Exploring Notch in Melanoma: A Recent Review of Its Role in Tumor Proliferation and Progression

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Abstract

Notch proteins are transmembrane receptors involved in regulating several cellular processes, including cell differentiation, proliferation, and tissue homeostasis. Aberrant activation of the Notch pathway, often due to mutations in its receptors, has been linked to tumor development and progression. This review consolidates research from January 2019 to September 2024, analyzing studies that utilized mixed methods, such as cell line assays, human tissue samples analysis, and animal models. Out of 28 studies, 22 qualified to be analyzed. Of the excluded studies, five of them evaluated Notch in other cell types associated with melanoma and one was a case report. Most findings suggest that Notch proteins are significant contributors to melanoma proliferation and/or progression. Notably, Notch1 has been the primary focus of these studies, supporting its involvement in cancer proliferation and progression.

I. Introduction

Notch proteins are transmembrane receptors that play roles in many cellular processes. In healthy tissues, Notch signaling is regulated and involved in several key functions. For example, Notch signaling regulates the balance between cell differentiation and proliferation, ensuring proper tissue formation and function [1] [2]. Notch proteins also direct cell-to-cell communication through Notch receptors on one cell and ligands on adjacent cells, coordinating cellular responses in tissues [3]. In addition, Notch regulates stem cells [4] [2] and the immune system [5] [6].

In cancer, Notch proteins have many roles that can vary depending on the tumor type and cell. Dysregulation of Notch signaling has been seen in various cancers, including melanoma, breast cancer, and leukemia. In some cases, aberrant activation of Notch signaling promotes tumorigenesis by increasing cell survival and proliferation. [7]. It can also function as a tumor suppressor [8]. Notch's role in cancer makes it a potential therapeutic target. Researchers are currently looking at Notch inhibitors that could disrupt its signaling in tumors while keeping its normal functions in healthy tissues [9]. Understanding Notch signaling can potentially develop effective cancer therapies.

Notch signaling can contribute to tumor development and progression in several ways [7]. Mutations in Notch receptors can lead to activation of the cancer-related pathways, which can lead to unchecked cell proliferation [10] [11]. Notch signaling can also increase the proliferation of cancer cells, which can promote tumor growth and maintain cancer stem cells [12]. Notch signaling can influence the formation of new blood vessels [13], which tumors need for their growth and metastasis, and influence immune responses, potentially helping cancer cells stay undetected [14]. Notch signaling can also increase the ability of cancer cells to metastasize [15].

Proposal

This study aimed to conduct literature review to answer the following research question: “Does Notch contribute to cancer proliferation and/or progression?”. This study aimed to understand the latest research on Notch proteins and genes' role in melanoma proliferation and/or progression. The study also aimed to research different Notch proteins and/or genes and identify if a specific Notch protein/gene contributes more than others. We conducted a literature review from January 2019 to September 2024 on PubMed and studied more than five years of research conducted on Notch proteins and genes to identify its role in melanoma proliferation and/or progression.

II. Methods

Data Collection

Pubmed was utilized to conduct the research using the following search criteria: (melanoma[Title]) AND (Notch*[Title]). Then the papers were filtered by the English language with papers published from January 2019 up to September 2024. After applying these parameters, full text of each of the papers was then analyzed in detail. Exclusion criteria were defined to ensure that only relevant research papers that focused on Notch proteins’ and/or genes' role in melanoma proliferation and/or progression were considered. Exclusion criteria included case reports, reviews and papers that were not relevant to the study like other cancer types or cell types. The overall process is illustrated in Fig. 1. Inclusion and exclusion criteria are illustrated in Fig. 2.

After that, a second analysis was conducted to answer the following questions: Is the data sufficient to answer if Notch contributes to cancer proliferation and/or progression? What is the specific type of Notch that was researched by the paper? Papers that showed the contribution of Notch proteins or genes, associated or not with another protein or gene, down or upstream the signaling pathway, regardless of mutation status were included.

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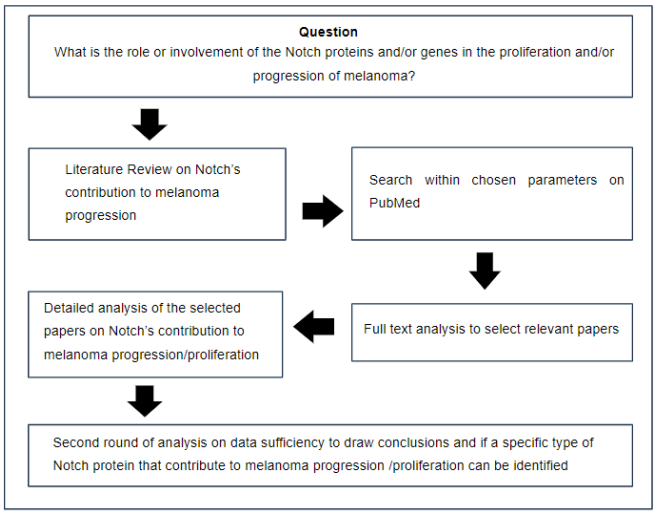

Figure 1: Paper selection process for literature review

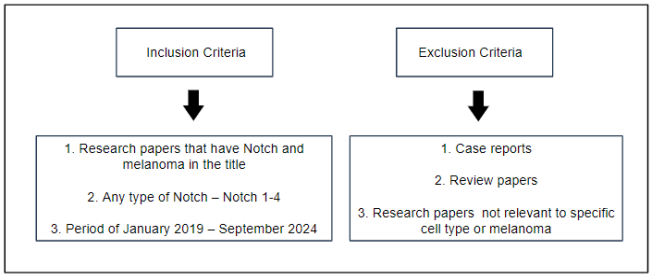

Figure 2: Inclusion and exclusion criteria

III. Results

After searching for papers on PubMed about Notch and melanoma applying the parameters discussed in the Methods section, the search yielded 28 studies. Out of 28 studies, 22 studies were about Notch in melanoma and qualified to be analyzed. Of the excluded studies, five of them evaluated Notch in other cell types closely associated with melanoma and one was a case report. This is illustrated in Fig. 3.

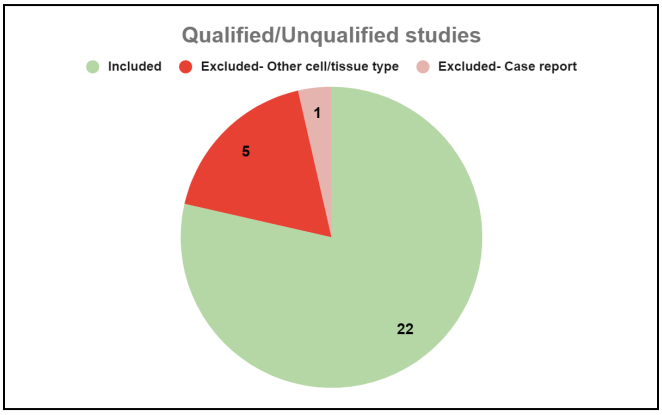

Figure 3: Share of qualified and unqualified studies analyzed. Unqualified studies involved case reports and studies that delved into different tissue or cell types other than melanoma.

The 22 deeply analyzed papers used a variety of methods. Experiments included cell line assays in 2D and 3D culture, such as viability, senescence and proliferation assays, cell death, cell cycle an, clonogenic assays, cell migration and invasion, genotyping, gene and protein expression. The papers also covered human tissue analysis, mostly on tissue microarrays in which tissues were evaluated by image analysis, bioinformatics using genome, gene and protein databases. The research also used xenografts in mice to better mimic the tumor microenvironment, with analysis of proliferation markers, protein expression, tumor growth and metastasis. Complete information about the included papers is presented in Table I.

Table I: Included papers, types of Notch studied and their contribution to cancer proliferation and/or progression.

Year	Reference	Notch Type	Does Notch contribute to cancer proliferation and/or progression?
2019	[16]	1	Data does not support a conclusion
	[17]	2	Yes
	[18]	1	Data does not support a conclusion
2020	[19]	1,2 and 3	Yes
	[20]	1 and 2	Yes
	[21]	1	Yes
	[22]	1	Yes
	[23]	1	Yes
2021	[24]	1	Yes
	[25]	1	Yes
	[26]	1	Yes
	[27]	3	Yes
2022	[28]	1	Yes
	[29]	1 and 2	Yes
	[30]	1,2,3 and 4	Data does not support a conclusion
	[31]	1	Yes
2023	[32]	3	Yes
	[33]	1	Yes
	[34]	1 and 2	No
2024	[35]	1	Yes
	[36]	1 and 3	Data does not support a conclusion
	[37]	1	Yes

Out of 28 research papers, 6 of them did not meet the criteria of inclusion. Five of them were studies that focused on studying how the Notch signaling pathway is activated for cells that are closely related to melanoma cells in the tumor environment. Therefore, although Notch was present in the paper title, and the research was about Notch's role on cancer progression, the studies did not specifically evaluate this protein or gene on the cancer itself. Additionally, one paper was a case report, and this meant that it had to be excluded due to our inclusion and exclusion parameters as depicted in Table II.

Table II: Excluded papers and reasons for exclusion

Year	Reference	Reason for exclusion
2019	[38]	Case report
2021	[39]	Notch was evaluated on fibroblasts associated with melanoma
2022	[40]	Notch was evaluated on endothelial cells co-culture with melanoma cell lines
2022	[41]	Notch was evaluated on T cells
2023	[42]	Notch was evaluated on astrocytes treated with extracellular vesicles from melanoma cell lines
2019	[43]	Notch was evaluated on mesenchymal stem cells derived fibroblasts associated with melanoma

Notch1 is the main focus of most of the included papers which comprise 19 out of 22 papers. Notch 1 was also studied along with other types of Notch in some papers which comprise 6 out of 22 papers. Notch 2 was the focus of 1 out of 22 papers and Notch 3 was the focus of 2 out of 22 papers as depicted in Fig. 4.

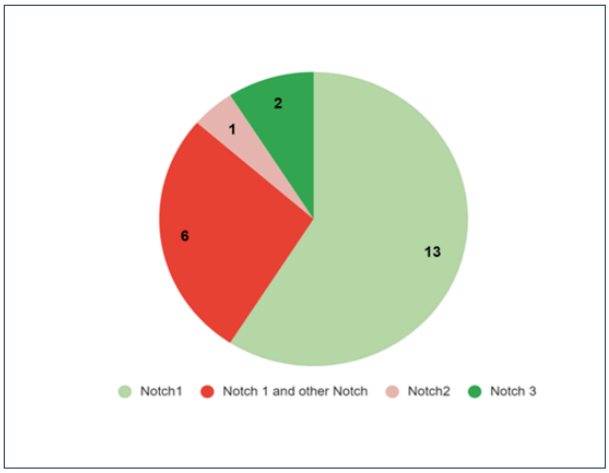

Figure 4: Share of Notch1, Notch2 and Notch3 across studies in melanoma research. Notch1 is predominantly studied. Notch2 and Notch3 were also studied in some of the papers analyzed.

IV. Discussion

The Notch signaling pathway is a series of molecular interactions, beginning with the binding of Notch receptors to ligands on adjacent cells, which leads to the cleavage of the Notch intracellular domain [44].

Notch receptor family is composed of Notch 1 to 4. Notch1's primary purpose is T-cell development, differentiating progenitor cells into T-cells through interactions with neighboring cells [45]. It also plays a role in neurogenesis by regulating the balance between neural progenitor cells and promoting their differentiation into neurons and glial cells. Dysregulation of Notch1 signaling can lead to disorders like T-cell acute lymphoblastic leukemia and neurodevelopmental issues. Notch2 is involved in B-cell development and differentiates hematopoietic progenitor cells into mature B-cells. It also contributes to processes in the immune system, helping to regulate responses [46]. Notch3 maintains vascular smooth muscle cells, which causes arterial development and stability. It also regulates blood vessel formation and remodeling, which is important for processes like angiogenesis [47]. Notch4 has many functions such as anti-inflammation, tissue repair, and lung inflammation [48].

In healthy tissues, this process regulates cell death, promotes proper development, and maintains tissue homeostasis by balancing cell proliferation and differentiation. However, in cancerous tissues, aberrant Notch signaling can lead to uncontrolled cell growth and survival, which can cause metastasis. The dysregulation of Notch pathways in cancer are caused by mutations in Notch genes, altered ligand expression, or changes in downstream signaling components, showing how Notch can be a tumor suppressor and an oncogene.

By analyzing if Notch proteins and/or genes contributed to cancer proliferation and/or progression, mixed results were found in our study. Most of this up-to-date research comprising of 17 out of 22 papers showed that Notch proteins can contribute to cancer proliferation and/or progression. We also demonstrated that recent research on Notch signaling in melanoma has primarily focused on Notch1, with some attention to Notch2 and Notch3.

In four papers the data does not support a specific conclusion. Although the papers described results on Notch protein or genes involvement on cancer, our analysis decided to interpret that there was not enough data to answer the specific question of this review. One of those papers was the only study that researched Notch4. Also, only one paper [34] has shown in an in *vivo* model that loss and decrease of Notch1 and Notch 2 appeared to help tumor growth and formation in mice, meaning that Notch signaling proteins were not correlated to melanoma proliferation.

Studies have shown that the Notch signaling pathway can be aberrantly activated in melanoma [49]. For example, overexpression of Notch receptors has been observed in melanoma tissues and cell lines [50]. Research has also shown that Notch signaling pathways are involved in the regulation of melanoma stem cells [51]. In melanoma, Notch signaling can promote EMT by regulating the expression of transcription factors and adhesion molecules, increasing the ability of the melanoma to metastasize [52] Researchers are also exploring the effects of Notch inhibitors in melanoma [53].

V. Conclusion

In conclusion, the majority of studies support the idea that Notch signaling plays an important role in the proliferation and progression of melanoma. Our research shows that, in recent years, Notch1 is the most researched protein or gene of the Notch receptor family, with many studies focusing on its effects in melanoma development.

It is important to note that the excluded papers also revealed a relevant landscape: recent research on the role of Notch in melanoma has increasingly explored other cell types within the tumor microenvironment that contribute to tumor development. In this study, these include fibroblasts, endothelial cells, T cells, and astrocytes, all of which play a role in modulating tumor behavior. Integrating these cellular interactions will be crucial for the success of new therapeutic targets or strategies.

VI. Acknowledgment

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VII. References

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