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Cell cycle regulatory markers in melanoma: New strategies in diagnosis and treatment

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Abstract

Background: Melanoma has been known as an aggressive type of skin cancer in recent years. Reports have distributed the spread rate of melanoma among white skin populations. Also, many studies have mentioned several causes of melanoma. Ultraviolet radiation was represented to be the most important reason for occurrence of melanoma. However, recent studies have found that a combination of factors, such as environmental and genetic factors, can contribute to occurrence of various cancers, specifically melanoma.

Methods: Different studies have been conducted on the efficacy of genetic disorders in melanoma. These surveys marked the key role of specific biomarkers in molecular and cellular processes, and investigations have found the expression of several genes in these processes. In addition, aberrant expression of these genes due to mutation and methylation can affect the whole process.

Results: The expression process of these genes is regulated by microRNAs. These new biomolecules have been considered as negative regulators because of managing molecular and cellular processes. MicroRNAs are small conserved regulators attached to their targets leading to rearrangement of gene expression. Adherence of these noncoding RNAs can cause mRNA degradation or inhibit its translation.

Conclusion: Recently, the application of specific genes in melanoma has been studied. In this review, the way melanoma is regulated because of these biomarkers and their demand through cell cycle in diagnosis, prognosis, and therapeutic periods was considered.

Keywords: Melanoma, Biomarkers, Cell cycle, Biomolecules

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Introduction

Cancer occurs due to several modifications in genes and their produced proteins which cause defects in the gene's structure and leads to malfunction of modified proteins. Lately, due to the increase in the rate of cancers, many researchers are focusing on identification of biomarkers which could help early diagnosis or prognosis. Melanoma, a severe skin cancer, has become more common in recent decades; thus, many studies have been conducted on its diagnosis, prognosis, and therapeutic components. In addition, multiple mutations, methylation, and other modifications have been introduced as initial factors in melanoma. In this review, some of these essential genes in the cell

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↑What is "already known" in this topic:
Various studies have concentrated on melanoma molecular alterations, such as mutation and/or malfunction of specific genes. Researchers have discovered some new mutated genes for the diagnosis and prognosis of this aggressive skin cancer. Furthermore, some molecular methods were applied as a therapeutic component for melanoma.

→What this article adds:
In this review, new researches and their results on novel diagnostic, prognostic, and therapeutic approaches were combined based on cell cycle regulatory biomarkers associated with melanoma.

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cycle of melanoma, which could be used in diagnostic procedures as well as therapy methods, are identified.

1.1. Prognosis and diagnosis biomarkers

1.1.1. MC1R

Melanocotin1 receptor (MC1R) is a transmembrane G protein receptor, located in cell membrane that can control melanogenesis (1). This mentioned biomolecule is upregulated in metastasis of melanoma tumors (2). Taylor et al have mentioned several variants of MC1R as risk factors in melanoma. In their study, 2 groups of sun-sensitive and sun-resistance phenotypes were investigated, which varied in susceptibility to ulceration and Breslow thickness of melanoma. Their results indicated that the former group was more in danger than the latter (2, 3). Also, Taylor et al in another study found a direct relationship between melanoma and haplotypes. Also, they mentioned that polymorphisms close to agouti signaling protein (ASIP) locus are the antagonist of MC1R, as a death marker in melanoma (2, 4). Since MC1R is overexpressed in melanoma, it was surveyed in multiple studies to understand its key role in melanoma molecular mechanisms. For instance, Qin et al stated that this biomolecule is a therapeutic component and introduced it as a good marker for prognosis (5).

1.1.2. IMP3

The other overexpressed marker in melanoma is insulin-like growth factor-II messenger RNA (mRNA)-binding protein-3 (IMP-3), which binds to its targeted RNA to regulate its expression. In the study of Pryor et al, IMP3, which is highly expressed in metastatic forms, was examined in different samples of metastatic and benign melanoma (6). Also, Chokoeva et al investigated both mentioned samples for which similar results have been reported. They have explained the relative collaboration between IMP3 expression level and dysplastic tumor rate. However, IMP3 expression level can be a great prognostic and diagnostic marker for malignant melanoma (7). Sheen et al found a correlation between IMP3 and high mobility group AT-hook 2 (HMGA2) expression in melanoma. Their report marked all HMGA2- positive to be IMP3 positive. Also, IMP3 can act as a regulator for HMGA2 by attaching to mRNA. Their relevance was ascertained in other cancer-related studies (eg, hepatocellular carcinoma) (8, 9). However, further studies should be conducted on IMP3 therapeutic functions in the future (10-12).

1.1.3. MITF

Microphthalmia-associated transcription factor (MITF) is a basic helix-loop-helix-leucine zipper (bHLH-LZ) transcription factor containing 10 isoforms, which is specifically expressed in skin cells due to differentiation (13, 14). Also, MITF is a nuclear factor resistant to chemotherapy treatments, therefore, it is a key prognostic component in melanoma. Multiple experiments affirmed the reliable diagnostic markers. For example, in Vetrini et al study, PCR results and IHC experiments were used to find new diagnosis and therapeutic biomarkers (13). Samija et al used MITF in PCR-detection for the first time. Their results marked RT-PCR analysis as more sensitive, as leaky expression of normal cells and impurity can be considered as positive samples (15). Several studies confirmed requisite expression of MITF in melanocyte differentiation (16-18). As an instance, Medic et al proved the coexpression of MITF and Pax3, an essential biomarker leading to various molecular adjustments. Their evidences represented the efficacy of Pax3 on MITF's expression. Increasing the level of MITF leaded to expressing the Dopachrome-tautomerase (Dct) gene and eventually melanocytic differentiation. Moreover, Pax3 is a tumorigenesis biomarker increasingly expressed in melanocyte tumor cells (19-21). Furthermore, MITF as a moderator factor can control the expression pattern of MLANA/MART1 and PMEL17, regulating the receptor and/or enhancer region of their promoters (22).

1.1.4. Bcl-XL and Mcl-1

Bcl-XL (B-cell lymphoma-extra-large) and Mcl-1 (myeloid cell leukemia sequence 1), which are increased in melanoma, have been reported as recent factors regulating STAT3 activity. These antiapoptotic markers can firmly express STAT3, which affects VEGF (vascular endothelial growth factor) and leads to angiogenesis. Scientists have suggested that STAT3 mRNA prevention may lead to reduction in VEGF protein level and eventually melanoma molecular therapy (23). In Zhuang et al study, lactate dehydrogenase (LDH) expression was investigated, and as LDH5 is an essential component in several diseases, its level was measured in melanoma patients. Recent studies demonstrated that as LDH5 was increased, Bcl-XL and Mcl-1 components were upregulated (23, 24). Thus, estimating LDH5 can be a molecular way to diagnose melanoma.

1.1.5. MMPs

Another biomarker, Matrix metalloproteinases (MMPs), including MMP1, MMP2, and MMP3, are inevitable factors of metastasis. These collagenase members are essential components in extracellular matrix degradation. Because of their function, scientists have always been interested in their application in the diagnosis and prognosis of melanoma (25, 26). In a study of Hofmann et al, a mouse model was experimented by reverse-transcription polymerase chain reaction (RT-PCR) for gene expression and Northern blot analysis for protein expression. Among the MMPs protein family, MMP2 is a metastatic marker in various melanomas cell lines (27). Other related studies conducted on the efficacy of MMP2 in metastasis and malignancies were considered (28). Moreover, Malaponte et al noted a relationship between MMP2 and transforming growth factor β (TGFβ) and indicated that TGFβ induced expression of MMP2 in melanoma progression (29).

1.1.6. Cell-free DNAs (cfDNAs)

Cell-free DNA (cfDNA) was first recognized in humans in 1948. They are present in the blood of cancer patients for decades and contain lots of information on tumor genetics. The previous research and other similar investigations represented a new diagnostic method for cancers

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using some sensitive molecular biology techniques, which have various benefits for selecting the best therapeutic methods to treat these cancers (30).

Several studies have used cfDNAs in the diagnosis and prognosis of cancers. Researchers isolated the plasma cfDNAs to determine the common mutations in BRAF, EGFR, KRAS, and PIK3CA in which the pattern of the mutations was similar to those of the tumor specific tissues in various cancers (31). The mentioned study and other recent surveys used different types of methods, including BEAMing measurement, allele-specific quantitative PCR, and other molecular methods, and they showed a perfect concordance of mutation profiling of the same genes in plasma cfDNA and tumor tissues (31).

In another study, BRAFV600E mutation was estimated in cfDNAs of 113 patients with malignant melanoma. They used droplet digital PCR (ddPCR) method for their analysis and settled this method as a precise diagnostic method for melanoma. Also, they indicated that this method can be used for treatment follow-up in patients (32).

Although many studies have proved the role of cfDNAs as a possible diagnostic method, more studies should be conducted to rely on cfDNAs as a diagnostic biomarker. Cost-effectiveness and being less invasive than other methods, such as biopsy, makes cfDNAs more considerable (33).

2.1. Therapeutic Biomarkers

As the rate of melanoma has been increasing among the white skin population in the recent decade, finding brand new therapeutic methods is of high importance. Albeit, our knowledge about diagnostic markers can be helpful in tracing novel therapies.

2.1.1. Bcl-2

Bcl protein family is an antiapoptotic factor which is upregulated in several tumors as well as melanoma. Therefore, utilization of anti-sense Bcl-2 drugs, such as Genasense, is considered for use in the treatment of melanoma (24).

2.1.2. BRAF

Mutation in BRAF has been discussed in various types of cancers. The se rine/threonine kinase family is essential for cell proliferation. Among the 3 isoforms containing ARAF, BRAF, and CRAF, BRAF mutation is more common. Studies have shown 30% of BRAF mutation in primary melanoma and 55% in metastatic forms. BRAF can play a major role in melanoma treatment because of its synergistic inhibition to repress melanocytic cell proliferation (34, 35).

2.1.3. CTLA4

In Kapadia et al study, cytotoxic T-lymphocyte antigen 4 (CTLA4) was distinguished as an identifier of variable antigens (36). CTLA4 blocking through specific antibodies and/or miRNAs' targeting CTLA4 has been shown to induce T-cell activity and eliminate melanocytic cancer cells which can be used to treat melanoma and other cancers (37).

2.1.4. MiR-221 and MiR-625

Using miRNAs is a common method for prognosis, diagnosis, and therapeutic aspects. Several studies have been performed to distinguish the roles of microRNAs in melanoma (38). Fellicetti et al detected the upregulation of miR-221 in melanoma (39). They proved that P27 is a cell cycle regulator attaching to cyclin D1, which controls cell proliferation. In another study, c-KIT, another cell cycle regulator, was authenticated to be miR-221's target (40).Therefore, miR-221 seems to be a multipotential diagnostic/therapeutic target in melanoma.

In one study on microRNA, miR-625 was used to treat melanoma; miR-625 was transduced to melanocytic cancerous cells which blocked melanoma progression; such studies strengthen the novel strategy of miRNA usage (41).

2.1.5. Sox-10 and Nestin; Melanoma Oncogenes

Krupkova et al noted that in melanocytic cancerous cells, nestin is a mutant gene. In addition, they showed genes' expression in progressive melanoma. Accordingly, using some anti-sense RNA due to nestin inhibition can be a simple specimen for therapy (42).

In another study, Su et al determined Sox-10 as another essential gene in progression of melanoma. They discovered that minichromosome maintenance complex component 5 (MCM5) is activated by Sox-10 and induced cell proliferation. Subsequently, Sox-10 can be repressed through some specific noncoding RNAs to inhibit cell cycle processes (43).

2.1.6. BRMS1

Multiple investigations have explored breast cancer metastasis-suppressor 1 (BRMS1) as an important prognostic marker. Li et al found that downregulation of BRMS1 is noticeable in metastatic melanoma. Also, they noted that this marker should be inhibited in breast cancer to decrease tumorigenicity. Li et al suggested that suppression of BRMS1 can be a new therapeutic strategy in melanocytic cell metastasis (44).

2.1.7. SiRNA in melanoma

The small interfering RNA (siRNA) is a favorable treatment strategy in oncology, but its efficacy is depended on the level of silencing the targeted genes in different cancers, including melanoma (32). It has been demonstrated that overactivation of signal transducer and activity of transcription 3 (STAT3) play a critical role in melanoma invasion and metastasis through targeting apoptosis components and MMP-2, improving the expression of cell cycle regulatory cyclin D1 and myc. Therefore, targeting STAT3 by siRNA is a credible therapeutic strategy for treating melanoma (45). He et al reported that BRAFV600E suppression using siRNA combined with PI3K or mTOR signaling pathway inhibitors was significantly effective in melanoma A375 cell line (46). Moreo-

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ver, it has been shown that using siRNA against NRAS (Q61R) in patients who are carrying this mutation can reduce oncogenic effects of NRAS during the downregulation of ERK, AKT, NF-kappa B, and cyclin D1 (47).

Recently, C-myc, MITF, ribonucleotide reductase (RR), and Rad51 siRNAs have been found to develop new treatment for melanoma cells in clinical trials (47).

Conclusion

Several studies found that various processes are involved in cancer pathology. The most important modification is genetic mutation. In addition, multiple genes have been found to be mutated in melanoma, including BRAF and Bcl-xL. Thus, knowledge of these modifications can improve the diagnosis and prognosis.

Besides mutation, methylation can be another essential change in transforming normal cells to abnormal ones. Many investigations have indicated that methylation of some specific genes affects transcription and translation processes. These molecular processes have been illustrated to be a modifier marker for cellular mechanisms, such as cell proliferation. Accordingly, increase in cell number can be regulated through forenamed modifications. Also, deficiency of these particular markers reduce adherence of cells.

This study focused on molecular factors affecting cell cycle in melanoma. In similar studies, some of the mentioned biomarkers have been used as a diagnostic marker and some as a therapeutic factor. Also, some of these markers have been distinguished as a diagnostic marker with other simultaneous mutation in various factors. Furthermore, cfDNAs, as a novel diagnostic approach for cancer, can be used instead of biopsy sampling.

Moreover, noncoding RNAs has become more considerable in recent decades. Multiple studies have demonstrated noncoding RNAs as a possible diagnosis and therapeutic markers for different diseases, such as cancers and neurodegenerative diseases. These noncoding molecules have been examined and have shown to have notable effects in diagnosis and treatment of melanoma. These small molecules could block some of the mutated genes and inhibit their translation into proteins.

Molecular biomarkers are a central part of personalized care and cancer therapy. However, decisionmaking based on usable criteria in new biomarker assays for clinical use have not yet been well established. Development of molecular biomarkers is principally difficult. While these factors has been identified as diagnostic, prognostic, and therapeutic components, future studies are required to confirm the utilization of these biomolecules. Recent studies have distinguished the efficacy of several genes in molecular and cellular processes. However, clinical trial of these outcomes should be accomplished to find their exact affect.

Conflict of Interests

The authors declare that they have no competing interests.

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