Review Article

CRTC1-TRIM11: A Novel Oncogenic Driver in Cutaneous Tumors – From Molecular Pathways to Therapeutic Target

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DOI: 10.21276/APALM.3439

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Submitted: 30-Aug-2024
Final Revision: 30-Nov-2024
Acceptance: 12-Jan-2025
Publication: 26-Feb-2025

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Abstract

The CRTC1 fusion gene has recently been identified as a novel oncogenic driver in cutaneous tumors, presenting new insights into tumorigenesis and potential therapeutic targets. This fusion results from a translocation involving the CRTC1 transcriptional coactivator and the TRIM11 ubiquitin E3 ligase, leading to the dysregulation of key cellular processes such as proliferation, apoptosis, and differentiation. The aberrant activation of signaling pathways by the CRTC1 fusion promotes unchecked cellular growth, contributing to the formation and progression of malignant lesions in the skin.

Because the fusion gene affects protein degradation and cellular signaling, it is clear that it plays a role in cancer development. This means that it could be a key target for therapy. Current research is focused on elucidating the molecular mechanisms by which CRTC1 drives tumor growth, intending to identify specific pathways that novel treatments can target. Inhibition of these pathways or disrupting the fusion gene's expression holds promise for developing more effective therapies.

Keywords:

CRTC1:TRIM11, Cutaneous Tumors, Cancer Genetics

Introduction

Cutaneous tumors represent a diverse group of neoplasms affecting the skin, with varying degrees of malignancy. The most common types include basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and malignant melanoma. Basal cell carcinoma, the most frequent, accounts for approximately 80% of non-melanoma skin cancers, while squamous cell carcinoma makes up around 20% [1]. Malignant melanoma, although less common, is the most aggressive and is responsible for the majority of skin cancer-related deaths [2]. While cutaneous tumors are varied, the identification of novel molecular drivers, such as the CRTC1::TRIM11 fusion gene, has provided new insights into the pathogenesis of these tumors. The discovery of this fusion gene highlights its pivotal role in tumorigenesis, offering potential for early diagnosis and targeted therapies [3].

Importance of Molecular Drivers in Tumorigenesis

The development and progression of cutaneous tumors are driven by a complex interplay of genetic and environmental factors. Molecular drivers, such as oncogenes and tumor suppressor genes, play a pivotal role in tumorigenesis by altering cell signaling pathways, promoting uncontrolled cell proliferation, and inhibiting apoptosis. The identification of specific molecular drivers in cutaneous tumors has not only improved our understanding of their pathogenesis but also paved the way for targeted therapies, which offer more precise and effective treatment options [3].

The discovery of novel oncogenic drivers, such as the CRTC1 fusion, underscores the importance of continuing research in this area. Such molecular alterations can serve as potential biomarkers for early diagnosis and as therapeutic targets, providing new avenues for personalized treatment strategies in patients with cutaneous tumors [4].

Molecular Pathways Involving CRTC1 Fusion Mechanism

The CRTC1 gene, when involved in fusion events, has been associated with various oncogenic processes in different types of tumors, including cutaneous tumors. The CRTC1 fusion is a novel oncogenic driver, particularly relevant in the context of skin cancers. This fusion event typically involves chromosomal rearrangements leading to the creation of a fusion transcript, which contributes to tumorigenesis.

Chromosomal Rearrangements

Chromosomal rearrangements leading to gene fusions can involve complex processes such as translocations, inversions, or interstitial deletions. These rearrangements bring together parts of two different genes, forming a new hybrid gene that can drive abnormal cellular processes. For example, in mucoepidermoid carcinoma (MEC), a type of salivary gland tumor, the CRTC1-MAML2 fusion results from a translocation between chromosomes 19 and 11, creating a fusion protein that acts as an oncogene by disrupting normal signaling pathways [5].

Fusion Transcript Formation

The fusion transcript resulting from the CRTC1 event involves the transcription of the newly formed fusion gene into a chimeric mRNA, which then translates into a fusion protein. This fusion protein can have aberrant functions compared to the original proteins encoded by the CRTC1 and TRIM11 genes, often leading to the activation of oncogenic pathways. In papillary thyroid carcinomas, a similar process is observed, where the RET tyrosine kinase domain undergoes fusion with other genetic elements, leading to oncogenic activation [6]. The specific fusion transcript involving CRTC1 and TRIM11 in cutaneous tumors likely follows a similar mechanism, where the fusion protein alters cellular signaling pathways to promote tumorigenesis [7].

Role in Oncogenesis: CRTC1 Fusion Protein in Tumorigenesis

The CRTC1 fusion protein, particularly when fused with TRIM11, is implicated in enhancing tumorigenic processes through several molecular mechanisms. One of the primary pathways influenced by CRTC1 is the Wnt/β-catenin signaling pathway. CRTC1 fusion proteins can upregulate Wnt signaling, leading to increased cell proliferation, migration, and survival, which are crucial steps in the initiation and progression of tumorigenesis [8].

Furthermore, CRTC1 acts as a potent coactivator of the CREB (cAMP Response Element-Binding Protein) transcription factor, which is pivotal in regulating genes involved in cell growth and survival. The fusion protein's ability to amplify CREB-mediated transcription results in the upregulation of oncogenic genes that drive tumorigenesis, including those involved in angiogenesis and

cell cycle regulation [9]. Additionally, CRTC1 is known to interact with other signaling molecules and pathways, such as the MAPK and PI3K/AKT pathways, further contributing to the malignant transformation of cells [10].

The dysregulation of these pathways underlies the aggressive nature of tumors harboring the CRTC1 fusion protein, making it a critical target for therapeutic intervention. The identification of TRIM11 as a fusion partner in these tumors suggests that the oncogenic potential of CRTC1 is significantly enhanced by the ubiquitin ligase activity of TRIM11, which may stabilize or enhance the activity of oncogenic proteins, thus promoting tumorigenesis [11].

Comparative Analysis: CRTC1::TRIM11 Fusion Protein in Cutaneous Tumors Versus Other Fusion Proteins

The CRTC1::TRIM11 fusion protein represents a novel oncogenic driver in cutaneous tumors, distinct in its pathological and clinical manifestations when compared to other fusion proteins found in both cutaneous and various other tumor types. Unlike more common fusions, such as BRAF::KIAA1549 in pilocytic astrocytoma or EWSR1::FLI1 in Ewing sarcoma, which are associated with well-characterized pathways leading to aberrant cell proliferation and survival, the CRTC1::TRIM11 fusion is relatively rare and was initially described in a subset of melanocytic tumors of the skin. This fusion is unique in its ability to induce a distinctive melanocytic differentiation while retaining the potential for local recurrence and metastasis, albeit with a generally indolent course. The morphological features of tumors harboring the CRTC1::TRIM11 fusion, including nests and bundles of epithelioid to spindle cells, can mimic other entities like clear cell sarcoma and metastatic melanoma, complicating accurate diagnosis without molecular confirmation [12].

Moreover, unlike ALK::EML4 in non-small cell lung carcinoma, where targeted therapies have been extensively developed and utilized, there are no established therapeutic protocols for CRTC1::TRIM11-positive tumors, though early studies suggest potential sensitivity to TRK inhibitors due to the involvement of neurotrophic signaling pathways [13]. The rarity and unique behavior of the CRTC1::TRIM11 fusion in cutaneous tumors underscore the need for further research to understand its oncogenic mechanisms and develop effective targeted therapies.

Diagnostic Relevance

The finding of the CRTC1::TRIM11 fusion in skin tumors, especially in the case of CMTCT (Cutaneous Melanocytic Tumor with CRTC1::TRIM11 Fusion), is very helpful for diagnosis. This new oncogenic driver is known to be an important biomarker in molecular profiling, helping to distinguish this type of tumor from other melanocytic lesions. The diagnostic process is enhanced by molecular techniques such as Next-Generation Sequencing (NGS) and Fluorescence In Situ Hybridization (FISH), which can detect the specific fusion genes involved in these tumors [14,15].

Identifying the CRTC1::TRIM11 fusion using molecular diagnostics is highly beneficial, as it enables a precise diagnosis and allows clinicians to tailor treatments for individuals with these specific genetic changes. For cutaneous tumors, this highlights the importance of incorporating molecular diagnostics into the clinical process, particularly for uncommon types like CMTCT that may be difficult to diagnose using conventional histopathological methods [16,17].

Histopathological Features

The connection between CRTC1 and certain histopathological features in skin tumors, especially melanocytic tumors, reveals several unique morphological patterns. Studies have shown that the CRTC1::TRIM11 translocation is associated with highly uniform and reproducible morphologic features. These tumors often exhibit a consistent histological appearance across various anatomical locations and age groups. The unique morphological patterns include uniform cellular architecture, specific

immunohistochemical profiles, and genetic traits that are essential for accurate diagnosis and prognosis.

For instance, Hanna et al.'s study found that cutaneous melanocytic tumors with CRTC1::TRIM11 translocation exhibit highly consistent histopathological features, including a unique cellular architecture that can be recognized across different patients, regardless of tumor location [18].

In a different study, Duan et al. described a cutaneous melanocytic tumor with the CRTC1::TRIM11 fusion, highlighting how this tumor differs from other melanocytic lesions due to its unique histopathological features, such as a distinct pattern of melanocytic proliferation and characteristic cellular morphology [15].

These findings emphasize the significance of CRTC1 in defining the histopathological features of certain skin tumors, particularly those involving melanocytic cells. The consistent morphological patterns observed across different cases suggest that CRTC1 is a key marker for these tumors and could serve as a valuable target for both diagnosis and treatment.

Prognostic Significance

The prognostic significance of CRTC1 in cutaneous tumors, particularly regarding survival rates, tumor aggressiveness, and recurrence risk, has been evaluated in several studies. However, the direct impact of CRTC1 on these prognostic factors remains an area of active research.

One study developed a machine learning-based intratumor heterogeneity signature to predict prognosis and immunotherapy benefits in skin cutaneous melanoma. The study demonstrated that the signature had a strong and stable performance in predicting overall survival rates, highlighting the potential role of CRTC1 in this context. This suggests that the presence of the CRTC1::TRIM11 translocation might be linked with worse survival outcomes, although further research is needed to confirm this directly [19].

In another study, it was found that patients with specific genetic profiles, such as those identified by the 31-gene expression profile test, showed a significantly higher likelihood of developing central nervous system metastasis, which correlates with a poorer prognosis. While this study did not focus specifically on CRTC1, it underscores the importance of genetic markers in determining prognosis in cutaneous melanoma [20].

These findings suggest that while CRTC1 may play a role in influencing prognosis, further studies are necessary to establish its direct impact on survival rates, tumor aggressiveness, and recurrence risk in cutaneous tumors.

Challenges and Future Directions

Research Gaps

Despite the progress in understanding the role of CRTC1 in cutaneous tumors, several key research gaps remain. These include a need for a deeper understanding of the molecular mechanisms by which CRTC1 contributes to tumorigenesis, the identification of biomarkers that can predict response to CRTC1-targeted therapies, and the development of robust preclinical models that accurately reflect human disease. Additionally, the long-term effects and potential resistance mechanisms associated with CRTC1-targeted therapies are yet to be fully elucidated.

Emerging Technologies

Emerging technologies hold great promise in advancing research on CRTC1. Techniques such as CRISPR-based gene editing

could be used to create more accurate models of CRTC1-driven tumors, allowing for more precise studies of its role in cancer. Next-generation sequencing could facilitate the identification of co-occurring mutations and other genomic features that influence the behavior of CRTC1-driven tumors. Single-cell analysis could provide insights into the heterogeneity of these tumors and how they evolve under therapeutic pressure, potentially leading to the discovery of new therapeutic targets or combination strategies.

These technologies, combined with a focused effort to address the existing research gaps, have the potential to significantly advance our understanding of CRTC1 in cutaneous tumors and pave the way for the development of effective targeted therapies.

Conclusion

The discovery of the CRTC1::TRIM11 fusion as an oncogenic driver in cutaneous tumors offers new insights into tumor biology and presents a promising therapeutic target. This fusion gene's role in disrupting key signaling pathways highlights the need for integrating molecular diagnostics into clinical practice. While targeting CRTC1::TRIM11 holds potential for novel treatments, further research is essential to overcome current challenges and translate these findings into effective therapies. Advancements in technology, such as CRISPR and next-generation sequencing, will be crucial in developing precise and personalized treatment strategies for these tumors.

Source of funding – No

Conflicts of interest – No

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