Chapter 4

Genetics, Autoimmunity, and Cancer

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Abstract

The majority of people consider cancer to be a single disease, but it is actually a collection of more than 1000 distinct abnormalities in cell and tissue function. However, all cancers have one trait in common: they are all diseases characterized by unregulated cell division. Under normal circumstances, the body regulates the generation of new cells quite precisely. Specific DNA abnormalities in cancer cells cause disruptions in cell communication and growth regulation that are typical in healthy cells. Cancer cells that have evaded these restrictions can become invasive and move to other regions of the body. At the molecular level, cancer is primarily a hereditary disease. It is crucial to understand the fundamental genetic alterations that occur at the somatic level when cancer progresses. The genetics of cancer at the germline layer is still one of the most intriguing and fascinating areas of cancer research, and it is becoming even more so as DNA sequencing technology improves. This has allowed researchers to identify the genetic underpinnings of previously unknown inherited diseases. Newer technologies have also

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made it economically feasible to test patients for the presence of common and hereditary cancer susceptibilities. As a result, cancer genetics has become a significant part of the volume of work in clinical genetics programs. This chapter focuses on cancer and autoimmune-related genetic and genomic components.

Keywords: autoimmunity, cancer, genetics, genomics, medicine

Introduction

The pros and challenges of incorporating genomics into conventional healthcare have been widely debated across the world (Collins and Guttmacher, 2001; Scheuner et al. 2008). There are reported examples of successful genetic risk assessment adoption in cancer care (Grimsey et al. 2010; Harris and Lötter, 2012; Jacobs, 2014). However, even when a risk assessment has been made, health professionals may not always feel competent in estimating risk, or be unclear about whose job it is, or do not always recommend patients to genetic counseling (Metcalfe et al. 2010; Meyer et al. 2010; Lanceley et al. 2012). There is still a lot to understand about how genetic diversity affects cancer risk (Jacobs, 2014). Most of the hereditary cancer genes found so far have significant penetration and confer a strong proclivity for cancer development. Because such genes are more difficult to find, there are fewer low-penetrance cancer genes recognized. Genes that change cancer risk in alternative ways are significantly difficult to identify, yet they may cause a large number of carcinogenesis collectively. The activation of proto-oncogenes and the loss of function of tumor suppressor genes cause each of the roughly hundred forms of cancer. Although cancer genomes are complicated, there are certain distinct mutational patterns that may be identified. Several cancer genes are present in abundance in some forms of cancer but are uncommon in others. Other cancer genes, on the other hand, are much more common. Recent investigation of individual cancer genomes has revealed that many mutations originate at extremely low frequency during carcinogenesis as a result of clonal selection. These findings suggest that there are a variety of combinations of cancer genes that can work together to promote tumor development (Azarnezhad and Mehdipour, 2017).

Cancer is a hereditary disease caused mostly by somatic mutations in tumor suppressor and oncogenes (e.g., K-ras and EGFR) (Kim and Jablons, 2017; Hanahan and Weinberg, 2000; 2011). Cancer, on the other hand, is

significantly complicated and diverse. Many other pathways, including epigenetics, immunological functions, and environmental variables, contribute to cancer genesis, evolution, metastasis, and acquisition of resistance to treatment in addition to genetic abnormalities. Furthermore, cancer is not a static disease; its attributes fluctuate as it adapts to various settings and habitats within the human body. As a result, identifying a specific target to treat and cure cancer is difficult (Kim and Jablons, 2017; Hanahan and Weinberg, 2000; 2011).

Genetic and epigenetic changes are the causes of human cancer. Numerous discoveries amassed over the last few years reveal that genetic and epigenetic modifications are not confined to protein-coding genes. Mechanisms that control cell proliferation, communication, and differentiation are essential for the precise orchestration of the cellular communities that make up our organs, systems, and ultimately bodies. While the list of cell actions that determine whether a cell is normal or carcinogenic appears lengthy, these seemingly independent traits are really governed by seven interacting processes in a domino-like fashion. And it is in these processes that highly specific molecules occur. Cells are prompted to divide by signal molecules. The signal molecule has an effect on the cell by initiating the first of several stages in the cell's communication route. The signal molecule interacts with a receptor molecule on the cell surface or in the cytoplasm, which is the second component of this route. The second type of molecule that regulates cell activity is the receptor. A molecule known as a signal transducer falls into the third group. This molecule gets the information the cell receives when the signal molecule connects to the receptor and generates another one inside the cell that keeps the information flowing. Transcription factors make up the fourth group of compounds. These variables control which genes are employed in the cell and, as a result, how cells appear and behave. Apoptotic proteins, which are included in the fifth group, instruct injured cells to commit suicide by apoptosis. Molecules that directly affect cellular division pathways fall into the sixth group. Proteins that repair DNA damage are the seventh and final type of molecule. All seven of these molecular groups operate normally in healthy cells. However, any of these categories does not operate normally in cancerous cells. Because all of the information for creating all of the regulatory molecules in all seven categories is encoded in the DNA sequences of particular genes, it means that these genes function normally in normal cells but not in cancerous cells. To put it another way, normal cells contain genes that encode normal proteins, but cancer cells have mutated versions of those same genes that encode aberrant proteins. Genetic coding is the process of

transferring genetic information to a protein in order to establish its function. As a result, groups of incorrectly functioning genes are at the center of cancer's cellular process (Bozzone, 2007; Kim and Jablons, 2017; Mehdipour, 2017; Roy and Datta, 2019).

Another important characteristic is the understanding of the role of the immune system in eliminating emerging cancerous lesions and micro-metastases (Roy and Datta, 2019; Hanahan, 2011). The regular functioning of the immune system assumes that its cells are continually monitoring cells and tissues, and that this surveillance of the immune system should eradicate the great majority of early neoplastic lesions and metastatic growths. Maybe the cancerous developments that make it past the immune system's scrutiny are immune to the immune system's efforts. There is, however, evidence to support and refute this hypothesis. It is well recognized that immune-compromised people are more likely to develop certain malignancies. Nevertheless, practically all these cancers are caused by viruses (Roy and Datta, 2019; Vajdic and Leeuwen, 2009). As a result, the immune system's involvement in such circumstances may be to remove virus-infected cells, albeit it is difficult to generalize this role to the overwhelming majority of malignancies. These findings suggest that, at least in some experimental models, the immune system has a role to play in cancer eradication. In several types of human cancer, antitumor immunological responses have also been observed (Nam and Murthy, 2004; Thomas-Tikhonenko, 2010). Finely tuned clinical observational studies establishing the relationship with statistical significance, as well as a greater molecular knowledge of cancers and the toxic millieu created by inflammation, all contributed to persuading scientists and clinicians of the reality of this link (Thomas-Tikhonenko, 2010; Sepulveda and Lynch, 2010). According to existing models, prolonged inflammation generates a milieu that promotes neoplastic progression (Coussens and Werb, 2002; Thomas-Tikhonenko, 2010; Sepulveda and Lynch, 2010). There is a clear-cut difference between the normal cellular microenvironment and the inflammatory states. In the case of an inflammatory environment, the striking increase in stimulated immune system cells and excessive amounts of inflammatory mediators is evident. Among others, eicosanoids, cytokines, chemokines, and nontoxicnon-toxic free radicals stemming from the reactive oxygen and nitrogen species (ROS and RNS, respectively) are more pronounced. Aforementioned inflammatory factors primarily regulate the course of immune response; however, they are known to partake in the activation of different mechanisms, namely, stimulation of mesenchymal and epithelial cells that is leading to tissue regeneration and healing. In such a case,

there is an inverse correlation between cellular proliferation and apoptosis, where apoptosis is being inhibited. It should be noted that angiogenesis is also enhanced for the stated regeneration. Finally in the inflammatory milieu, physiological protections of the organism are overwhelmed by the constant stress caused by the oxidative stressors, which particularly leads to striking damaging of cellular subunits, such as proteins, lipids, and even the nuclear DNA. This all adds up to a more favorable environment for the formation of a changed neoplastic cell (Thomas-Tikhonenko, 2010; Sepulveda and Lynch, 2010).

The Theory of the Cancer Genetics

When somatic cells in the body divide, new cells are produced. Each has a complete set of chromosomes. During cell division, anything might go wrong, and chromosomes can become damaged, lost, or abandoned. When these events occur, cells that arise may contain excess chromosomes, chromosomes that have missing sections, chromosomes that break and then reattach the fragments wrongly, or even chromosomes that are missing totally. To correctly balance the activity of genes, cells must have complete normal chromosomes present in the correct quantities. Due to chromosomal abnormalities (Bozzone, 2007), uncontrolled cell division and cancer can emerge when this finely managed scenario breaks down. Most human tumors are caused by germline or somatic cell abnormalities. These flaws might be chromosomal, such as chromosomal dislocations, or specific gene mutations. Individual proteins produced from defective genes have significant metabolic implications as a result of such abnormalities. Furthermore, genes are typically arranged as metabolic circuits, and incorrect transcription of a gene can have cascading effects on a circuit (Roy and Datta, 2019).

However, definitive cells in the body have a system in place to prevent telomere shortening. These are the cells that develop into gametes (eggs or sperm). These germ cells produce the enzyme telomerase, which repairs the telomeres lost during replication, bypassing the cellular aging mechanism. The only other cells in the human body that may synthesize telomerase and so become immortal are cancer cells. Cells in 90% of human cancers generate telomerase. As a result, even if they are damaged or aberrant, these cells ignore the signals that instruct them to die. These cells subsequently continue to multiply and, more than likely, gather more genetic abnormalities, making

them even more aggressive. This genetic disorder may prove lethal in the end (Bozzone, 2007).

One of the hypotheses that has emerged from research into the genetics of cancer is that a sequence of isolated events might drive a cell toward malignancy. There is a final straw where chromosomal, telomere, and gene errors and faults avalanche and the pace of fault accumulation accelerates. Although not evident in all cancers, general genetic instability raises the chances of many cancers developing into comprehensive, aggressive, and invasive tumors. In most cases, the instability is caused by a mutation or chromosomal flaw, which leads to other mutations and abnormalities. Cancer development is undeniably influenced by genetic instability (Bozzone 2007).

Cancer researchers distinguish three types of cancer: sporadic, familial, and hereditary. Hereditary factors do not appear to play a role in the development of sporadic tumors. There is no family-related history of the particular cancer, and there is no reason to believe that the genetic component of the disease is anything more than a several mutations that happened in a cell and eventually resulted in a tumor. Familial neoplasms occur when there are a few incidences of the disease in a family, but there is no discernible pattern. It is improbable that cancer will be passed down through generations in cases of family cancer. There is likely to be a pattern of inherited and environmental variables that impact the differential risk of acquiring cancer. Cancer susceptibility can be passed down from one generation to the next, rather than merely from one cell to the next. Inherited cancers are uncommon, making up just 5 to 10% of all malignancies. Still, studies of these malignancies are significant, as they have demonstrated that genes play a definite role in cancer formation. Likewise, knowledge of genes involved in genetically determined malignancies has led to new perspectives on non-hereditary and more prevalent cancers (Bozzone, 2007; Roy and Datta, 2019).

Defects in tumor suppressor genes or proto-oncogenes, as well as chromosomal issues that impact the normal function of suppressor genes or proto-oncogenes, can increase the risk of cancer. Whether errors are novel or acquired from parents, these genetic abnormalities can lead to tumor growth. Investigations and research on factors in human tumors show that carcinogenesis is caused by the aggregation of many genetic flaws, which reinforces the cascading nature of oncogenesis (Bozzone, 2007; Roy and Datta, 2019).

The Oncogenes

Given that certain normal genes can malfunction and turn cells into cancerous states, it is crucial to examine how these genes, also known as proto-oncogenes, behave in typical situations. After all, proto-oncogenes are not like timed bombs in cells, ready to explode. Indeed, proto-oncogenes all code for proteins that are required for cell proliferation, survival, or differentiation in some way. Some proto-oncogene-encoded proteins, for example, are growth factors and are involved in cell communication pathways, while others become receptor proteins for such growth factors. Some are intracellular signal molecules that convey information obtained at the cell surface, where receptors attach to growth factor molecules, to places inside the cell and its nucleus. Some proteins even bind directly to DNA to alter gene expression, regulating specific genes to influence the creation of specific proteins. These kinds of protein work together to control cell division in a complicated mechanism (Bozzone, 2007). Because the proteins expressed by specific proto-oncogenes may govern cell division, it stands to reason that if some or all of these genes are mutated, the protein molecules they encode might become defective, causing cell proliferation to remain in an "always active state." To put it another way, proto-oncogenes can be converted into oncogenes, which can cause cancer if they are present in cells (Bozzone, 2007).

Proto-oncogenes change into oncogenes in all situations due to a change in gene structure, location, or function, resulting in excessive protein synthesis or the development of a hyperactive, uncontrolled protein. An oncogene can become a proto-oncogene by undergoing particular genetic modifications. For starters, a mutation in which one of the four bases of DNA's genetic code is changed to a different base might result in the creation of a new protein. A point mutation is defined as a change in one base of the DNA code. The oncogene "ras" is a representation of an oncogene that arises from a single alteration in the gene's DNA sequence. In the second group, genes can be amplified in some cases. This implies that they become duplicates and implant them into the cell's chromosomes. Consequently, a cell may have too many copies of a proto-oncogene, resulting in excessive protein production and oncogenic activity despite the normal gene structure. Among others, a proto-oncogene that turns oncogenic when amplified is the oncogene "N-myc." In the third group, chromosomes can be broken and their components rearranged. If a proto-oncogene is transferred to a new site on the chromosome, it may become uncontrolled and trapped in the "on" position, leading to oncogenic

behavior. The gene "c-myc" is oncogenic due to its translocation on the chromosome. Some of these genes are identified in tumor viruses as oncogenes, but the majority of them are proto-oncogenes that turn oncogenic without entering a virus. Proto-oncogenes encode proteins that regulate cell growth or survival. To become an oncogene, some sort of modification or shift in gene structure, location, or function is required for all proto-oncogenes (Bozzone 2007).

Well-over 100 oncogenes have been found, all of which are derived from normal genes involved in cell growth and survival. To begin with, cells require growth hormones to promote cell division. When oncogenesis is active, it encodes a growth factor that is produced on a constant basis. As a result, cells with an operational oncogene emit the same growth factor that causes their own proliferation, in other words, they encourage their own cell division. Subsequently, to continue the communication channel, growth factors must attach to cell surface receptors. An aberrant form of a growth factor receptor is encoded by the oncogene "erb-B." Even when no growth factor is available, this defective receptor acts as if it is bound all the time. Next, when growth factors and receptors attach to each other, the communication channel is continued by molecules inside the cell. Oncogenes known as "src" and "ras" create aberrant intracellular signal molecules that activate other cascades. The pathway's signal will eventually reach the chromosomes, causing changes in gene expression. The oncogenes "c-myc" and "c-fos" generate transcription factors, which are DNA-binding molecules that control gene activity. These transcription factors, including "c-myc" and "c-fos," overstimulate gene expression and cause excessive proliferation. Lastly, cells have to choose between dividing to generate new cells and dying. The oncogene "bcl-1" produces a protein that prevents cells from committing suicide. Damaged cells that should die fail to do so while "bcl-1" is active and instead divide, resulting in a population of faulty cells. Proto-oncogenes are important regulators of cell growth. Cell division is overstimulated when they transform into oncogenes and act abnormally (Bozzone 2007).

MicroRNAs as Oncogenes

MiRNAs that are significantly elevated in human malignancies are thought to play an oncogenic role. MiR-155 was the first miRNA to be postulated to have an oncogenic role after its increase was discovered in human B-cell lymphomas together with a host noncoding RNA called the B-cell integration cluster on chromosome 21q23 (Eis et al. 2005; Lee and Croce, 2017). MiR-21 was the first to disclose specific miRNA expression. MiR-21 is the most

widely elevated miRNA in practically all malignant tumors, including hematological and consistent tumors (Krichevsky and Gabriely, 2009; Lee and Croce, 2017). In the non-coding gene C13orf25 at 13q31.3, a single cistronic miR-17-92 collection containing six miRNAs is situated at 800 base pairs (Olive et al. 2013). Lymphomas typically amplify this location (Lee and Croce, 2017).

Tumor Suppressors

Tumor suppressor genes that have been mutated or damaged are unable to limit cell proliferation, whereas oncogene activity often drives cells to continue cell division even when it is inappropriate. Tumor suppressor genes encode proteins that determine whether cells survive and, if they do, whether they replicate. Only a few dozen genes in each human cell encode tumor suppressors, despite the fact that each cell has more than 30,000 genes. Even if only one of these tumor suppressor genes is malfunctioning, it can have major health repercussions. Tumor suppressor genes are known as "gatekeeper genes" because their absence allows for uncontrolled cell growth. There are also "caretaker genes" that are covered in the repairmen of DNA and chromosomal sorting during cell division (Bozzone, 2007). Caretaker genes are necessary for genomic integrity, but they have little effect on cell growth. Tumor suppressor genes affect cells in a number of different ways. Tumor suppressor genes encode proteins that fall into one of four functional groups. To begin with, there are proteins within the cell that prevent cells from progressing through a specific stage of the cell cycle of growth and division. Second, certain proteins serve as receptors for hormones or chemical signals that instruct cells not to divide. Third, some proteins prevent cell division when DNA is broken or when chromosomes are aberrant. Fourth, if DNA or chromosomal damage is too severe to repair, some proteins will cause apoptosis, or "cell death." Tumor suppressor genes produce proteins that evaluate whether cells should be permitted to proliferate and/or survive in all instances (Bozzone 2007). The suppressor p53, which is transcripted by the p53 gene, is by far the most significant. In 50% of all human cancers, including hereditary and noninherited types, this tumor suppressor is altered or deleted. When DNA is badly damaged, the control system, which contains p53, requires cells to cease proliferating or die through apoptosis. In addition to random mutations or cellular mishaps, there are several events and chemicals that impact the p53 protein. Although the tumor suppressor function of the p53

protein is vital, it is only one of the reasons why it is important in cells. Many issues, such as DNA damage, hypoxia, nucleotide imbalance, and disruption of the mitotic spindle, activate p53 genes as part of an overall response pathway to cellular stress. The defensive actions of the cell against various threats are governed by the p53 protein. The p53 protein, along with a few other components, can determine how much damage has been done to DNA and chromosomes. p53 is a transcription factor, which is a type of molecule that controls whether other genes are activated or not. Genes influence the creation of other proteins when they are active. No proteins are produced when genes are switched off, and therefore dormant. When DNA is broken, p53 controls the genes responsible for mending it, regulating cell division, and guiding apoptosis. If the damage is not too severe, p53 stops the cell's growth and division cycle and guides repair. P53 triggers apoptosis because there is too much injury (Bozzone, 2007).

Another tumor suppressor gene, for example, produces a protein that can halt the cell division process. Although altered tumor suppressor genes have been linked to numerous forms of inherited tumors, they are also seen in non-hereditary tumors. Several tumor suppressors are also critical in the progression of several tumors. As a result, the protein it encodes is missing, which typically suppresses cell growth, and a tumor ultimately develops. It is worth noting that normal proto-oncogene protein products promote cell division, whereas normal tumor suppressor protein products prevent cell division (Bozzone, 2007). In many circumstances, an activating protein and an inhibiting protein are found at the same stage in the same route. The tumor suppressor gene "NF-1" is altered in diverse incarnations of leukemia and nervous system malignancies, for example. Normally, the normal action of the "NF-1" gene suppresses the function of the protein produced by the proto-oncogene "ras." When the "NF-1" protein is faulty, it does not prevent the "ras" protein from activating cell division, resulting in uncontrolled cell proliferation. The delicate balance between cell division activators and inhibitors can be challenging at times. "TGF-β" is a chemical signal released by normal cells that prevents cell division in a variety of cells (Bozzone, 2007). As a result, the receptor becomes inactive and cell division proceeds. Other steps in the regulatory cascade can go awry even when the TGF-β signal connects to a normal receptor. TGF-β inhibits cell division under normal conditions by interacting with another protein named p15. The p15 protein is absent in various malignancies, and consequently, the signal to terminate cell division is not effectively passed on. An intricate agreement between activating chemicals encoded by proto-oncogenes and inhibitory agents from

tumor suppressors determines whether cells should live and proliferate (Bozzone, 2007).

MicroRNAs as Tumor Suppressors

When loss of activity of a miRNA is related to malignancy of a normal cell, it can behave as a suppressor, much like a protein-coding gene. According to Lee and Croce (2017), the function of a miRNA can be lost due to chromosomal mutation, epigenetic silencing, and/or changes in miR processing. The 30-kb deletion region between the LEU2 gene from the 13q14.2 region, the most documented chromosomal abnormality, produced two miRNAs, reported as miR-15a and miR16-1 (Calin et al. 2002; 2004; 2005; Lee and Croce, 2017). Because the miR-15a/miR16-1 cluster was shown to target the anti-apoptotic protein BCL-2, the miR-15a/16-1 cluster was postulated to have a suppressing role. As a result, in individuals with chromosomal deletions or, less commonly, mutations, low levels of miR15a/miR-16-1 may promote BCL-2 protein production (Calin et al. 2002; 2004; 2005; Lee and Croce, 2017). In addition, miR-29b-1/miR-29a of the miR-29 family, were discovered on chromosome 7q32, a frequently deleted location in different cancer types (Garzon et al. 2008; 2009; Lee and Croce, 2017). The downregulated miR-29 family was also shown to be inversely linked with upregulated oncogenic products, notably “BCL-2” and “MCL-1” (Xu et al. 2014; Lee and Croce, 2017), strongly implying a tumor suppressor role (Lee and Croce, 2017).

Biomarkers in Cancers

Because late discovery typically leads to a poor prognosis due to metastasis to other organs, early detection of the malignant phenotype is one of the most important variables in cancer diagnosis that determines favorable outcomes of cancer treatment choices. Global profiling of total miRNAs is a time-consuming and expensive procedure that should not be performed on each patient sample. Identification of a small number of miRNAs may be done quickly. A solid understanding of precise and cheap biomarkers for each kind of human cancer is crucial in this regard. A microRNA signature is the recommended course of action. The discovery of miRNA signatures in diverse forms of human cancer encouraged many researchers to dig deep to identify the most important miRNAs, even after taking into account the genetic and historical background of different specimens. If possible, such miRNAs might

be used as diagnostic and prognostic biomarkers. MiR-15/16 clusters, for example, have been discovered to be regularly eliminated and downregulated (Calin et al. 2004; Lee and Croce, 2017). When miRNA profiles from 166 human bladder tumor samples were compared with miRNA profiles from 11 normal bladder samples, only three out of 15 miRNAs were determined to represent the miRNA signature linked with tumor aggressiveness. These three miRNA signatures have the potential to be valuable prognostic indicators. Although miRNA signatures obtained from extensive profiling of a variety of patient samples can be effective diagnostic and prognostic indicators, there are still significant differences in profiling methods (Lee and Croce, 2017). The majority of miRNA profiling was done on RNA samples taken directly from patients' cancer tissue retrieved through biopsies. Alternatively, circulating RNAs, or RNA extracts from plasma and serum, have been proposed as a noninvasive, low-cost, and quick cancer diagnostic technique (Tsang and Lo, 2007; Lee and Croce, 2017). Proliferation, apoptosis, invasion, metastasis, angiogenesis, and maintenance have all been found to be influenced by miRNAs in human malignancies. Furthermore, specific miRNA expression patterns are linked to carcinogenesis and progression. High-throughput characterization of miRNA expression in a range of human cancer patient samples revealed a distinct signature of unregulated miRNAs in malignancies. The discovery of definitive miRNA signatures can be used to develop diagnostic and prognostic tools, as well as therapeutics (Lee and Croce, 2017).

Tumor Immunology

The connection between carcinogenesis and immunity begins at the onset of the disease. Regular immune cells are thought to target aberrant cells for death as part of normal immune surveillance. However, cancer cells appear to elude destruction in a variety of ways. The absence of co-stimulatory signal generation by the cancer cell, as well as its inherently low immunogenicity, might result in immune tolerance of the malignant cell (Murphy, 2011; Yandle, 2014; Jacobs et al. 2014). Immune editing, which involves the continuing killing of aberrant cells recognized by the immune system and the survival of cancer cells expressing antigens that are poorly recognized by the immune system, may also contribute to cancer escape from immune control. A crucial number of live cancer cells without antigens capable of eliciting a substantial immune response is eventually achieved, allowing the tumor to proliferate unabated (Schreiber et al. 2011; Yandle, 2014; Jacobs et al. 2014).

Different types of immune cells can be shown in various regions of the tumor and surrounding tissue, and among them are cells that are hypothesized to inhibit immune responses in tumors (Murphy, 2011; Yandle, 2014; Jacobs et al. 2014). Cancerous cells also appear to regulate their immunological surroundings by releasing pro-inflammatory and other cytokines, keeping immune responses aimed at cancer cells suppressed. Immune cell subgroups appear to play a role in guaranteeing the survival of cancer cells and the spread of metastases (Pollard, 2004). Cancerous cells, immune cells, and extracellular matrix components interact in ways that might lead to tumor suppression or development. The dynamic and intricate interactions between cancer cells and their immediate surroundings are considered to have a role in their abnormal behavior (Bissell and Radiski, 2001; Lu et al. 2012). Finally, these factors add to the complicated character of cancer biology (Yandle, 2014; Jacobs et al. 2014).

Conclusion

There are various reasons why the characterization of cancer types remains incomplete despite increasing research in the field. Among the many postulated reasons, some of them are more prevalent. To name a few, the following can be stated: (1) unclear genetic patterns present in "gatekeeper genes" and their associated pathways lead to obscure mapping of dominant traits; (2) the lack of convincing data to represent each clinical phase of a given malignancy in a population; and (3) genetic heterogeneity of patients diagnosed with cancer that leads to conflicting clinical patterns. Cancer genes have been discovered in all the most common kinds of cancer, despite these roadblocks. The expanded use of sequencing methods on cancers holds the prospect of revealing a substantial number of new cancer genes in the future. Circulating tumor DNA and cells are two potential molecular indicators for cancer diagnosis in the early stages (Murtaza et al. 2013; Bianchi et al. 2014; Kim and Jablons, 2017; Kim, 2017). Genetic or proteomic abnormalities of specific cells or tissues can be analyzed in a large number of cells or tissues using microarray technology (Shim and Lee, 2017; Kim, 2017). Many conserved gene expression profiles connected to novel therapeutic targets or predicting prognosis in terms of survival or recurrence-free survival in various malignancies have been uncovered using these methods, which outperform conventional staging systems. Microarray technology is also commonly employed in other investigations, such as identifying SNP linked to cancer

risk, variations, expression profiling, and cancer genome profiling (Shim and Lee, 2017; Kim, 2017). Furthermore, pedigree-based evaluation is the key for cancers and clinical discoveries, as it allows scientists and clinicians to discover the most suitable target genes, the most appropriate personalized management and, if needed, their relatives who carry the cancer risk, and the rational mentoring for target-based diagnosis (Azarnezhad and Mehdipour, 2017; Mehdipour, 2017). To progress into the present era of "personalized" or "precision" medicine (PM), which may be described as a medical care choice and response based on a patient's genetic, epigenetic, histopathological, or any other patient data, a novel conceptual framework of cancer therapy was required.

References

Azarnezhad, A., and Mehdipour, P., (2017). Cancer genetics at a glance: The comprehensive insights. In P. Mehdipour (Ed.) *Cancer Genetics and Psychotherapy*. (pp. 79-390). Springer International Publishing AG.

Bianchi, D. W., Parker, R. L., Wentworth, J., Madankumar, R., Saffer, C., Das, A. F., Craig, J. A., Chudova, D. I., Devers, P. L., Jones, K. W., Oliver, K., Rava, R. P., Sehnert, A. J., and Care Study Group. (2014). DNA sequencing versus standard prenatal aneuploidy screening. *The New England Journal of Medicine*, 27; 370(9), 799-808.

Bissell, M. J., and Radiski, D. (2001). Putting tumours in context. *Nature Reviews Cancer*, 1, 46-54.

Bozzone, D. M. (2007). *Biology of Cancer: Cancer Genetics*. Infobase publishing, New York. ISBN 0-7910-8818-9.

Calin, G. A., Dumitru, C. D., Shimizu, M., Bichi, R., Zupo, S., Noch, E., Aldler, H., Rattan, S., Keating, M., Rai, K., Rassenti, L., Kipps, T., Negrini, M., Bullrich, F., and Croce, C. M. (2002). Frequent deletions and down-regulation of micro- RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. *Proceedings of the National Academy of Sciences of the United States of America*, 99, 15524-15529.

Calin, G. A., Ferracin, M., Cimmino, A., Di Leva, G., Shimizu, M., Wojcik, S. E., Iorio, M. V., Visone, R., Sever, N. I., Fabbri, M., Iuliano, R., Palumbo, T., Pichiorri, F., Roldo, C., Garzon, R., Sevignani, C., Rassenti, L., Alder, H., Volinia, S., Liu, C. G., Kipps, T. J., Negrini, M., and Croce, C. M. (2005). A MicroRNA signature associated with prognosis and progression in chronic lymphocytic leukemia. *The New England Journal of Medicine*, 353, 1793-1801.

Calin, G. A., Liu, C. G., Sevignani, C., Ferracin, M., Felli, N., Dumitru, C. D., Shimizu, M., Cimmino, A., Zupo, S., Dono, M., Dell'Aquila, M. L., Alder, H., Rassenti, L., Kipps, T. J., Bullrich, F., Negrini, M., and Croce, C. M. (2004). MicroRNA profiling reveals distinct signatures in B cell chronic lymphocytic leukemias. *Proceedings of the National Academy of Sciences of the United States of America*, 101, 11755-11760.

Collins, F. and Guttmacher, A. (2001). Genetics moves into the medical mainstream. *JAMA The Journal of the American Medical Association*, 286, 2322-2324.

Coussens, L. M., and Werb, Z. (2002). Inflammation and cancer. *Nature*, 420, 860-867.

Eis, P. S., Tam, W., Sun, L., Chadburn, A., Li, Z., Gomez, M. F., Lund, E., and Dahlberg, J. E. (2005). Accumulation of miR-155 and BIC RNA in human B cell lymphomas. *Proceedings of the National Academy of Sciences of the United States of America*, 102, 3627-3636.

Garzon, R., Garofalo, M., Martelli, M. P., Briesewitz, R., Wang, L., Fernandez-Cymering, C., Volinia, S., Liu, C. G., Schnittger, S., Haferlach, T., Liso, A., Diverio, D., Mancini, M., Meloni, G., Foa, R., Martelli, M. F., Mecucci, C., Croce, C. M., and Falini, B. (2008). Distinctive microRNA signature of acute myeloid leukemia bearing cytoplasmic mutated nucleophosmin. *Proceedings of the National Academy of Sciences of the United States of America*, 105, 3945-3950.

Garzon, R., Heaphy, C. E., Havelange, V., Fabbri, M., Volinia, S., Tsao, T., Zanesi, N., Kornblau, S. M., Marcucci, G., Calin, G. A., Andreeff, M., and Croce, C. M. (2009). MicroRNA 29b functions in acute myeloid leukemia. *Blood*, 114, 5331-5341.

Grimsey, E., Howlett, D., Allan, S., et al. (2010). Implementation and progress review of a nurse-led family history risk assessment clinic. *European Journal of Cancer*, 8, 241.

Hanahan, D., and Weinberg, R. A. (2000). The hallmarks of cancer. *Cell,* 7; 100(1), 57-70.

Hanahan, D., and Weinberg, R. A. (2011). Hallmarks of cancer: the next generation. *Cell,* 4; 144(5), 646-674.

Harris, K., and Lötter, B. (2012). Focus on patients with a family history of cancer. *Cancer Nursing Practice*, 11, 14-19.

Jacobs, C. (2014). Putting cancer genetics into context. pp. 3-8. In C. Jacobs, P. Webb and L. Robinson (Eds.) *Genetics for Health Professionals in Cancer Care: From Principles to Practice* (pp. 3-8). Oxford University Press.

Jacobs, C., Webb, P., and Robinson, L. (2014). *Genetics for Health Professionals in Cancer Care: From Principles to Practice*. Oxford University Press. ISBN 978–0–19–967 284–4.

Kim, J. (2017). *Cancer Genetics and Genomics for Personalized Medicine*. Taylor and Francis Group, Pan Stanford Publishing Pte. Ltd. ISBN 978-1-315-36476-6 (eBook).

Kim, J. and Jablons, D. (2017). Personalized medicine for cancer: Introduction and overview of the book. In J. Kim (Eds.) *Cancer Genetics and Genomics for Personalized Medicine* (pp. 1-15). Taylor and Francis Group, Pan Stanford Publishing Pte. Ltd.

Krichevsky, A. M., and Gabriely, G. (2009). miR-21: a small multi-faceted RNA. *Journal of Cellular and Molecular Medicine*, 13, 39-5332.

Lanceley, A, Eagle, Z., Ogden, G., et al. (2012). Family history and women with ovarian cancer: is it asked and does it matter? An observational study. *International Journal of Gynecological Cancer*, 22, 254-259.

Lee, T. J., and Croce, C. M. (2017). MicroRNAs in human cancers. In J. Kim (Eds.) *Cancer Genetics and Genomics for Personalized Medicine* (pp. 239-265). Taylor and Francis Group, Pan Stanford Publishing Pte. Ltd.

Lu, P., Weaver, V., and Werb, Z. (2012). The extra-cellular matrix: a dynamic niche in cancer progression. *Journal of Cell Biology*, 196, 395-406.

Mehdipour, P. (2017). *Cancer Genetics and Psychotherapy*. Springer International Publishing AG. ISBN 978-3-319-64550-6 (eBook).

Meyer, L. A., Anderson, M. E., Lacour, R. A., et al. (2010). Evaluating women with ovarian cancer for BRCA1 and BRCA2 mutations: missed opportunities. *Journal of Obstetrics and Gynaecology*, 115, 945-952.

Murphy, K. (2011). *Janeway's Immunobiology*, 8th edn. New York: Garland Science.

Murtaza, M., Dawson, S. J., Tsui, D. W., Gale, D., Forshew, T., Piskorz, A. M., Parkinson, C., Chin, S. F., Kingsbury, Z., Wong, A. S., Marass, F., Humphray, S., Hadfield, J., Bentley, D., Chin, T. M., Brenton, J. D., Caldas, C., Rosenfeld, N. (2013). Noninvasive analysis of acquired resistance to cancer therapy by sequencing of plasma DNA. *Nature,* 2; 497(7447), 108-112.

Nam, J. H., and Murthy, S. (2004) *Chronic Inflammation and Cancer in Various Organ Systems*. Springer Basel AG, Birkhauser Verlag Basel, Basel.

Olive, V., Li, Q., and He, L. (2013). Mir-17-92: a polycistronic oncomir with pleiotropic functions. *Immunological Reviews,* 253, 158-166.

Phillips J, Murray P, Kirk P 2001. *Biology of Disease*, 2nd edn. Oxford: Blackwell Science.

Pollard, J. (2004). Tumour-educated macrophages promote tumour progression and metastasis. *Nature Reviews Cancer*, 4, 71-78.

Roy, M., and Datta, A. (2019). *Cancer Genetics and Therapeutics.* Springer Nature Singapore Pte. Ltd. ISBN 978-981-13-9471-3.

Scheuner, M., Sieverding, P., Shekelle, P. (2008). Delivery of genomic medicine for common chronic adult diseases: a systematic review. *JAMA The Journal of the American Medical Association*, 299, 1320-1334.

Schreiber, R. D., Old, L. J., and Smyth, M. J. (2011). Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. *Science*, 331, 1565-1570.

Sepulveda, A. R., and Lynch, J. P. (2010). Genetic instability and chronic inflammation in gastrointestinal cancers. pg: 351-398. In A. Thomas-Tikhonenko (Ed.) *Cancer Genome and Tumor Microenvironment* (pp. 351-398). Springer New York Dordrecht Heidelberg London. e-ISBN 978-1-4419-0711-0.

Shim, J. J., and Lee, J. S. (2017). Genome- based personalized Medicine in liver cancer. In J. Kim (Eds.) *Cancer Genetics and Genomics for Personalized Medicine* (pp. 39-53). Taylor and Francis Group, Pan Stanford Publishing Pte. Ltd.

Thomas-Tikhonenko, A. (2010). *Cancer Genome and Tumor Microenvironment*. Springer New York Dordrecht Heidelberg London. e-ISBN 978-1-4419-0711-0.

Tsang, J. C., and Lo, Y. M. (2007). Circulating nucleic acids in plasma/serum. *Pathology*, 39, 197-207.

Vajdic, C. M., and van Leeuwen, M. T. (2009). Cancer incidence and risk factors after solid organ transplantation. *International Journal of Cancer*, 125, 1747-1754.

Xu, L., Xu, Y., Jing, Z., Wang, X., Zha, X., Zeng, C., Chen, S., Yang, L., Luo, G., Li, B., and Li, Y. (2014). Altered expression pattern of miR-29a, miR-29b and the target genes in myeloid leukemia. *Experimental Hematology and Oncology*, 3, 17-3619-3-17.

Yandle, A. (2014). Cancer biology. In C. Jacobs, P. Webb and L. Robinson (Eds.) *Genetics for Health Professionals in Cancer Care: From Principles to Practice* (pp. 36-46). Oxford University Press.