associated with genetic interventions. Achieving genuine informed consent requires ongoing communication, education, and respect for the autonomy of study participants. Equitable access to gene editing technologies is also important to prevent further health disparities. Ethical frameworks should prioritize inclusivity and address societal inequities in the distribution and accessibility of gene editing therapies for cancer and other genetic diseases. Transparent communication with the public is essential in shaping the ethical landscape of gene editing in cancer research, as public understanding and acceptance influence the direction of research and its impact on society. The complexity of ethical concerns in gene editing for cancer research creates a challenging situation. It is crucial to find a middle ground between scientific advancement and ethical obligations. This can only be achieved through continuous communication, collaboration, and a transparent approach. The ethical frameworks in this field should be adaptable, address new obstacles, and incorporate various viewpoints. By doing so, researchers can ensure that the potential advantages of gene editing in cancer research are utilized responsibly and fairly.

7.6 Discussion

Functional genomics has become an indispensable tool for drug target identification, revolutionizing the landscape of drug discovery. Emerging technologies in functional genomics have ushered in a new era of possibilities, offering transformative tools to unravel the intricacies of gene function and regulation. One of the revolutionary technologies is the advancement of single-cell genomics. Traditional bulk genomic analyses often mask cellular heterogeneity, but single-cell technologies, such as single-cell RNA sequencing (scRNA-seq), enable the profiling of individual cells, providing unprecedented insights into cellular diversity and the dynamic nature of gene expression (Jovic et al. 2022). This breakthrough has profound implications for cancer research, immunology, and developmental biology, allowing

researchers to dissect complex tissues and uncover cell-specific gene expression patterns with high resolution. In the realm of CRISPR-based technologies, the development of CRISPR screening methodologies has expanded the scope of functional genomics studies. High-throughput CRISPR screens enable the simultaneous perturbation of thousands of genes, facilitating the identification of novel gene functions and interactions at an unprecedented scale (Bock et al. 2022). This approach has the potential to uncover synthetic lethal interactions in cancer cells, paving the way for the development of targeted therapies with enhanced specificity. The integration of functional genomics with artificial intelligence (AI) and machine learning represents another frontier with substantial impact. AI algorithms can analyze vast datasets generated by functional genomics experiments, uncovering hidden patterns and predicting gene functions or interactions (Caudai et al. 2021). This synergy between genomics and AI has the potential to accelerate the pace of discovery, leading to more precise identification of therapeutic targets and biomarkers in diseases like cancer. Advancements in epigenomics, including technologies like CRISPR-based epigenome editing and single-cell epigenomic profiling, offer a deeper understanding of the noncoding regions of the genome and their role in gene regulation (Rubin et al. 2019). A major challenge of modern functional genomics is how to mechanistically link specific noncoding variants with gene regulation and the associated disease processes. Unraveling the complexities of epigenetic modifications provides insights into disease mechanisms and opens avenues for therapeutic interventions that target epigenetic dysregulation. Despite the tremendous promise of these emerging technologies, critical considerations must accompany their adoption. Ethical concerns regarding the potential misuse of gene editing technologies, data privacy in the era of big genomics data, and equitable distribution of benefits must be addressed to ensure responsible and inclusive progress in functional genomics (Naveed et al. 2015). This multidimensional approach improves the prioritization of drug targets based on their relevance to disease biology, ultimately increasing the success rates of therapeutic interventions.

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