VIA MEDICA

REVIEW ARTICLE

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# Mechanisms of neoplastic cell survival using melanoma as an example

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Oncology in Clinical Practice
DOI: 10.5603/ocp.98830

ISSN 2450–1654
e-ISSN 2450–6478

## ABSTRACT

We discuss various mechanisms of carcinogenesis using melanoma as an example. The article presents the cellular mechanism inducing pathological angiogenesis in neoplastic cells and the significance of the inflammatory process in carcinogenesis. A good understanding of the pathophysiology of tumors is key to creating new drugs and new forms of treatment. Exploring the mechanisms of tumor formation contributes to improving new therapies (new drugs, immunotherapy) and achieving higher survival rates in patients suffering from melanoma and other cancers. The article allows for a better understanding of the mechanisms of carcinogenesis.

**Keywords**: melanoma, angiogenesis, mutation, proliferative signals

Oncol Clin Pract

## Introduction

In the body of a healthy individual, cells grow, differentiate to perform their functions, and die, and a healthy balance between these processes is maintained. "Worn out" cells are replaced by new ones formed through cell division. During this process, an error can occur, leading to the formation of an abnormal cell. If abnormal cells are formed in the body, apoptosis of these cells is initiated. However, if the abnormal cell is not detected and apoptosis is not initiated, carcinogenesis can occur. This article discusses the mechanisms of carcinogenesis using melanoma as an example.

Melanoma is a type of malignant skin cancer derived from melanocytes [1, 2]. This cancer often metastasizes through the mechanisms of tumor cell migration and angiogenesis of abnormal blood vessels [3]. Every year, just in the UK, melanoma is diagnosed in over 16,000 people according to Neoplasm Research UK statistics, with a survival rate of 87% for 10 or more years [4]. Current trends suggest that this number could rise to 510,000 cases by 2040, with an annual death toll of 96,000 [5].

## Avoiding immune destruction

Cancer cells have various and very complex strategies to avoid destruction by the immune system, such as the exhaustion of T cells, which leads to the loss of their function, inhibition of the immune system, and accumulation of signaling factors and metabolites that interrupt mechanisms in immune system cells [6]. Initially, mutated cells are detected by the innate or adaptive immune response. Immune cells, such as NK cells and T cells, interact with interleukins secreted by melanoma cells, which increases inflammatory responses to induce apoptosis of melanoma cells [7]. During tumor

Received: 21.03.2024 Accepted: 08.05.2024 Early publication: 21.06.2024

progression, resistance to effector cells is observed as mutations occur in tumor cells supporting rapid proliferation and genetic instability [7]. Each mutation increases resistance to immune responses. This instability supports the selection of less immunogenic clones, increasing the survival rate of tumor cells. Among the soluble molecules that contribute to avoiding the immune response are vascular endothelial growth factor (VEGF), TNFs, TGF Beta, IL-6, IL-10, Fas-L, Fas, and PGE2 [7, 8]. PGE2 is believed to contribute to the development and metastasis of melanoma in animal models, hence it is thought that PGE2 plays a similar role in the human body. The mutation of the *BRAF* gene (*BRAFV600E*) leading to immune evasion through the activation of the mitogen-activated protein kinase (MAPK) pathway was detected in 66% of melanomas [8]. The MAPK signaling pathway is crucial in regulating cytokines and their functions [8]. Sumimoto et al. (2006) [8] demonstrated that both the MAPK pathway and the STAT3 pathway are important in reducing the immune response through the production of immunosuppressive molecules such as IL-10 or VEGF. Tumor cells, through the production of VEGF, IL-8, and IL-10 in their microenvironment, also damage dendritic cells, which are unable to present antigens to CD8+ T lymphocytes [9]. Increased metabolism of tumor tissue results in the formation of many metabolites that have immunosuppressive effects on T lymphocytes, leading to their exhaustion, which results in the loss of their effector functions and inability to destroy tumor cells [7]. Ongoing research on immunotherapy is exploring whether exploiting the antagonistic effects of co-inhibitory receptors such as programmed death-1 (PD-1) and cytotoxic T lymphocyte antigen-4 (CTLA4) would stimulate an anti-tumor response instead of causing T-cell depletion. The Food and Drug Administration (FDA) has approved the use of a monoclonal antibody targeting PD-1 for treatment of such cancers as squamous cell carcinoma of the head and neck, renal cell carcinoma, non-small cell lung cancer, and melanoma [10]. The combination of anti-PD1 and anti-CTLA4 therapy has been shown to enhance anti-tumor activity and increase progression-free survival (PFS) and 5-year survival compared to using anti-PD-1 therapy alone [11]. In 2022, an anti-LAG3 drug, which can be also combined with anti-PD-1 therapy, was approved for the treatment of unresectable or metastatic melanoma.

## Sustaining proliferative signals

Sustaining proliferative signals is another hallmark of cancer. Cancer cells maintain high levels of proliferation using three main pathways — Akt, MAPK/Erk, and mTOR [12]. Disruptions in the PI3K/Akt signaling pathway are linked to two mutations that lead to the increased internal activity of PI3K [12]. Akt is a proto-oncogene (also known as protein kinase B or PKB) and regulates cell metabolism, proliferation, and protein synthesis [12]. Activation of Akt occurs through integrins, B and T cell receptors, and PI3K (lipid kinase). When the Akt pathway is activated, it induces the production of phosphatidylinositol (3,4,5) trisphosphates (PIP3), i.e. lipids that help dock proteins in the plasma membranes [12]. A gene called phosphatase and tensin homolog (*PTEN*), responsible for suppressing many tumors, cell growth, proliferation, and apoptosis, often mutates or is completely lost in cancer cells [12, 13]. *PTEN* inhibits Akt signaling by dephosphorylating PIP3. In the cellular membrane, Akt can be phosphorylated by phosphoinositide-dependent kinase-1 (PDK1), resulting in partial activation, while full activation can be achieved by phosphorylation by mTORC2 [12]. Akt signaling balances cell growth via the mTOR pathway and the TSC1/TSC2 complex. Phosphorylation of CDK inhibitors p21 and p27 by the Akt pathway induces proliferation. The PI3K/Akt cell signaling pathway is altered in cancer cells [14, 15]. Melanocytes in melanoma exhibit resistance to PI3K inhibitors due to increased reactivation of Akt, limiting the inhibition of proliferation, and allowing melanoma cells to proliferate [16]. The feedback mechanism is involved in the development of melanoma as it is linked to the reactivation of Akt using the mTORC2 complex, especially its protein — RICTOR — which is overexpressed in melanocytes, leading to disruption of the feedback mechanism and activation of Akt [16]. This suggests that the RICTOR protein plays a significant role in the development of melanoma. MAPK activates many signaling cascades that support growth, proliferation, and survival mechanisms transmitted from the cell surface to the nucleus [12]. The aforementioned mutation in *BRAF*, which plays a significant role in avoiding immune destruction, is also important in sustaining proliferative signals. Mutations in *BRAF* and *RAS* lead to abnormalities in signaling via MAPK — increased signaling via MAPK — which induces rapid cell proliferation in melanomas [17].

## Inducing angiogenesis

Due to the high demand for nutrients and oxygen and the need to remove unnecessary metabolites, neoplastic tissue induces the process of angiogenesis [12]. The mechanisms of angiogenesis are very complex. As the demand for oxygen increases, creating a hypoxic environment, the tumor stimulates the development of blood vessels through hypoxia-inducible factor 1 (HIF-1) and other hypoxia-regulated genes that stimulate the expression of

multiple genes contributing to angiogenesis [12, 18]. Vascular Endothelial Growth Factors (VEGF) are key mediators illustrating some of the mechanisms supporting angiogenesis within neoplastic tissue. Several studies have shown that the VEGF-A type has the greatest impact on angiogenesis. In the neoplastic cell, VEGF secretion leads to the formation of a vascular network, which may be leaky due to its abnormal structure, facilitating metastasis [19, 20]. In the melanoma microenvironment, both inhibitors and stimulators of angiogenesis are secreted. It is believed that if there is an imbalance between inhibitors and stimulators in favor of stimulators, it leads to angiogenesis [21]. Tumor cells can overexpress VEGF, which is an angiogenic factor [3]. VEGF binds to two receptors called the VEGFR1/fms-like tyrosine kinase (Flt-1) and VEGFR2/kinase insert domain receptor (KDR)/fetal liver kinase 1 [3]. A stimulatory effect is observed when VEGF binds to VEGFRs, which stimulates vascular endothelial cells to migrate and proliferate [3]. VEGFR1 plays a critical role in pathological angiogenesis in melanoma [3]. VEGF-A enhances the motility and proliferation of endothelial cells, promoting angiogenesis [3]. Koizumi et al. (2022) [3] indicate that the VEGF-A/VEGFR1 signaling pathway may have clinical significance in improving metastasis management of melanomas.

## Tumor promoting inflammation

Immune cells promote the inflammatory process for effective recognition of antigens and damaged cells to destroy them. The inflammatory process is self-limiting [12, 22]. Neoplastic cells hijack inflammatory mechanisms to enhance their survival chances. Chronic inflammation in skin tissue strengthens the immunosuppressive microenvironment [22]. Factors produced by damaged immune cells stimulate neoplastic cells [12]. The most important pro-inflammatory mechanisms operate via NF-κB signaling, immune checkpoint signaling, inflammasome signaling, and tumor-infiltrating immune cell markers. Nuclear factor κB proteins are responsible for regulating genes that affect innate and adaptive immunity [12]. The NF-κB/Rel complex is bound to IκB inhibitory proteins, creating a complex in the cytoplasm. When the cell is stimulated, this complex falls apart due to the phosphorylation of IκB. Once IκB is phosphorylated, it is removed by the ubiquitin-proteasome system, releasing NF-κB/Rel [12]. The free NF-κB/Rel complex undergoes modifications such as phosphorylation, acetylation, and glycosylation. The activated free NF-κB/Rel complex enters the nucleus where it can regulate the expression of many genes. NFκB signaling in neoplasms is altered, leading to disruptions in gene expression, which results in inflammation within the neoplastic microenvironment [12, 23, 24]. The X-linked inhibitor of apoptosis protein (*XIAP*) is one of the genes whose expression in melanoma cells is elevated. Overexpression of *XIAP* is linked to several cellular events such as growth promotion, IL8 secretion, and neutrophil recruitment [23]. *XIAP* stimulates RIPK2 signaling in melanomas, leading to IL8 secretion, which induces neutrophil infiltration and progression of melanoma [23]. In addition to the pro-inflammatory functions of NFκB signaling, it can inhibit inflammasomes through inflammasome-dependent caspase 1 activation [23]. Inflammasome activation stimulates the cleavage of Caspase-1 and some cytokines such as IL-18 and IL-1β to enhance inflammation [12]. The role of inflammasomes in tumorigenesis needs to be better understood because, in some cases, they contribute to pro-inflammatory responses but can also lead to immunosuppression [25].

## Conclusions

The aforementioned hallmarks of cancer, in this case, melanomas, indicate that tumors are very effective in developing strategies to survive, proliferate, sustain cellular functions, and grow in the human body. Melanoma cells can avoid immune destruction, promote inflammation, induce angiogenesis, and sustain a high rate of proliferation through various signaling pathways and recruitment of many factors acting against the human body. A deep understanding of cancer hallmarks is essential for improving patient management methods and reducing the number of deaths. The MAPK signaling pathway is the focus of many studies because various combinations of MAPK inhibitors promise advancement compared to existing standard therapy [26].

## Article Information and Declarations

### Author contributions

K.Kasperowicz: prepared the first draft of the manuscript, manuscript revision and literature review; A.G., K.Kowalik: final preparation of the manuscript and substantive supervision; A.M.: final supervison.

### Funding

None.

### Acknowledgments

None.

### Conflict of interest

Authors declare no conflict of interest.

### Supplementary material

None.

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