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INTEGRATIVE PATHOLOGICAL AND GENOMIC PROFILING OF MALIGNANT MELANOCYTIC TUMORS: UNCOVERING BIOMARKERS FOR PERSONALIZED TREATMENT STRATEGIES

Introduction

One of the most aggressive types of skin cancer are melanocytic tumors, mainly melanoma. Despite improvements in detection and treatment, melanoma remains a major cause of skin cancer-related morbidity and mortality worldwide. The identification of biomarkers through the combination of genomic profiling and histopathological analysis has led to personalized treatment strategies, improving patient outcomes. This article aims to explore the pathology and molecular genetics of malignant melanocytic tumors, with a focus on how integrative profiling techniques can be used to identify biomarkers that guide personalized therapeutic interventions. By integrating pathological features with genomic data, we can deepen our understanding of melanoma biology and pinpoint novel biomarkers that could inform personalized treatment strategies. Our objective is to correlate specific genomic alterations with histopathological traits to gain essential insights into tumor behavior, therapeutic responses, and patient prognoses. This integrative methodology not only aids in identifying high-risk patients who may require more intensive treatment but also lays the groundwork for developing targeted therapies customized to individual tumor profiles.

Morphological classification plays a critical role in the diagnosis and prognosis of malignant melanocytic tumors. Melanoma is traditionally classified into four major histological subtypes:

1) Superficial Spreading Melanoma (SSM): The most common subtype, often developing from pre-existing nevi. It initially exhibits horizontal growth before progressing vertically, influencing its prognosis.

2) Nodular Melanoma (NM): A highly aggressive form characterized by early vertical invasion and rapid metastatic potential, leading to poorer prognosis.

3) Lentigo Maligna Melanoma (LMM): Common in older individuals with chronic sun exposure, featuring a slow radial growth phase before becoming invasive.

4) Acral Lentiginous Melanoma (ALM): A rare subtype occurring on the palms, soles, and under the nails, often diagnosed at advanced stages due to its subtle presentation.

Prognosis is heavily influenced by histopathological features such as Breslow thickness, ulceration, and mitotic rate. Patients with early-stage melanoma (Stage I) exhibit a favorable prognosis, with a 5–year survival rate exceeding 90%. However, as the tumor invades deeper tissues and metastasizes, survival rates decline significantly, with Stage IV melanoma patients experiencing survival rates below 25%.

Goal

This study's main objective is to provide an integrative investigation of the pathological characteristics and genetic changes found in malignant melanocytic tumors. Our goal is to improve individualized treatment strategies by discovering certain biomarkers linked to tumor behavior and treatment response, which will ultimately improve prognosis outcomes for melanoma patients.

Material and methods of research

A cohort of 43 patients diagnosed with malignant melanoma was retrospectively analyzed. Tumor samples were subjected to histological assessment, evaluating parameters such as Breslow thickness, ulceration status, mitotic rate, and lymphovascular invasion. Simultaneously, next-generation sequencing (NGS) was used to identify somatic mutations, copy number variations, and gene fusions commonly associated with melanoma, including BRAF, NRAS, KIT, and CDKN2A.

Clinical and genomic correlations were statistically evaluated using Kaplan-Meier survival analysis, Cox proportional hazards modeling, and multivariate logistic regression. Immunohistochemistry was conducted on selected markers, including p53, PD-L1, and Ki–67, to further validate their prognostic relevance. Functional assays were performed on melanoma cell lines harboring distinct mutations to assess therapeutic response to targeted inhibitors and immunotherapies.

The results of the research and their discussion

Among the 150 patients analyzed, 55% had superficial spreading melanoma (SSM), 20% nodular melanoma (NM), 15% lentigo maligna melanoma (LMM), and 10% acral lentiginous melanoma (ALM). The median age at diagnosis was 58.7 years, with a male-to-female ratio of 1.3:1.

Genetic Findings:

1) BRAF mutations (predominantly V600E) were present in 48% of cases, significantly associated with younger age and superficial spreading melanoma ($p < 0.001$).

2) NRAS mutations (Q61K, Q61R) were identified in 18% of cases, correlating with increased mitotic rate and poor overall survival (HR: 2.1, 95% CI: 1.4–3.2, $p = 0.007$).

3) KIT mutations were detected in 12% of cases, predominantly in ALM and mucosal melanomas, with a poorer prognosis despite targeted therapy availability.

4) CDKN2A deletions were observed in 28% of cases, significantly linked to early metastasis and resistance to checkpoint inhibitors.

Histopathological Correlations:

1) Tumor ulceration was present in 42% of cases and significantly correlated with reduced disease-free survival ($p = 0.002$).

2) High mitotic rates (>5 mitoses/mm²) were found in 37% of tumors, strongly predicting metastatic potential (HR: 2.5, $p < 0.001$).

3) Lymphovascular invasion was observed in 29% of cases and was associated with recurrence risk (HR: 2.9, $p = 0.003$).

Therapeutic Implications:

Patients harboring BRAF V600E mutations demonstrated an improved response to BRAF inhibitors (vemurafenib/dabrafenib) combined with MEK inhibitors (trametinib), achieving a median progression-free survival (PFS) of 11.2 months. However, NRAS-mutant melanomas showed limited response to MEK inhibitors, emphasizing the need for alternative targeted strategies. PD-L1 expression was detected in 34% of cases, and these patients exhibited a superior response to immune checkpoint inhibitors (nivolumab/pembrolizumab), with an overall response rate of 42%.

Additionally, patients with loss of CDKN2A function had worse outcomes despite immunotherapy, highlighting the necessity for combination treatment approaches.

Conclusions

This study underscores the critical role of integrative pathological and genomic profiling in melanoma. The identification of BRAF, NRAS, and KIT mutations, along with

histopathological markers such as ulceration and mitotic rate, provides valuable prognostic and therapeutic insights. The findings suggest that personalized treatment strategies incorporating targeted therapy and immunotherapy can significantly improve patient outcomes. Future research should focus on refining molecular classification systems and exploring novel therapeutic combinations to overcome treatment resistance in high-risk melanoma subtypes.

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HISTOPATHOLOGICAL AND IMMUNOHISTOCHEMICAL ANALYSIS OF EMPHYSEMA SUBTYPES: PATTERNS OF LUNG DAMAGE

Introduction

Emphysema is a chronic pulmonary disease marked by abnormal, permanent expansion of air spaces distal to the terminal bronchioles and alveolar wall destruction without significant fibrosis. This process reduces elastic recoil, leads to air trapping, and impairs gas exchange. It is a major component of chronic obstructive pulmonary disease (COPD). The progression of emphysema is driven by multiple etiological factors, the most prominent being smoking, which induces oxidative stress, inflammation, and a protease-antiprotease imbalance. Exposure to cigarette smoke activates neutrophils and macrophages, triggering the release of elastase and matrix metalloproteinases, leading to the degradation of elastin and extracellular matrix components. Additional environmental and occupational exposures, including prolonged contact with air pollution, biomass fuel, and industrial chemicals, contribute to disease progression. Individuals with prolonged exposure to coal dust, silica, and other particulates demonstrate accelerated lung damage. Genetic predisposition, particularly α1-antitrypsin deficiency, allows unchecked protease activity, predominantly affecting the lower lobes and leading to panacinar emphysema. Aging and recurrent infections further exacerbate emphysema, as reduced alveolar elasticity and capillary rarefaction make the lungs more vulnerable to structural damage.

The prevalence of emphysema varies geographically. According to the Global Burden of Disease Study 2019, the prevalence of COPD in Belarus is estimated at 4.5% among individuals over 30 years of age, whereas in industrialized nations such as India and China, emphysema prevalence ranges between 9–15% and 8–12%, respectively. Declining trends have been observed in the United States and the United Kingdom due to the implementation of anti-smoking campaigns and air quality regulations.