Gene Expression and Mutational Profile in BAP-1 Inactivated Melanocytic Lesions of Progressive Malignancy from a Patient with Multiple Lesions

Yan Zhou [1][iD]**, Andrew C. Nelson** [1,2][iD]**, Yuyu He** [1,2]**, Sarah A. Munro** [3]**, Kyu Young Song** [1,2][iD]**, Evidio Domingo-Musibay** [2,4][iD] **and Alessio Giubellino** [1,2,*][iD]

[1] Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN 55455, USA; zhou1237@umn.edu (Y.Z.); nels2055@umn.edu (A.C.N.); hexxx876@umn.edu (Y.H.); songx047@umn.edu (K.Y.S.)
[2] Masonic Cancer Center, University of Minnesota, Minneapolis, MN 55455, USA; musib024@umn.edu
[3] Minnesota Supercomputing Institute, University of Minnesota, Minneapolis, MN 55455, USA; smunro@umn.edu
[4] Department of Medicine, University of Minnesota, Minneapolis, MN 55455, USA
[*] Correspondence: agiubell@umn.edu

Abstract: BAP-1 (BRCA1-associated protein 1) inactivated melanocytic lesions are a group of familial or sporadic lesions with unique histology and molecular features. They are of great clinical interest, at least in part due to the potential for malignant transformation and association with a familial cancer predisposition syndrome. Here, we describe a patient with multiple spatially and temporally distinct melanocytic lesions with loss of BAP1 expression by immunohistochemistry. RNA sequencing was performed on three independent lesions spanning the morphologic spectrum: a benign nevus, an atypical tumor, and a melanoma arising from a pre-existing BAP1-inactivated nevus. The three lesions demonstrated largely distinct gene expression and mutational profiles. Gene expression analysis revealed that genes involved in receptor protein kinase pathways were progressively upregulated from nevus to melanoma. Moreover, a clear enrichment of genes regulated in response to UV radiation was found in the melanoma from this patient, as well as upregulation of MAPK pathway-related genes and several transcription factors related to melanomagenesis.

Keywords: BAP1; melanocytic lesions; melanoma; UV radiation response; MAPK; receptor protein kinase

1. Introduction

BAP1 (BRCA1-associated protein 1) gene, located on chromosome 3p21, is a tumor suppressor gene that encodes a deubiquitination enzyme regulating several key cellular pathways [1]. Inherited germline inactivating mutations in BAP1 have recently been found associated with a cancer predisposition syndrome, initially described in two unrelated families by Wiesner et al. [2]. It is characterized by the occurrence of multiple epithelioid melanocytic neoplasms resembling Spitz nevi and increased susceptibility for developing several malignancies in the affected individuals, including uveal melanoma, cutaneous melanoma, renal cell carcinoma, mesothelioma, and other tumors [3,4]. A variety of mutations in both coding and noncoding regions throughout the *BAP1* gene has been identified in the melanocytic lesions and can impair its protein function [5]. Interestingly these lesions harbor a *BRAF* V600E mutation, and characterization of this feature has helped distinguish them from Spitz lesions, which do not have this mutation in their genetic background [2,3,6]. Furthermore, in lesions with combined morphologies, *BRAF* V600E was found in all melanocytes, whereas *BAP1* mutation was restricted to the epithelioid cells, suggesting that the *BAP1*-inactivated melanocytic tumors might arise from common acquired nevi [2,7].

Besides presenting as a part of the familial cancer syndrome, *BAP1*-inactivated melanocytic tumors, including benign-appearing nevi, atypical tumors, and melanomas can also occur in a sporadic fashion [8,9]. For both the familial and sporadic lesions, prior studies found that only a minority of the *BAP1*-inactivated melanocytic lesions progress to melanoma, suggesting a relatively low malignant potential [3,7,10]. For an isolated lesion, a conservative complete excision with close clinical follow-up is the standard of care. When multiple occurrences of such melanocytic lesions are present in the same individual, genetic counseling and testing for germline *BAP1* mutation are recommended. However, a considerable number of patients who presented with multiple cutaneous BAP1-inactivated melanocytic lesions had no prior history of *BAP1*-associated malignancies [5], and long-term follow-up is usually recommended.

While many cases of *BAP1*-inactivated melanocytic tumors have been reported to date in the literature, data on the gene expression profile of these lesions is limited, and little we know about the differential expression of genes of progressively malignant lesions in this category of melanocytic neoplasms. To explore the expression profiles of a full spectrum of *BAP1*-inactivated lesions, here we performed RNA sequencing on three lesions from a young patient with a nevus, an atypical tumor, and a melanoma with BAP1 loss. We also compared the gene expression profiles among the lesions to explore potential markers of tumor progression.

2. Materials and Methods

One melanocytic nevus, one atypical tumor, and a melanoma, all with loss of BAP1 expression, from the same patient were selected for subsequent RNA extraction and sequencing studies. Histologic diagnoses of these lesions were confirmed by an expert second opinion.

2.1. RNA Sequencing

Unstained slides prepared from the archival paraffin-embedded tissue of the three specimens were macro-dissected to obtain RNA from lesional tissue. Total RNA was extracted and purified using an RNeasy FFPE Kit (Qiagen, Germantown, MD, USA). RNA samples were then quantified and analyzed for quality (Agilent RNA 6000 Nano Kit, Agilent, Santa Clara, CA, US). Library preparation and targeted gene enrichment were performed with the TruSight RNA Pan-Cancer Panel Kit according to the manufacturer's protocol (Illumina, San Diego, CA, USA). Libraries were sequenced on the Illumina NextSeq 550 System. FASTQ file analysis was performed using the Illumina BaseSpace RNA-Seq Alignment Application 2.0.2. Gene-level counts [11] were created using this pipeline developed and supported by Illumina.

Annovar [12] (15 April 2018 version) was used to annotate the variant call files with clinical genomic information, including gnomAD minor allele fractions, COSMIC cancer listings, and NCBI ClinVar clinical significance. Variants that meet the following criteria were kept: (1) alternate allele depth (AD) > 5 and VAF $\geq$ 5% or (2) AD = 4 or 5 and VAF $\geq$ 15%. Plus, we excluded small indels in repetitive sequence with VAF < 10%. Annotated and quality-filtered variant calls were reviewed by a board-certified molecular pathologist for potential or known clinical significance using established professional guidelines [13].

2.2. RNA Expression and Pathway Analysis

Gene-level counts from the BaseSpace RNA-Seq Alignment Application were analyzed using custom R scripts and open-source R packages. Any genes that did not have at least 1 cpm (count per million) were removed. A 1.5-fold cutoff of log2 cpm values was used to evaluate gene expression differences between any of the two samples. Several approaches were used for pathway analysis based on all the differentially expressed genes: GO term enrichment analysis, ToppGene Suite [14] and EnrichR [15–17] for functional enrichment analysis, and Gene Set Enrichment Analysis (GSEA) [18].

3. Results

3.1. Case Presentation

A 31-year-old man presented with a history of multiple atypical melanocytic lesions, biopsied at an outside institution. He first presented subsequently at our hospital with an ear lesion in the right superior helix with the clinical appearance of a papule, which was tender. On histology, there was a severely atypical compound melanocytic proliferation with abundant pagetoid scatter of single melanocytes across the breath of the epidermis and multiple dermal mitoses (mitotic index of 5 per mm^2) (Figure 1A–C). The ki67 stain demonstrated a modest increase in the labeling of dermal melanocytes, while p16 expression was lost in the atypical melanocytes, which suggested *CDKN2A* genomic loss. BAP1 immunohistochemistry demonstrated a loss in part of the lesion. Altogether a diagnosis was rendered of melanoma developing in the context of a melanocytic nevus with associated *BAP1* genomic loss (melanoma ex-"BAPoma"). The Breslow thickness was 0.75 mm with no ulceration, no vascular invasion, and no regression, placing the pathologic staging as a pT1a lesion.
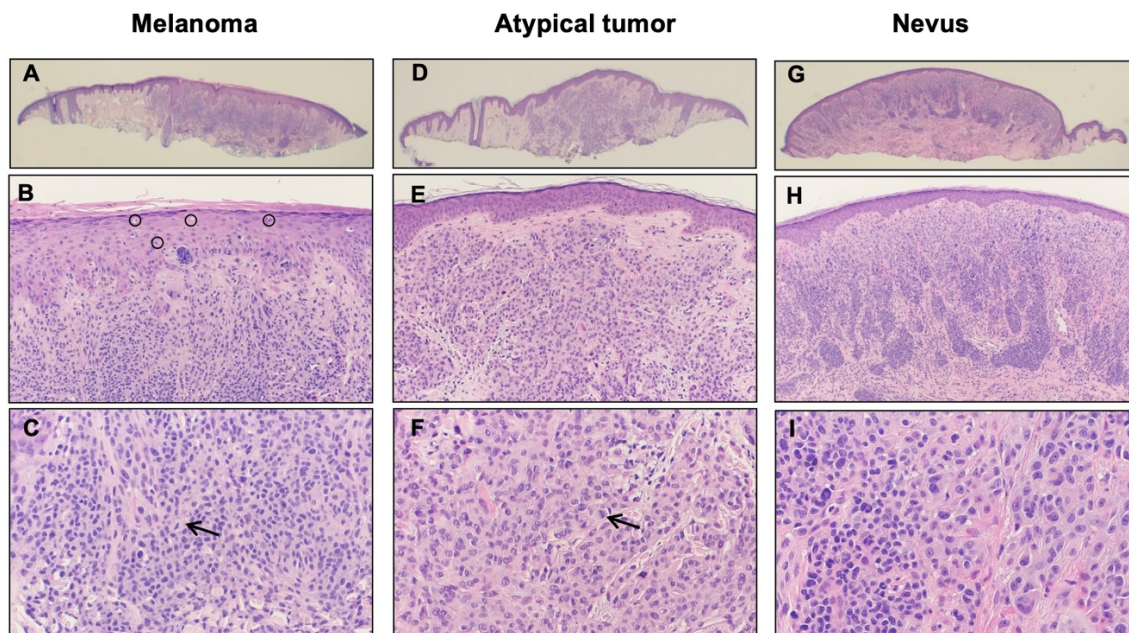

Figure 1. Histopathology of three representative lesions. (**A–C**) Melanoma; an atypical compound melanocytic proliferation with a nevoid appearance at low power (**A**), with abundant pagetoid scatter of single melanocytes within the epidermis ((**B**), circles) and multiple dermal mitoses ((**C**), arrow); (**D–F**) atypical tumor; a predominantly dermal melanocytic proliferation of atypical yet monomorphous large oval melanocytes with occasional mitoses ((**F**), arrow); (**G–I**) nevus; a dermal proliferation of small regular melanocytes in conjunction with large ovoid melanocytes (**I**). Circles (**B**): pagetoid spread of the tumor cells. Arrows (**C,F**): mitoses.

Another lesion was detected one year later in the right posterior ear, presenting clinically as a 2 mm pink pearly papule. Histologically the lesion presented as a mostly intradermal proliferation of large, oval melanocytes with abundant pale cytoplasm and large but monomorphous vesicular nuclei and small nucleoli, sparse mitoses, and with loss of BAP1 expression (Figure 1D–F). A final diagnosis of atypical Spitz nevus with *BAP1* loss was rendered.

The following year, other melanocytic lesions were removed, including a lesion in the posterior neck with a clinical appearance of a dome-shaped lesion. On histology, the lesion presented as a dermal melanocytic proliferation composed of a regular melanocytic nevus in conjunction with more ovoid melanocytes with *BAP1* loss (Figure 1G–I). Given

the histologic and immunohistochemical features, this lesion was classified as a BAP-1 inactivated nevus ("BAPoma").

3.2. Gene Expression and Mutation Analyses

We performed a pairwise exploration of the relative differences in gene expression levels between these lesions (Figure 2A–C). A total of 40 upregulated and 53 downregulated genes were identified in the atypical tumor compared to the *BAP1*-inactivated nevus, 26 upregulated and 106 downregulated genes in the melanoma compared to the atypical tumor, and finally, 51 upregulated and 158 downregulated genes in the melanoma compared to the BAP1-inactivated nevus. Among the genes upregulated in the atypical tumor compared to the nevus were: *SOX10*, the receptor tyrosine kinases *ROS1* and *NTRK3*, *PLA2G2A*, and *HOXA11*, while *DUSP2*, *PDGFD*, and *ELN* were downregulated (Figure 2A). *PAX3*, a transcription factor involved in melanocyte development, the receptor tyrosine kinase *KIT*, *CDKN1C*, and *EPHA5* were upregulated in the melanoma compared to the atypical nevus, while *NTRK3* and *ROS1* were downregulated in the same comparison (Figure 2B). Finally, Figure 2C illustrates a volcano plot of the comparison of the melanoma versus the nevus, with notable upregulation of *KIT*, *PAX3*, *SOX10*, *CDKN1C*, and *DUSP9*, and downregulation of *ATF3* and *DUSP2*.
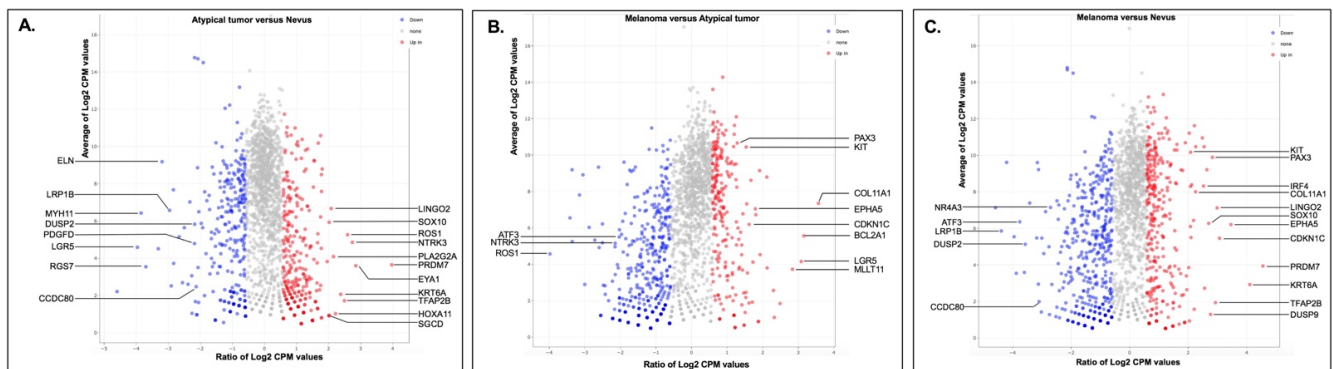

Figure 2. The MA plots showing upregulation and downregulation of the genes between each of the two BAP1-inactivated melanocytic lesions. (**A**) Atypical tumor versus Nevus; (**B**) Melanoma versus Atypical tumor; (**C**) Melanoma versus Nevus.

By analyzing and comparing the relative expression levels of the top 50 most variable genes among the three lesions, we identified a group of differentially expressed genes (Supplemental Figure S1). We then wanted to explore which genes are progressively upregulated or downregulated from a benign *BAP1*-inactivated nevus to a *BAP1*-inactivated melanoma. Figure 3 illustrates this concept. Overall, genes that are progressively upregulated from nevus to atypical tumor to melanoma include *SOX10*, a transcription factor important in melanocytic differentiation, the protein tyrosine kinases *IGF1R*, *KIT* (the latter mutated in acral melanoma, mucosal melanoma, and melanoma of chronically sun-damaged skin) and *EPHA5*, the transcription factor *PAX3* (involved in melanocyte development), the Dual Specificity Phosphatase *DUSP9*, *WNT11* and *IRF4/MUM1* (a gene regulated by MITF in melanocytic cells). In contrast, genes that are progressively downregulated from nevus to atypical tumor to melanoma include *NCAM1* (implicated in cell-cell adhesion and reportedly downregulated in several human cancer, suggesting a tumor repressor role), *HSPA1A*, *DKK1* (a secreted inhibitor of the β-catenin dependent Wnt signaling pathway and involved in induction of cancer evasion of immune surveillance), the growth factor *PDGFD*, the protein phosphatase *DUSP2* (involved in the negative regulation of members of the mitogen-activated protein kinase (MAPK) superfamily), and *LRP1B* (frequently mutated in melanoma) [19].
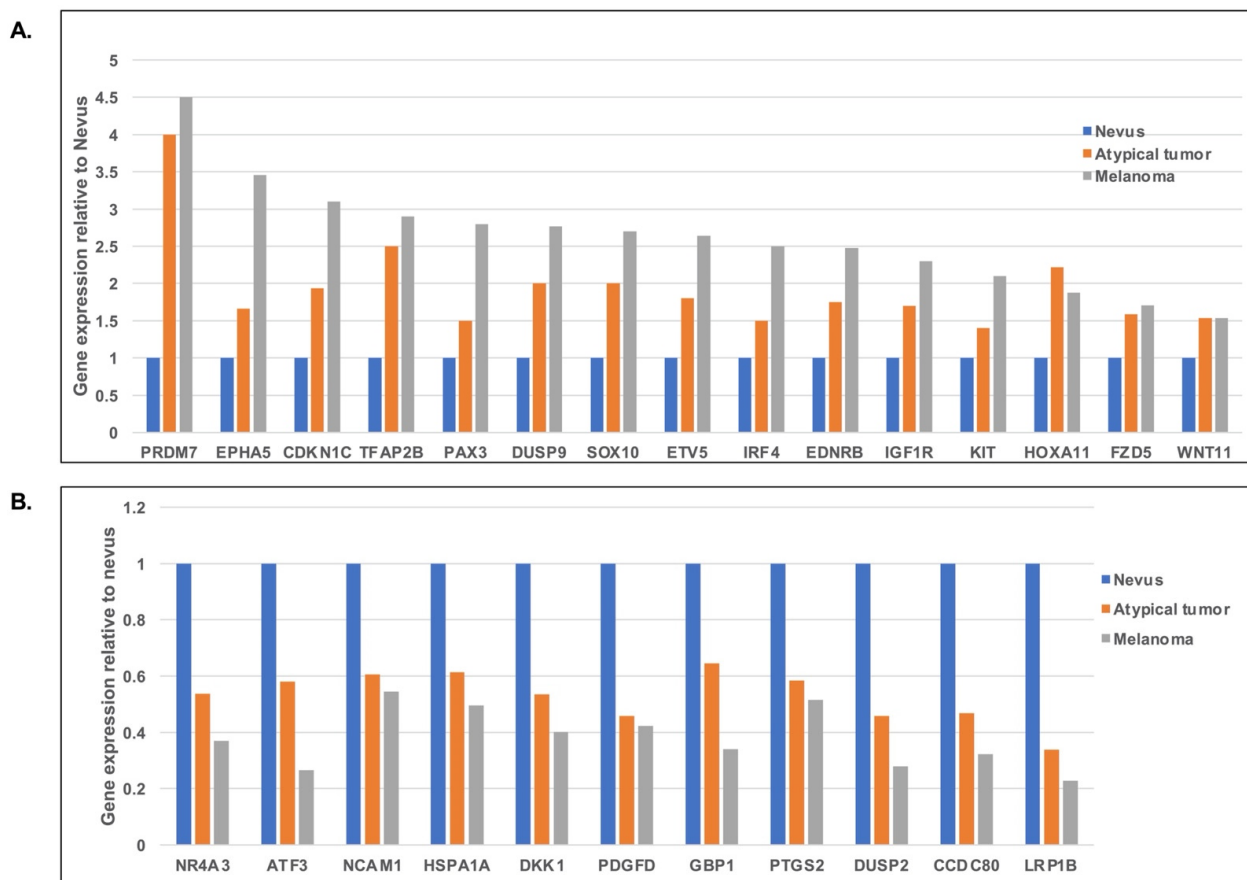
Figure 3. (**A**) Relative expression levels of the genes showing the upregulated trend of expression from nevus, atypical tumor to melanoma. (**B**) Relative expression levels of the genes showing the downregulated trend of expression from nevus, atypical tumor to melanoma.

In order to understand the collective functions and the cellular molecular pathways related to the differentially expressed genes in our samples, we performed gene set enrichment analysis. Using the Hallmark gene sets within the EnrichR software analysis, when comparing the atypical tumor with the nevus, there was a clear modulation of the epithelial-mesenchymal transition pathway, as well as upregulation of the KRAS signaling pathway and interleukin/STAT signaling, and downregulation of TNF-α signaling. When comparing the melanoma with both the nevus and the atypical tumor, it was interesting to observe regulation of the UV response, particularly important in melanomagenesis. Specifically, genes upregulated or downregulated in response to UV radiation involve *CDKN1C*, *CDK2*, *COL11A1*, *KIT*, and *IGF1R*, the majority of which are identified as differentially upregulated in melanoma versus atypical tumor or nevus (Figures 2B,C and 3A). In this comparison, there was also the regulation of TNF-α signaling and epithelial-mesenchymal transition (Figure 4A,B).

GO term enrichment analysis was also performed and showed that expression profiles involving the extracellular region and component of the membrane were enriched progressively from nevus to atypical tumor to melanoma (Supplemental Figure S2). Particularly, pathways related to protein kinase activity in general as well MAPK activity and protein tyrosine kinase activity were significantly upregulated in both the atypical tumor and melanoma compared to the nevus (Supplemental Table S1).
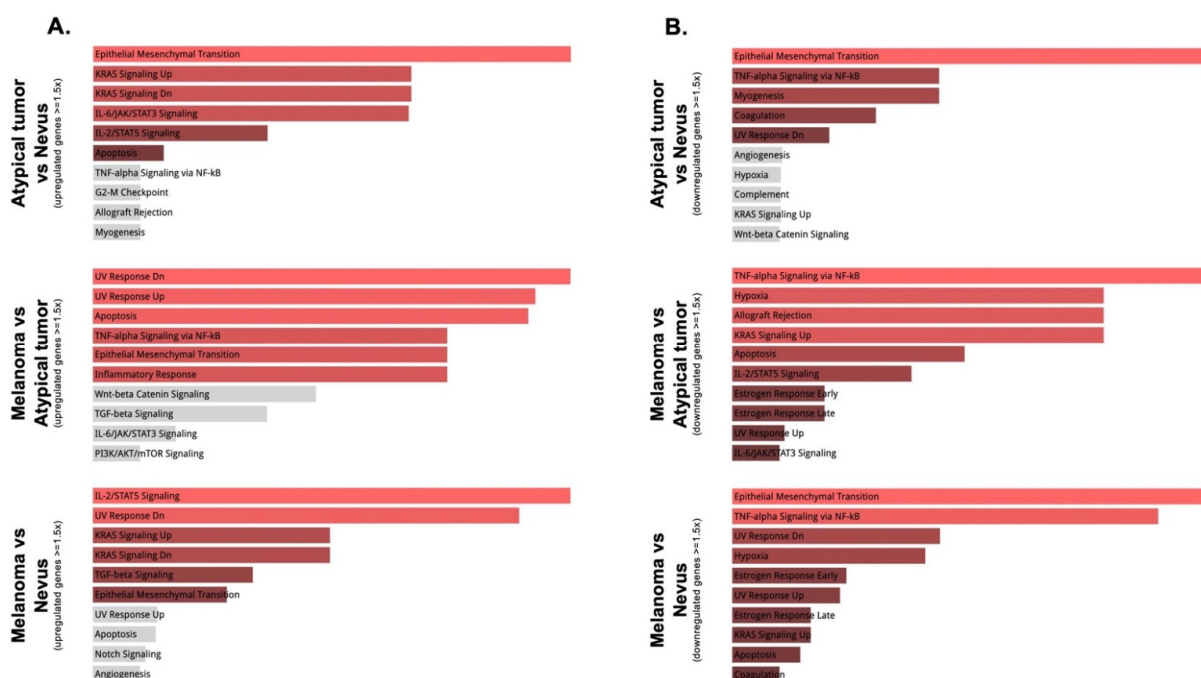
Figure 4. Gene enrichment analysis using the EnrichR platform. Upregulated (**A**) and downregulated (**B**) pathways (in the Hallmark category) in the following comparisons: Atypical tumor versus Nevus; Melanoma versus Atypical tumor; and Melanoma versus Nevus. Statistical significantly enriched terms are displayed in red, while gray bars are not statistically significant.

Genes harboring pathogenic or likely pathogenic mutations were heterogeneous across the three lesions (Table 1). *NIPBL*, *AKAP9*, and *EP400* were mutated in both the nevus and atypical tumor, although the specific mutations were different between the two lesions. In addition, mutations in *PDGFRB*, *HIF1A*, and *MAP2K1* genes were identified in the nevus, and mutations in *HDAC2*, *PRK2*, *ARID2*, *BRCA2*, *NOTCH3*, *NOTCH2*, *BRAF*, *CSF1R*, and *PTEN*, among others, were found in the atypical nevus. To be noted, *BRAF* V600E was identified in both atypical tumors and melanoma. The mutation in *BAP1* was captured in the melanoma, as well as mutations in *KMT2A* (a known cancer driver mutation in melanoma) and *TIAM1* (a gene involved in the RAC1 signaling pathway affecting cell shape and migration).

Table 1. List of genes with identified pathogenic or likely pathogenic mutations in the BAP-1 inactivated nevus, atypical tumor, and melanoma.

Lesion	Gene	Mutation	Type
Nevus	*NIPBL*	p.Q338X	stopgain
	AKAP9	p.Q2911X	stopgain
	EP400	p.E2200X	stopgain
	CREBBP	p.Q1075X	stopgain
	COL1A1	p.P817fs	frameshift deletion
	ZNF687	p.Q474X	stopgain
	PDGFRB	p.Q412X	stopgain
	ASPH	p.R659X	stopgain
	NT5C2	p.Q173X	stopgain
	NIN	p.Q1291X	stopgain
	HIF1A	p.Q379X	stopgain
	CHD2	p.Q366X	stopgain
	USP7	p.Q822X	stopgain
	MYO18A	p.Q830X	stopgain
	KPNB1	p.Q111X	stopgain
	RPS6KA3	p.R383W	nonsynonymous SNV
	TBL1XR1	p.S332F	nonsynonymous SNV
	MAP2K1	p.A172V	nonsynonymous SNV

Table 1. *Cont.*

Lesion	Gene	Mutation	Type
Atypical tumor	*NIPBL*	p.Q1567X	stopgain
	AKAP9	p.Q2480X	stopgain
	EP400	p.Q148X	stopgain
	CAD	p.Q30X	stopgain
	PPP1CB	p.Q293X	stopgain
	BIRC6	p.Q1072X	stopgain
	COL6A3	p.Q2366X	stopgain
	TFG	p.Q266X	stopgain
	EIF4A2	p.Q209X	stopgain
	AFF4	p.Q537X	stopgain
	ARHGAP26	p.R120X	stopgain
	MAML1	p.Q683X	stopgain
	DST	p.Q1890X	stopgain
	HDAC2	p.Q128X	stopgain
	PTK2	p.Q734X	stopgain
	SYK	p.Q239X	stopgain
	NUMA1	p.Q832X	stopgain
	PICALM	p.Q256X	stopgain
	EED	p.Q302X	stopgain
	SIK3	p.Q675X	stopgain
	KDM5A	p.R266X	stopgain
	PRICKLE1	p.Q348X	stopgain
	ARID2	p.Q720X	stopgain
	NUP107	p.Q236X	stopgain
	BRCA2	p.Q2943X	stopgain
	TCF12	p.Q605X	stopgain
	TOP2A	p.Q517X	stopgain
	ITGB3	p.Q616X	stopgain
	SMARCA4	p.R978X	stopgain
	NOTCH3	p.Q646X	stopgain
	CSNK2A1	p.Q71X	stopgain
	NCOA3	p.Q478X	stopgain
	ETS2	p.Q234X	stopgain
	EP300	p.Q523X	stopgain
	OFD1	p.Q39X	stopgain
	AR	p.Q825X	stopgain
	ZMYM3	p.Q763X	stopgain
	BMPR1A	p.R244X	stopgain
	NOTCH2	p.Q1814X	stopgain
	TPR	p.Q2344X	stopgain
	BRAF	p.V600E	nonsynonymous SNV
	CSF1R	p.A781V	nonsynonymous SNV
	PTEN	p.T277I	nonsynonymous SNV
Melanoma	*LRPPRC*	p.G1050fs	frameshift insertion
	EXT2	p.R215X	stopgain
	SPEN	p.Q3373X	stopgain
	BAP1	p.Y223X	stopgain
	AHR	p.Q705X	stopgain
	KMT2A	p.Q1207X	stopgain
	CDH1	p.Q388X	stopgain
	RABEP1	p.Q225X	stopgain
	CLTC	p.Q1358X	stopgain
	SUGP2	p.R831X	stopgain
	TIAM1	p.Q714X	stopgain
	BRAF	p.V600E	nonsynonymous SNV

4. Discussion

BAP1-inactivated melanocytic lesions exist in a spectrum that goes from benign melanocytic nevi, usually combined ("BAPomas"), to intermediate lesions with atypical features (akin to the atypical Spitz tumor) and ending with malignant melanoma. While initially categorized within the Spitz family of melanocytic lesions, genetic analysis has revealed a molecular profile, including the presence of *BRAF* mutation, that is not compatible with this classification. Thus, in the recent WHO classification, these lesions have been classified separately as combined melanocytic lesions with a distinct morphologic and molecular signature (*BAP1* inactivation and *BRAF* V600E mutation). From their first description in the seminal paper by Wiesner et al. [2], there has been a lot of interest in

these lesions as a paradigm for newly recognized melanocytic lesions with distinct histo-logic morphology and a well-defined molecular signature. The last WHO classification of cutaneous tumors classifies *BAP1*-inactivated lesions in a separate category, recognizing its unicity. However, besides the pathognomonic mutation, little is known regarding the gene expression profile and other gene mutations occurring in these lesions. To our knowledge, this is the first study to compare gene expression levels in a series of *BAP1*-inactivated melanocytic lesions of progressive malignancy, from nevus to atypical tumor to melanoma in a single patient.

The same WHO classification released in 2018 put an accent on the role of UV-related damage in melanocytic tumorigenesis by dividing the most common melanocytic lesions in those related to low cumulative solar damage (CSD) and high CSD. *BAP1* mutation may occur as the driver genetic event in low CSD melanoma, but there is not a specific relation with sun—damage reported for the new category of *BAP1*-inactivated lesions. In our study, we found a clear enrichment of genes regulated in response to UV radiation, based on the Molecular Signature Database (MSigDB), suggesting that sun damage is a relevant step in the multistep process of tumor progression in these lesions.

Our study possesses potential clinical significance by suggesting multiple therapeutic targets in patients with *BAP1*-inactivated melanoma, the treatment for whom is otherwise limited to conventional therapies. These targets may involve genes in protein kinase pathways or governing transcriptional regulation, as discussed below. Based on our analysis, activation of protein kinase pathways, especially the MAPK pathway, is largely observed in the atypical tumor and melanoma arising from *BAP1*-inactivated nevus compared to nevus, consistent with current knowledge of melanocytic progression. MAPK activation represents a common aberrant signaling pathway in cutaneous melanoma associated with a wide variety of somatic genetic alterations. This knowledge has resulted in effective targeted therapies targeting this pathway; the success of BRAF inhibitors alone or in combination with MEK inhibitors [20] is a testament to the importance of molecular and mechanistic studies to understand the pathogenesis and discover relevant targets for cancer therapy. Thus, our findings support the use of similar therapeutic regimens in our patient as adjuvant treatment. To further support this, we found downregulation of the protein phosphatase *DUSP2*, involved in the negative regulation of members of the MAPK superfamily, and upregulation of the KRAS signaling pathway. In addition, genes encoding protein tyrosine kinases, *KIT* and *EPHA5*, relevant receptors upstream of the MAPK pathway, are particularly highly expressed in the melanoma compared to *BAP1*-inactivated nevus. Interestingly, a mutation in the *MAP2K1* gene was identified in the BAPoma from our patient; similar mutations in this gene have been reported in a large spectrum of melanocytic lesions, including BAPomas [21].

IGF1R (insulin-like growth factor I receptor), another receptor tyrosine kinases found to be upregulated in our sample, has been found to have anti-apoptotic properties and to be overexpressed in multiple cancers including melanoma [22], where may represent a potential therapeutic target.

Among the protein kinase activation pathways, the expression levels of *ROS1* and *NTRK3* are only upregulated in the atypical tumor compared to the nevus and melanoma. Interestingly, various kinase fusions, including *ROS1* and *NTRK3*, were found in Spitz melanocytic lesions [23]. These various fusion events are mostly mutually exclusive and are believed to be an early event in tumorigenesis [24], but do not necessarily confer malignant potential and are actually present often in benign or intermediate lesions, but rarely in melanoma.

Another interesting group of upregulated genes in the atypical tumor and the melanoma is related to sequence-specific DNA binding and regulatory region nucleic acid binding, specifically transcriptional regulation. This gene category includes *HOXA11*, *SOX10*, *ETV5*, *IRF4*, *PAX3*, *PRDM7*, *TFAP2B*, and *WNT11*. Among those, the transcription factor SOX10 has been shown to be involved in melanomagenesis in animal models [25,26] and, more recently, in the regulation of melanoma cell invasion, through the regulation of melanoma

inhibitory activity (MIA) expression [27]; thus SOX10, besides its role as a marker of melanocytic differentiation in diagnostic pathology, represents a potential therapeutic target for melanoma. SOX10 was also found to regulate immunogenicity in melanoma through IRF4 (interferon regulatory factor 4)/MUM1 [28], another transcription factor discovered in our dataset. *IRF4* is a gene regulated by MITF in melanocytic cells, and it was also found to have a functional variant associated with increased Breslow thickness, conferring a worse survival in melanoma [29]. *WNT11* was shown to play an important role in neural crest migration and appears to have a role in the aberrant activation of Wnt signaling in melanoma. Finally, *PAX3* (paired box gene 3 transcription factor) was shown, in conjunction with the transcription factor *ETS1*, to promote melanoma cells proliferation and metastasis by increasing the expression of MET, the HGF receptor [30]. Altogether, these findings highlight the role of several transcription factors as critical players in melanoma. Given their role as focal and convergence points of several signaling pathways and their role in tumor progression and resistance to therapy [31], these transcription factors are potential targets to explore for the development of future therapy for melanoma, including those arising in the background of *BAP1* inactivation.

There are some limitations in our study that we need to acknowledge. First, only three samples from the same patient were available at the time of the experiment; thus, these data represent a single set of lesions, and future studies on multiple samples from several patients will be needed to generalize any of the biomarkers identified. Second, only a panel of 1400 cancer-related genes were analyzed, and the source material was formalin-fixed and paraffin-embedded, a challenging source that is prone to RNA fragmentation impacting the number of genes that we were able to capture with our assay. Future experiments on a larger panel of genes or the entire transcriptome may reveal additional significant markers of tumor progression in this type of lesion.

5. Conclusions

In conclusion, our study suggests that a *BAP1*-inactivated nevus, an atypical tumor, and melanoma with the same background from the same patient possess distinct gene expression profiles, with notable upregulation of genes involved in protein kinase pathways in the progression from nevus to melanoma. Moreover, we found a clear enrichment of genes regulated in response to UV radiation in the melanoma from this patient, as well as upregulation of MAPK pathway-related genes and several transcription factors related to melanomagenesis. Current treatments for patients with *BAP1*-inactivated melanoma are limited to conventional therapies used in other more common melanomas, which may not address the molecular mechanisms of these lesions entirely. Thus, our study may suggest potential novel targets for personalized therapy in these patients.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/genes13010010/s1, Figure S1: Heatmap showing the z-scored expression levels of the genes that are differentially expressed among the three lesions, Figure S2: Gene enrichment analyses between (A) Atypical tumor versus Nevus; (B) Melanoma versus Atypical tumor; (C) Melanoma versus Nevus, Table S1: Selected pathways that are upregulated and the involved genes in these pathways between either of the two BAP1-inactivated lesions.

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