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Vimentin in melanoma: diagnostic and therapeutic applications. Mini-Review

Abstract

Melanoma, the deadliest form of skin cancer, poses a significant global health challenge due to its high metastatic potential and resistance to conventional therapies. Vimentin, an intermediate filament protein typically expressed in mesenchymal cells, plays a crucial role in various cellular processes, including cell motility, invasion, and metastasis. Different authors discuss the scientific value of using Vimentin as the diagnostic marker for invasive types of cancer, including various kinds (oral, hematogenous, amelanotic, etc.) of Melanoma. Recently, several investigators suggested the possible clinical application of the monoclonal antibodies inhibiting Vimentin activity for vimentin-targeted tumor-specific therapy. Another approach could be developing small molecule inhibitors targeting vimentin or its interacting partners. Authors have found promising results using pannexin 1, or inhibitors of aPKC and other inhibitors of vimentin activity could reduce tumor growth in in-vivo experiments. The development of more specific and effective vimentin-targeted therapies and diagnostic approaches holds significant promise for improving the outcome of melanoma patients.

Keywords: vimentin, melanoma, skin cancer, epithelial cells, immunohistochemical markers

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Introduction

Melanoma, the deadliest form of skin cancer, poses a significant global health challenge due to its high metastatic potential and resistance to conventional therapies.[1,2,3] Vimentin, an intermediate filament protein typically expressed in mesenchymal cells, plays a crucial role in various cellular processes, including cell motility, invasion, and metastasis.[4,5] Its aberrant expression in various epithelial cancers, including melanoma, has gathered significant attention as a potential diagnostic and therapeutic target.[4–6] This review will explore the current understanding of Vimentin's role in melanoma diagnosis and treatment, analyzing the available evidence and highlighting areas requiring further research.

The role of Vimentin in EMT and melanoma progression

Vimentin's significance in melanoma extends beyond its diagnostic role; it plays a crucial part in the progression and metastasis of the disease. A key mechanism underlying this role is the Epithelial-to-Mesenchymal Transition (EMT).[1–5,7] Studies have demonstrated that Vimentin expression in melanoma correlates with increased migration and invasion capabilities in vitro and in vivo.[1–3,7]

EMT is a process where epithelial cells lose their cell-cell junctions and acquire mesenchymal characteristics, gaining increased motility and invasiveness.[3,7] Vimentin is a hallmark of EMT, with its up-regulation often accompanying the down-regulation of epithelial markers such as E-cadherin.[1–3,7]

However, the precise mechanisms by which Vimentin contributes to melanoma progression remain incompletely understood.[4,5] While its role in EMT and cell motility is well-established, further research is needed to elucidate its interaction with other signaling pathways and its contribution to drug resistance and tumor microenvironment interactions.[4,5]

Abnormal expression of Vimentin as a diagnostic marker in melanoma

Vimentin's diagnostic utility in melanoma stems from its association with tumor progression and metastasis. Several studies have demonstrated increased Vimentin expression in melanoma cells compared to normal melanocytes.[3,7–9]

The Vimentin overexpression.[9] correlates with increased tumor growth, invasion, and poor prognosis.[4,5] Therefore, immunohistochemical staining for Vimentin can serve as a valuable adjunct in diagnosing melanoma, particularly in distinguishing it from other malignancies with similar microscopic appearances.[10,11]

Jensen et al.,[12] investigated serum biomarkers associated with response to immune checkpoint blockade in metastatic melanoma patients. They found that elevated levels of PRO-C3, C1M, C3M, and C4M (collagen markers) and Vimentin were associated with progressive disease, suggesting the potential of using these markers to predict treatment response.[12] However, further research is needed to validate these findings and explore their clinical utility.

Man Li et al.,[7] and Warters et al.,[13] validate Vimentin's role as a potential biomarker for melanoma hematogenous metastasis. Comparing different tissue melanoma models, researchers have found significantly higher Vimentin expression in the B16M group ($P< 0.05$).[7] Immunohistochemistry investigation revealed a significant association between Vimentin overexpression and a higher incidence of hematogenous metastasis ($P< 0.05$).[7] Cox Proportional Hazards Model Analysis independently confirmed TNM stage as a significant predictor of poor prognosis in melanoma patients ($P = 0.004$)[7] Man Li et al.,[7] concluded that Vimentin can be used as a marker of melanoma metastasis and help with the definition of the level of poor prognosis in the melanoma pathogenesis.[7]

For instance, Elgendy and Hussien's study[8] investigated the diagnostic significance of S-100 protein, Vimentin, and HMB-45

monoclonal antibodies in oral melanomas. Their findings revealed that all three markers were significantly expressed in all studied melanoma samples. Immunostaining of Vimentin expression was reported in the twelve tissue samples, with mild positive cytoplasmic staining in 2/12 samples, moderate positive reactivity in 4/12 cases, and strong positivity in 6/12 cases of all specimens.[8] This example highlights the diagnostic utility of Vimentin immunohistochemical expression as the diagnostic tool in oral melanoma cases.[8]

Xu et al.,[11] investigated the significance of using S-100 and Vimentin in the Immunohistochemical diagnostic of primary nasal mucosal malignant melanoma. According to the authors, PNMMM was reactive to S-100 protein and Vimentin in 90% and 77.5% cases, respectively, without reactivity to Keratin.[11]

Similarly, Deepak et al.,[14] and Ryan et al.,[15] have reported using Vimentin immunohistochemistry in the differential diagnosis of amelanotic melanoma, which lacks melanin pigmentation and presents a diagnostic challenge. In these cases, Vimentin staining and other melanocytic markers, like S-100 and HMB-45, help confirm the diagnosis.[14,15]

Furthermore, studies have shown a correlation between Vimentin expression and poor patient survival.[16–18] Ekmekcioglu et al.,[16] found that iNOS and nitrotyrosine expression in metastatic melanoma correlated with poor survival, suggesting a potential link between Vimentin and these markers.[16]

However, it is crucial to acknowledge the possible limitations of using Vimentin as a sole diagnostic marker. Vimentin expression is not exclusive to melanoma; it is also found in other mesenchymal tumors.[4,5]

Moreover, the study by Romano RC, et al.,[15] highlights the potential diagnostic pitfalls associated with aberrant intermediate filament expression in melanoma. They found anomalous expression of Vimentin and other intermediate filaments in a significant subset of melanoma cases, potentially leading to misdiagnosis if not considered carefully.[15] This report emphasizes the need for a comprehensive histopathological evaluation and the use of a panel of markers for accurate diagnosis of melanoma.[15]

Therefore, an accurate diagnosis requires a panel of immunohistochemical markers, including S-100, HMB-45, and other melanocytic markers.[8,10,11] Furthermore, the Vimentin expression level can vary among melanoma subtypes and stages, potentially impacting its diagnostic sensitivity and specificity.[8] More research is needed to define the optimal cutoff values for Vimentin expression to improve its diagnostic accuracy.[7]

Vimentin as a therapeutic target in melanoma

Given Vimentin's significant role in melanoma progression, it has become an attractive therapeutic target. Several strategies are being explored to target Vimentin for cancer therapy.[1,2,4,5,19] Another approach involves the development of Vimentin-targeting treatments that can reverse endothelial cell energy and promote immune infiltration, thereby supporting anti-tumor immunity.[20]

As an example of Vimentin-targeted therapy, Pal et al.,[1] investigated the role of Fisetin in anti-cancer mechanisms. Fisetin, a naturally occurring flavonoid in various fruits and vegetables, has garnered significant attention for its diverse biological activities.

Pal et al.,[1] treated in vivo studies using athymic mice injected with BRAF-mutated A375 melanoma cells with the combination of Fisetin and Sorafenib compared to either agent alone. The study showed a more significant reduction in the expression of EMT-related transcription factors and matrix metalloproteinases (MMPs) (MMP-2 and MMP-9) in xenograft tumor tissues.[1]

It appears that Sorafenib primarily inhibits the MAPK pathway, while Fisetin targets the PI3K pathway. These pathways are crucial in regulating EMT and driving cell invasion and metastasis.[1] Coordination of action prevents the activation of compensatory pathways and enhances the overall anti-metastatic melanoma effect.[1] Bioluminescent imaging demonstrated a significant reduction in lung metastases in mice treated with Fisetin and Sorafenib combined with either agent alone.[1]

As we noticed, Pal et al.,[1] investigated primarily BRAF-mutated melanoma, and more research is needed to determine Fisetin's efficacy in other melanoma subtypes. Long-term in vivo studies are also necessary to evaluate Fisetin's potential long-term toxicity and safety, especially when combined with Sorafenib.

Similarly, Zhang et al.,[2] found that Vitexin, another flavonoid, inhibited melanoma cell invasion and metastasis by down regulating Vimentin and other EMT markers.[2] The study focuses solely on in vitro investigations using human melanoma cell lines A375 and C8161.[2] Zhang et al.,[2] reported no in vivo experiments on Vitexin. This obstacle determines the need for further in vivo research to confirm these findings in a living organism.

In another study, Zhang et al.,[21] investigated the effects of Alantolactone (ALT) on melanoma cells, revealing that ALT inhibited cell proliferation, migration, and invasion while promoting apoptosis by suppressing the Wnt/β-catenin signaling pathway.[21] While not directly targeting Vimentin, this study highlights the importance of considering multiple pathways involved in melanoma progression.[21]

Peuela et al.,[19] investigated the role of Pannexin 1 (Panx1) in melanoma progression and found that Panx1 knockdown led to down regulation of Vimentin and reduced tumor growth in vivo.[19] This study suggests that targeting Panx1, which up-regulates Vimentin during melanoma progression, could be a viable therapeutic strategy.[19]

The study by Ratnayake et al.,[3,7] and Wishrawana et al.,[9,22] investigated the role of protein kinase C (PKC) in melanoma EMT. Studies show that PKC-ι promotes melanoma cell survival and progression by upregulating Vimentin dynamics during epithelial-mesenchymal transition (EMT)[3,7] and found that PKC activation leads to Vimentin activation via the TGFβ/Par6/RhoA pathway.[3] Inhibition of PKC-ι leads to decreased Vimentin expression, impacting the invasive characteristics of melanoma cells, such as the formation of lamellipodia, filopodia, and invadopodia.[7] This inhibition promotes apoptosis and reduces melanoma cell migration and invasion.[7] Further research into the upstream regulators of Vimentin expression, such as PKC, could identify novel therapeutic targets for melanoma.[3,7]

Moreover, studies have explored the effects of inhibiting other pathways involved in Vimentin regulation and melanoma progression. Zhou et al.,[23] demonstrated that combining PKC and COX-2 inhibitors synergistically suppressed melanoma metastasis.[23] The combination therapy impaired actin polymerization, induced MET, and decreased MMP secretion, all of which could indirectly influence Vimentin expression.[23] This obstacle suggests that combining therapies targeting different pathways involved in melanoma progression could be more effective than targeting Vimentin alone.[23]

Sharma et al.,[24] investigated the role of cyclin-dependent kinase 5 (CDK5) in melanoma metastasis and found that CDK5 phosphorylates Vimentin, promoting metastasis.[24] Inhibition of CDK5

blocked melanoma metastasis in mouse models, suggesting CDK5 as a potential therapeutic target to modulate Vimentin and suppress metastasis.[24] This research represents a novel therapeutic approach focusing on Vimentin regulation.

Another strategy involves developing Vimentin-binding peptides or antibodies specifically targeting and inhibiting Vimentin function.[4,5] Van Loon's work[20] demonstrated that extracellular Vimentin acts as a vascular immune checkpoint molecule, and distressing it can simultaneously alleviate immune suppression and repress tumor angiogenesis.[20] This approach holds promise for combining Vimentin-targeting vaccines with immune checkpoint blockade therapies for enhanced efficacy.[20]

While this approach is still in its early stages, developing Vimentin-binding mini-peptides has generated further impetus for Vimentin-targeted tumor-specific therapy.

Conclusion

According to studies, Vimentin plays a multifaceted role in melanoma and could serve as a diagnostic marker and a therapeutic target. Its overexpression correlates with tumor progression, hematological metastasis, and poor prognosis. Immunohistochemical staining for Vimentin can be a valuable tool in diagnosing different types of melanomas, hematogenous metastases, and possible survival predictors in conjunction with other melanocytic markers. Its non-specificity to varying subtypes of melanoma and some other types of cancer necessitates a comprehensive diagnostic approach. Vimentin's involvement in EMT highlights its potential as a therapeutic target, with various strategies being explored to inhibit its function and suppress melanoma metastasis. Further research is crucial to fully elucidate Vimentin's intricate roles in melanoma biology and refine therapeutic strategies targeting this essential protein. This approach includes investigating the upstream signaling pathways regulating Vimentin expression, identifying novel Vimentin inhibitors, and evaluating the efficacy of combined therapies targeting Vimentin and other melanoma-associated pathways such as PI3K, PKC-ι, etc. The agent targeting specific pathways sometimes works more efficiently with known drugs such as sorafenib. The development of more specific and effective Vimentin-targeted therapies holds significant promise for improving the outcome of melanoma patients.

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Conflict of interest

The authors declare that there is no conflict of interest.

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