Chapter 8

Genetic Mutations and Ubiquitination in Melanoma Growth and Metastasis

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Abstract

Upon neoplastic transformation, melanoma is intrinsically prone to metastasis, which marks the most dangerous aspect of the disease and dubs it one of the most challenging cancers to treat. BRAF/MEK oncokinase inhibitors and immunotherapies have shown considerable promise in some patients, but the clinical benefits are often short-lived due to rapid development of resistance. Recently, ubiquitination enzymes have emerged as potential therapeutic targets. These enzymes can be targeted to increase expression of tumor suppressors and impede activation of oncogenic signaling pathways mediating cell proliferation and tissue invasion. This chapter describes some of the common genetic mutations in melanoma, ubiquitinating and deubiquitinating enzymes that are linked to melanoma progression, metastasis, and therapeutic resistance.

Keywords: A20, BAP1, BRAF, CDKN2A, CYLD, DUB, E-cadherin, ERK, melanoma, N-cadherin, Snail1, TRAF6, UBE2S, ubiquitination, USP

1. Introduction

Melanoma is the most aggressive form of skin cancer. The 5-year survival rate for metastatic melanoma is less than 20%. The incidence of melanoma is on the rise especially among the young population. The NIH SEER program estimated that 87,110 people were diagnosed with melanoma in the United States in 2017, accounting for 5.2% of all new cases of cancer, which is 1.2% higher than the melanoma cases reported in 2007. About 11% of the newly diagnosed patients would succumb to the disease due to uncontrollable metastatic tumor growth [1, 2]. This chapter describes the common genetic mutations and posttranslational modifications crucial for melanoma growth, survival and dissemination, with a particular focus on enzymes regulating ubiquitination.

2. Melanoma staging and diagnosis

Melanoma treatment plans are designed based on the stage of the disease. In 2017, the American Joint Committee on Cancer (AJCC) published the 8th edition of the tumor, lymph node, and metastasis (**TNM**) system. The **T** recognizes tumor thickness or the depth of the cancer in the skin and characterizes the tumor as being ulcerated or non-ulcerated. The **N** is used to establish whether the cancer has spread to the proximal lymph nodes and finally, the **M** stands for metastasis and gives information if the cancer has spread to distant lymph nodes or other organs [3]. Using the TNM numbers along with elaborate clinical and pathological assessments, the cancer is assigned a stage. Further histological analyses allow pathologists to assign a 'grade' to the tumor which is an indication of the abnormality of the tumor cells. Both staging and grading are crucial to determine the course of treatment and give an overall prognosis for the disease. Although it is under debate whether a linear progression is the primary theme, cutaneous melanomas can progress from a precursor lesion, namely benign nevi which becomes dysplastic, to melanoma in situ, and finally to invasive melanoma. A nevus is a benign aggregation of melanocytes that is formed at the junction of the dermis and epidermis or within the dermis. When the nevus shows signs of cytological atypia and change in growth, it becomes dysplastic. Melanoma in situ, also called as the stage (0) melanoma, is when the transformed melanocytes are still within the epidermis or the dermal/epidermal junction. Lastly, when the transformed melanocytes invade the dermis and gain access to other cell tissues and/or the vascular system, they turn into metastatic melanoma [4]. The development of melanoma involves multifactorial and heterogeneous biologic processes that are controlled at the genetic, transcriptional, and posttranslational levels [5, 6].

3. Genetic mutations

3.1. Germline mutations in melanoma

Certain genetic changes predispose an individual to an increased risk of melanoma. These changes include point mutations, amplifications, deletions or translocations. CDKN2A is one of the first genes linked to the familial atypical mole melanoma (FAMM). Deletion or loss of heterozygosity of CDKN2A increases patient susceptibility to developing melanoma [7]. Consistently, germline deletion of Cdkn2a in mice sensitizes animals to developing cutaneous melanoma when coupled with an activating HRAS mutation in the melanocytes [8]. While the CDKN2A gene codes for two proteins, p16 INK4A and p15 ARF, p16 INK4A loss-of-function is responsible for spontaneous and carcinogen induced melanoma [9]. CDK4 and RB1 are two other genes with germlines mutations linked to familial susceptibility to melanoma. CDK4, a kinase involved in regulating cell cycle, is amplified or mutated in human melanomas with some studies showing 100% of all the affected family members harboring a specific CDK4 mutation [10, 11]. Inactivation of RB1 tumor suppressor causes hereditary retinoblastoma and increases the risk of developing melanoma by about 80-fold [12]. Variants of the melanocortin-1 receptor (MC1R) are associated with fair pigmentation and melanoma risk [13]. The

presence of a CDKN2A mutation gave a hazard ratio of 13.35, and the MC1R variants increase the hazard ratio by 3.72-fold [14].

3.2. Somatic mutations in melanoma

Ultraviolet (UV) radiation induces somatic gene mutations and is the major risk factor for melanoma [6, 15]. The RAS/RAF/MEK/ERK signaling pathway is commonly mutated in melanoma. Among the RAS GTPase family members, NRAS is the most frequently mutated protein with activating mutations detected in up to 56% of benign nevi and 26% of metastatic melanoma [16, 17]. Activating mutations of BRAF are found in about 70% of cutaneous melanomas, and 90% of these mutations are of the BRAF(V600E) (valine to glutamic acid substitution) [18, 19]. There is a well-established correlation between sun-exposure and the development of BRAF mutations [15, 20]. BRAF(V600E) mutation is observed in the benign melanocytic nevi, indicating that this mutation alone is not sufficient for malignant transformation [19, 21]. Other genetic changes such as CDKN2B loss are required for the progression from benign melanocytic nevus to melanoma [22]. Random mutagenesis screens have revealed that ERK point mutations impart resistance to RAF and MEK inhibitors, although such mutations are infrequent [23].

4. Melanocyte origin and its intrinsic effects on melanoma metastasis

Melanoma is intrinsically prone to metastasis [4]. Melanocyte precursors are derived from highly migratory neural crest cells, which give rise to a number of differentiated cells including the melanocytes. During this process, they express several canonical neural crest markers such as SOX8, SOX9, SOX10, Snail1, and Snail2. The strong metastatic potential of melanoma can be attributed to the plethora of mutations acquired over the development of the disease and to the aberrant reactivation of some of the transcriptional factors such as Sox5, Sox10, and Snail1 that are crucial for the melanocyte differentiation program [24–26].

The Wnt signaling pathway plays a major role in melanocyte differentiation and migration mainly through the activation of the microphthalmia-associated transcription factor (MITF) [27]. MITF promotes melanocyte differentiation and melanin production, in addition, MITF is often upregulated in melanomas associated with poor prognosis [28]. β-catenin dependent MITF activation induces proliferation of melanoma cells and inhibition of β-catenin leads to a cell cycle arrest along with downregulation of MITF [29]. Hyperactivated Wnt signaling has been reported in about 30% of melanoma samples [30] and is shown to promote melanomagenesis. On the other hand, there are also reports that demonstrate loss of β-catenin decreases melanoma cell proliferation, but promotes invasion and predicts poor prognosis [31]. This discrepancy is predominantly because the Wnt proteins utilize three distinct signaling pathways with different mediators [29]. The canonical Wnt signaling pathway entails activation of the frizzled surface receptors by the Wnt ligand, leading to the formation of a vast protein complex on the cell surface. This leads to a cascade of events, resulting in the nuclear translocation of β-catenin which then acts as a co-activator to regulate target gene expression [32]. A non-canonical Wnt signaling pathway involves activation of GTPases such as RAC1 and

RHOA, and MAP kinase such as JNK, downstream of the frizzled receptor. A second noncanonical pathway includes activation of phospholipase C (PLC) that promotes the release of intracellular Ca^{2+}, leading to the expression of target genes involved in cell migration and inflammation [33]. The noncanonical Wnt signaling is shown to stimulate cytoskeletal remodeling, increase cell survival, and promote invasive characteristics [34, 35]. Both the canonical and the noncanonical Wnt signaling pathways are involved in the promotion of melanoma cell proliferation and epithelial-mesenchymal translation (EMT) [29, 36].

5. Ubiquitination in melanoma

Posttranslational modification (PTM) is a reversible and dynamic process that regulates protein function at a posttranslational level and plays crucial roles in signal transduction, gene regulation, vesicle transportation, and protein degradation. PTMs include phosphorylation, ubiquitination, sumoylation, methylation, acetylation, glycosylation and N-nitrosylation. Dysregulation of PTM results in pathogenesis including cancer [37]. Phosphorylation is catalyzed by protein kinases and is the core mediator of signal transduction. Oncogenic mutations of the protein kinases, most notably BRAF(V600E), result in constitutive phosphorylation and activation of the downstream targets such as the MEK and ERK kinases [38]. Kinase-mediated signals are also regulated by other PTMs including ubiquitination.

Ubiquitination (Ub) is a rather complex process involving a substantial series of variable components. Mono-Ub involves a covalent attachment of a 76 amino acid ubiquitin polypeptide to a lysine residue of a target protein. Poly-Ub involves attachment of additional ubiquitin moieties to one of the seven lysine (K) residues (K6, K11, K27, K29, K33, K48 and K63) or the methionine residue (M1) of the proceeding ubiquitin, forming structurally and functionally distinct polymers. If more than one K-residues are involved, it is called a heteropolymeric chain and, if a single K-residue is involved, it is called as a homopolymeric chain, such as K48-Ub and K63-Ub [39]. Different Ubs carry out distinct functions, ensuring the robust control of essentially every cellular process spanning from signal transduction, DNA-repair, vesicle transportation, cell division, differentiation, and migration [40]. While K48-Ub generally marks protein for proteasomal degradation, K63-Ub regulates signal transduction, RNA splicing, protein sorting, DNA repair and immune response [41–43].

Ubiquitination generally requires a three-step process: the E1 enzyme catalyzes the first step by activating an ubiquitin moiety in the presence of ATP and the E2 conjugase carries the ubiquitin via covalent bonding, and works together with an E3 ligase to complete ubiquitin ligation with the target protein [44]. There are two known E1 enzymes, UBA1 and UBA6 [45]. The canonical UBA1 is characterized as a potential target for the treatment of hematologic malignancies [46]. The noncanonical UBA6 suppresses epithelial-mesenchymal transition of mammary epithelial cells [47]. The role of UBA1 and UBA6 in melanoma is not well-understood.

5.1. Ubiquitin conjugases in melanoma

There are about 50 known E2 conjugating enzymes. Each of them contains a conserved cysteine residue that accepts the ubiquitin molecule activated by the E1 enzyme. A number of E2

enzymes have been implicated in melanoma. For example, Rad6 promotes melanoma development and progression by inducing nuclear translocation of β-catenin [48]. Overexpression of E2-EPF UCP (ubiquitin carrier protein) promotes melanoma metastasis, while its downregulation decreases tumor invasion [49]. UBE2S targets VHL protein for proteasomal degradation via a K48-Ub-mediated process. UBE2S is overexpressed in metastatic melanoma cell lines and mediates the degradation of VHL and a consequent upregulation of HIF-1α and VEGF proteins to promote distant metastasis and angiogenesis [50].

5.2. Ubiquitin ligases in melanoma

There are over 600 putative E3 Ubiquitin ligases in the human genome. These enzymes display substrate specificity, and have attracted tremendous attention for therapeutic targeting. The SCF ubiquitin ligases constitute the largest family of E3 ligase enzymes characterized by an F-box component that interacts with the substrate. Among the SCF family members, β-TrCP (beta transducing repeats containing protein) is upregulated in melanomas with BRAF(V600E) mutation and a corresponding increase of NF-κB activity [51]. Another SCF family member, SCF-Skp2 is shown to promote melanoma cell cycle progression by degradation of CDK inhibitors such as p27 and p57 [52]. FBXW7, a component of the SCF-FBW7 E3 complex, is mutated in 8.1% of melanoma patients and some of these mutations interfere with its substrate binding, leading to oncogenic activation of substrates including Notch1 [53, 54]. FBXW7 inactivating mutations are detected in melanomas without the typical BRAF(V600E) and NRAS(G12D/G13R/Q61K/L/S) mutations [55]. Knockdown of FBXW7 in melanoma cell lines leads to the upregulation of NOTCH1, HEY1, and the downstream effectors Cyclin E, Aurora A and Myc, resulting in increased tumorigenesis [56–58].

The E3 ligase MDM2 regulates p53 and its expression in melanoma correlates with increased malignancy, tumor thickness and invasion [59]. TRAF6 is a K63-Ub ligase overexpressed in primary and metastatic melanoma, and it promotes tissue invasion by stimulating MMP9 activation [60]. TRAF6 recruitment and activation is regulated by EGFR through the oncoprotein, DCBLD2 (discoidin, CUB, and LCCL domain-containing protein) in a number of cancers including melanoma [61]. TRAF6 together with p62 also regulates mTOR activation via K63-Ub which is important for the mTORC1 and mTORC2 complex formation [62]. TRAF2 mediates K63-Ub of GβL (mTOR LST8 homolog) thereby preventing mTORC1 complex formation. Mutations in the K63-Ub site of GβL are shown to promote chemoresistance of melanoma cells in vitro and in the xenograft mouse model [63].

The E3 ubiquitin ligase RNF125 negatively regulates the retinoic acid-inducible gene I (RIG-I) signaling pathway by targeting RIG-I for proteasomal degradation [64]. It also regulates p53 and innate immune adaptor protein TRIM14 [65, 66]. Deletion and missense mutations in RNF125 are linked to the overgrowth syndrome [67]. RNF125 is regulated by MITF and SOX10 transcription factors and its downregulation elevates JAK1 and EGFR signaling, and underlies resistance of melanoma cells to the BRAF inhibitor, vemurafenib [68].

Oncogenic RAS and BRAF mutants drive tumor growth through hyperactivation of ERK1/2 kinases and concomitantly induce ERK-dependent negative feedback. Relief of this feedback inhibition by RAF inhibitors contributes to the attenuation of the therapeutic potency in BRAF mutant melanomas [69]. Ubiquitination-dependent degradation of BRAF constitutes for one of

the negative feedback mechanisms [70]. The $APC^{/C}$ E3 ligase complex activator FZR1 but not FBXW7 tumor suppressor controls BRAF oncogene function [70, 71]. FZR1 as a direct target of ERK and CyclinD1/CDK4 kinases and its phosphorylation inhibits APC^{FZR1}, leading to increased expression of a cohort of oncogenic APC^{FZR1} substrates important for melanomagenesis [71].

The E3 ubiquitin ligase Trim7 is activated by the Ras/RAF/MEK/ERK pathway via MSK1-mediated phosphorylation, and consequently mediates K63-Ub of the AP-1 co-activator RACO-1, leading to RACO-1 protein stabilization and increased AP-1-dependent gene expression [72]. The c-Jun/RHOB/AKT pathway confers resistance to BRAF mutant melanoma cells from BRAF and MEK inhibitors [73]. Trim7 may represent a potential target for combination therapies to mitigate therapeutic resistance.

5.3. Deubiquitinating enzymes in melanoma

Ubiquitination is a reversible process and a group of enzymes called the deubiquitinases (DUBs) cleave the isopeptide linkage between the polyubiquitin chains and the target proteins. There are five major families of deubiquitinases: ubiquitin-specific proteases (USP), ubiquitin carboxyl-terminal hydrolases (UCH), Jab1/MPN domain associated metalloisopeptidase domain proteins, Machado-Joseph Domain (Josephin domain) containing proteins (MJD) and Otubain/Ovarian tumor domain containing proteins (OTU) [74]. Major functions of DUBs involve rescuing incorrectly ubiquitinated proteins from degradation and modulating target protein function. DUBs play important roles in DNA repair, apoptosis, cell proliferation, kinase activation, and chromatin remodeling, and they can function as tumor suppressors as well as oncogenes [75].

5.3.1. Deubiquitinating enzymes acting as tumor suppressor

5.3.1 a **BAP1** (BRCA-associated protein 1) is a deubiquitinase belonging to the ubiquitin C-terminal hydrolases family (UHCs). BAP1 binds to BRCA1, and acts a tumor suppressor. Loss of function of BAP1 due to germline mutations leads to the tumor predisposition syndrome which increases the risks of uveal and cutaneous melanomas, and malignant mesotheliomas. Individuals who carry the mutated BAP1 gene develop melanocytic lesions later in their life and some of those benign lesions can transform into cutaneous melanomas [76]. In addition to its deubiquitinase function, BAP1 possess a nuclear localization signal that allows it to translocate to the nucleus and interact with proteins such as HCF-1 to regulate cell growth [77].

5.3.1 b **A20** (TNFAIP3) is a deubiquitinase commonly induced by inflammatory cytokines via NF-κB. It has an innate deubiquitinating activity imparted by the OUT zinc finger domain that allows it to interact with ubiquitinated substrates and maintain specificity. A20 inhibits auto-ubiquitination of the K63-Ub E3 ligase TRAF6, and consequently inhibits IKK/NF-κB activation [78]. Independent of its deubiquitinating functions, A20 disrupts the interaction between the E2 conjugase (UBE2N) and the E3 ligase (TRAF2/TRAF6), and consequently promotes K48-Ub and proteasomal degradation of these enzymes [79]. A20 is characterized as a potent tumor suppressor in non-Hodgkin's lymphomas including diffuse large cell lymphoma, mantel cell lymphoma and ocular marginal zone B-cell lymphoma [80], but its role in melanoma is not at all clear. Increased expression of A20 in $CD8^+$ T cells results in impaired

anti-tumor immunity in a melanoma animal model, while knockdown of A20 in $CD8^+$ T cells increases cytokine production and decreases melanoma tumor burden [81].

5.3.1 c **CYLD** is a deubiquitinase that preferentially removes K63-Ub and M1-Ub from target proteins [82, 83]. CYLD has been identified as a tumor suppressor on account of its loss-of-function correlating to a number of cancers including melanoma [53, 84]. In addition to gene deletion and mutation, CYLD is downregulated by Snail1 at the transcriptional level and by microRNAs including mir-186 and mir-767 at the post-transcriptional level [85, 86]. Furthermore, CYLD is subject to proteolytic inactivation by MALT1, a paracaspase known to promote melanoma growth and metastasis through JNK/c-Jun signaling pathway [87]. CYLD exhibits anti-oncogenic effects by regulating cell proliferation, angiogenesis, and tumor cell differentiation [88].

CYLD inhibits K63-Ub of a plethora of target proteins. Among these are Bcl3, TRAF2/6, Tak1, plk1, lck, HDAC6, Dvl, and c-Jun/c-Fos AP1 subunits [89–93]. In the absence of CYLD, Bcl3 along with NF-κB is recruited to the Cyclin D1 promoter to facilitate its transcription to induce G1 to S cell cycle progression. CYLD inhibits JNK activation and expression of the β1-integrin in non-melanoma and melanoma cells with a corresponding decrease in cell proliferation and increase in apoptosis [88, 89]. On the other hand, CYLD regulates cell motility via inhibition of HDAC6-mediated deacetylation of tubulin and cortactin, by directly binding to the catalytic domain of HDAC6 [94, 95].

EMT and metastasis are orchestrated by an array of gene regulators, such as TWIST1/2, SNAIL1/2, ZEB1/2 and FOXC2 [96]. Snail1-mediated suppression of CYLD is crucial for melanoma progression and metastasis [97]. CYLD regulates EMT by facilitating the maintenance of E-Cadherin expression and inhibiting N-Cadherin expression in melanoma [84]. E-cadherin is a crucial protein facilitating cell-cell adhesion, maintaining cytoskeletal stability and regulating cell polarization. Germline mutations in E-cadherin predispose individuals to a higher risk of breast and gastric cancers [98]. E-cadherin appeared downregulated in melanoma predominantly due to the alterations in the tumor microenvironment rather than genetic mutations as reported in some gynecological cancers [99]. Loss of E-cadherin expression/function increases melanocyte proliferation due to impaired interaction with keratinocytes [100]. When melanocytes are cultured in vitro, in the absence of the basal keratinocytes, they not only display increase in doubling time but also begin expression of melanoma-related markers such as β3-integrin, MUC18, melanotransferrin, and other growth factor receptors. These melanocytes regain their normal phenotype when co-cultured with keratinocytes [100]. E-cadherin also regulates the activation of β-catenin, c-Myc and Cyclin D1.

N-cadherin is expressed in melanoblasts during embryonic development, which helps cell migration from the neural crest to the epidermis by the way of interacting with fibroblasts and endothelial cells. In adults, upregulation of N-cadherin potentiates the ability of melanoma cells to invade through the stroma and interact with the vascular endothelial cells and fibroblasts, which facilitates migration of cancer cells. N-cadherin has also been demonstrated to stabilize β-catenin thereby promoting anti-apoptotic proteins and inhibiting pro-apoptotic proteins such as Bad [101]. Normal melanocytes do not express N-Cadherin, while melanoma cells display moderate to strong expression of N-cadherin with a corresponding decrease in the expression of E-cadherin. This phenomenon termed as the 'cadherin switching' is a hallmark of EMT [102].

Snail1 also regulates the expression of Notch-4, MMP-2, TIMP-1, SPARC, and T-PA, among others, in melanoma cells [103]. Notch4 and SPARC expression can be directly regulated by Snail or indirectly via E-cadherin [103]. MMP-2 is a matrix metalloprotease that is involved in remodeling of the extracellular matrix through degradation of cell adhesion proteins and in turn facilitating tumor cell migration and invasion [104]. SPARC is a potent inducer of MMP-2, and downregulation of Snail1 decreases the expression of MMP-2 and SPARC [103, 104], as well as T-PA, a protease that converts plasminogen to active zymogen [105], leading to reduced degradation of the extracellular matrix and subsequent invasion. Notch signaling mediates melanoma-endothelial cell and melanoma-keratinocyte communications, facilitating melanoma cell migration and metastasis [106, 107]. Notch 4 expression in melanoma is stimulated by Snail, independent of the repression of E-cadherin [103]. Notch inhibition enhances the efficacy of ERK and ERBB inhibitors for melanoma growth arrest [108, 109].

5.3.2. Deubiquitinating enzymes required for melanoma growth and metastasis

Deubiquitinases (DUB) have a role in stem cell maintenance and tumor growth [110]. Among the 89 DUBs examined in over 300 different tumor samples of breast, colon, lung, stomach, kidney, prostate, non-Hodgkin's lymphoma, and melanoma, 22 DUBs are significantly dysregulated in at least one tumor type [111]. Specifically, three DUBs, USP10 (ubiquitin specific peptidase 10), USP11 and USP22, are expressed significantly higher in metastatic melanoma compared to benign nevi and primary tumor. In addition, expression of USP10 and USP22 is significantly correlated to the presence of ulceration and the Breslow index, a prognostic parameter indicating the depth of tumor invasion. USP10, USP11 and USP22 regulate deubiquitination of target proteins crucial for melanoma transformation and metastasis [111]. For example, USP22 deubiquitinates chromosomal binding proteins H2A-Ub1 and H2A-Ub2, and consequently activates transcription factors and induces epigenetic modifications favorable for cancer growth and metastasis [112].

USP7 mediates degradation of tumor suppressors such as p53, MDM2, FOXO and PTEN [110]. USP14 is expressed at increased levels in melanoma cells compared to melanocytes, and its high expression correlates with melanoma progression and poorer survival. Knockdown or pharmacological inhibition of USP14 impairs viability of melanoma cells irrespective of the mutational status of BRAF, NRAS and TP53, and overcomes resistance to MAPK inhibitors. This was accompanied by accumulation of poly-ubiquitinated proteins, mitochondrial dysfunction, ER stress, and a ROS production [113].

USP9X, another member of the USP family, is responsible for attenuating the degradation of Mcl-1, an anti-apoptotic protein in melanoma and other cancers [53]. USP9X deubiquitinates, and stabilizes ETS-1, a transcription factor involved in regulation of angiogenesis, cell migration, proliferation and cellular differentiation in melanoma [114]. Phenethyl ITC, an inhibitor of USP9X, is currently in a Phase I trial for the treatment of melanoma and leukemia and Phase II trials for oral and lung cancer [53]. WP1130 (degrasyn) is another agent that inhibits USP9X and promotes the accumulation of protein-ubiquitin conjugates, leading to formation of aggresomes and apoptosis. This agent is shown to decrease melanoma cell growth both in vitro and in vivo melanoma models [115].

6. Conclusion

Melanoma is an aggressive disease intrinsically prone to metastasis. Germline and sporadic mutations are responsible for the initiation and progression of the disease and PTMs such as ubiquitination play dominant roles in melanoma growth and metastasis, and offer wealth of opportunities for therapeutic targeting. With better mechanistic understating of specific functions of the ubiquitinating enzymes as well as the deubiquitinases, new targeted therapies are expected to emerge in the foreseeable feature.

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References

[1] Howlader N NA, Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). https://seercancergov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017

[2] Horner M, Ries L, Krapcho M, Neyman N, Aminou R, Howlader N, et al. SEER Cancer Statistics Review, 1975-2006. Bethesda, MD: National Cancer Institute. 2009

[3] Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, Meyer L, Gress DM, Byrd DR, Winchester DP. The eighth edition AJCC Cancer staging manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA: a Cancer Journal for Clinicians. 2017;**67**(2):93-99

[4] Shain AH, Bastian BC. From melanocytes to melanomas. Nature Reviews. Cancer. 2016;**16**(6):345

[5] Roh MR, Eliades P, Gupta S, Tsao H. Genetics of melanocytic nevi. Pigment Cell & Melanoma Research. 2015;**28**(6):661-672

[6] Lo JA, Fisher DE. The melanoma revolution: From UV carcinogenesis to a new era in therapeutics. Science (New York, New York). 2014;**346**(6212):945-949

[7] Aoude LG, Wadt KAW, Pritchard AL, Hayward NK. Genetics of familial melanoma: 20 years after CDKN2A. Pigment Cell & Melanoma Research. 2015;**28**(2):148-160

[8] Chin L, Garraway LA, Fisher DE. Malignant melanoma: Genetics and therapeutics in the genomic era. Genes & Development. 2006;**20**(16):2149-2182

[9] Chin L. The genetics of malignant melanoma: Lessons from mouse and man. Nature Reviews. Cancer. 2003;**3**(8):559

[10] Fletcher O, Easton D, Anderson K, Gilham C, Jay M, Peto J. Lifetime risks of common cancers among retinoblastoma survivors. Journal of the National Cancer Institute. 2004;**96**(5):357-363

[11] Muthusamy V, Hobbs C, Nogueira C, Cordon-Cardo C, McKee PH, Chin L, Bosenberg MW. Amplification of CDK4 and MDM2 in malignant melanoma. Genes, Chromosomes and Cancer. 2006;**45**(5):447-454

[12] Eng C, Li FP, Abramson DH, Ellsworth RM, Wong FL, Goldman MB, Seddon J, Tarbell N, Boice JD Jr. Mortality from second tumors among long-term survivors of retinoblastoma. Journal of the National Cancer Institute. 1993;**85**(14):1121-1128

[13] Valverde P, Healy E, Sikkink S, Haldane F, Thody AJ, Carothers A, Jackson IJ, Rees JL. The Asp84Glu variant of the melanocortin 1 receptor (MC1R) is associated with melanoma. Human Molecular Genetics. 1996;**5**(10):1663-1666

[14] Box NF, Duffy DL, Chen W, Stark M, Martin NG, Sturm RA, Hayward NK. MC1R genotype modifies risk of melanoma in families segregating CDKN2A mutations. American Journal of Human Genetics. 2001;**69**(4):765-773

[15] Maldonado JL, Fridlyand J, Patel H, Jain AN, Busam K, Kageshita T, Ono T, Albertson DG, Pinkel D, Bastian BC. Determinants of BRAF mutations in primary melanomas. Journal of the National Cancer Institute. 2003;**95**(24):1878-1890

[16] Stas M, Degreef H, Demunter A, De Wolf-Peeters C, van den Oord JJ. Analysis of N-and K-ras mutations in the distinctive tumor progression phases of melanoma. The Journal of Investigative Dermatology. 2001;**117**(6):1483-1489

[17] Papp T, Pemsel H, Zimmermann R, Bastrop R, Weiss DG, Schiffmann D. Mutational analysis of the N-ras, p53, p16INK4a, CDK4, and MC1R genes in human congenital melanocytic naevi. Journal of Medical Genetics. 1999;**36**(8):610-614

[18] Libra M, Malaponte G, Navolanic PM, Gangemi P, Bevelacqua V, Proietti L, Bruni B, Stivala F, Mazzarino MC, Travali S. Analysis of BRAF mutation in primary and metastatic melanoma. Cell Cycle. 2005;**4**(10):1382-1384

[19] Pollock PM, Harper UL, Hansen KS, Yudt LM, Stark M, Robbins CM, Moses TY, Hostetter G, Wagner U, Kakareka J. High frequency of BRAF mutations in nevi. Nature Genetics. 2003;**33**(1):19-20

[20] Edwards R, Ward M, Wu H, Medina C, Brose M, Volpe P, Nussen-Lee S, Haupt H, Martin A, Herlyn M. Absence of BRAF mutations in UV-protected mucosal melanomas. Journal of Medical Genetics. 2004;**41**(4):270-272

[21] Yazdi AS, Palmedo G, Flaig MJ, Puchta U, Reckwerth A, Rütten A, Mentzel T, Hügel H, Hantschke M, Schmid-Wendtner M-H. Mutations of the BRAF gene in benign and malignant melanocytic lesions. The Journal of Investigative Dermatology. 2003;**121**(5): 1160-1162

[22] McNeal AS, Liu K, Nakhate V, Natale CA, Duperret EK, Capell BC, Dentchev T, Berger SL, Herlyn M, Seykora JT, et al. CDKN2B loss promotes progression from benign melanocytic nevus to melanoma. Cancer Discovery. 2015;**5**(10):1072-1085

[23] Goetz EM, Ghandi M, Treacy DJ, Wagle N, Garraway LA. ERK mutations confer resistance to mitogen-activated protein kinase pathway inhibitors. Cancer Research. 2014;**74**(23):7079-7089

[24] Dong C, Wilhelm D, Koopman P. Sox genes and cancer. Cytogenetic and Genome Research. 2004;**105**(2-4):442-447

[25] Ernfors P. Cellular origin and developmental mechanisms during the formation of skin melanocytes. Experimental Cell Research. 2010;**316**(8):1397-1407

[26] Gupta PB, Kuperwasser C, Brunet J-P, Ramaswamy S, Kuo W-L, Gray JW, Naber SP, Weinberg RA. The melanocyte differentiation program predisposes to metastasis after neoplastic transformation. Nature Genetics. 2005;**37**(10):1047

[27] Ploper D, Taelman VF, Robert L, Perez BS, Titz B, Chen H-W, Graeber TG, von Euw E, Ribas A, De Robertis EM. MITF drives endolysosomal biogenesis and potentiates Wnt signaling in melanoma cells. Proceedings of the National Academy of Sciences. 2015;**112**(5):E420-E4E9

[28] Hartman ML, Czyz M. Pro-survival role of MITF in melanoma. The Journal of Investigative Dermatology. 2015;**135**(2):352-358

[29] Xue G, Romano E, Massi D, Mandalà M. Wnt/β-catenin signaling in melanoma: Preclinical rationale and novel therapeutic insights. Cancer Treatment Reviews. 2016;**49**:1-12

[30] Larue L, Delmas V. 5.2. 3.1. LEF 5.2. 3.2. ICAT 5.2. 3.3. Proven targets of beta-catenin in melanocytes and melanoma 5.2. 3.3. 1. Mitf-M 5.2. 3.3. 2. Dct. Frontiers in Bioscience. 2006;**11**:733-742

[31] Arozarena I, Bischof H, Gilby D, Belloni B, Dummer R, Wellbrock C. In melanoma, beta-catenin is a suppressor of invasion. Oncogene. 2011;**30**(45):4531

[32] Brugmann SA, Goodnough LH, Gregorieff A, Leucht P, ten Berge D, Fuerer C, Clevers H, Nusse R, Helms JA. Wnt signaling mediates regional specification in the vertebrate face. Development. 2007;**134**(18):3283-3295

[33] Gómez-Orte E, Sáenz-Narciso B, Moreno S, Cabello J. Multiple functions of the noncanonical Wnt pathway. Trends in Genetics. 2013;**29**(9):545-553

[34] Iden S, Collard JG. Crosstalk between small GTPases and polarity proteins in cell polarization. Nature Reviews. Molecular Cell Biology. 2008;**9**(11):846

[35] Sahai E, Marshall CJ. RHO–GTPases and cancer. Nature Reviews. Cancer. 2002;**2**(2):133

[36] Kovacs D, Migliano E, Muscardin L, Silipo V, Catricalà C, Picardo M, Bellei B. The role of Wnt/β-catenin signaling pathway in melanoma epithelial-to-mesenchymal-like switching: Evidences from patients-derived cell lines. Oncotarget. 2016;**7**(28):43295

[37] Krueger KE, Srivastava S. Posttranslational protein modifications current implications for cancer detection, prevention, and therapeutics. Molecular & Cellular Proteomics. 2006;**5**(10):1799-1810

[38] Jørgensen K, Holm R, Mælandsmo GM, Florenes VA. Expression of activated extracellular signal-regulated kinases 1/2 in malignant melanomas: Relationship with clinical outcome. Clinical Cancer Research. 2003;**9**(14):5325-5331

[39] Komander D, Rape M. The ubiquitin code. Annual Review of Biochemistry. 2012;**81**: 203-229

[40] Yau R, Rape M. The increasing complexity of the ubiquitin code. Nature Cell Biology. 2016;**18**(6):579-586

[41] Doil C, Mailand N, Bekker-Jensen S, Menard P, Larsen DH, Pepperkok R, Ellenberg J, Panier S, Durocher D, Bartek J. RNF168 binds and amplifies ubiquitin conjugates on damaged chromosomes to allow accumulation of repair proteins. Cell. 2009;**136**(3):435-446

[42] Lauwers E, Jacob C, André B. K63-linked ubiquitin chains as a specific signal for protein sorting into the multivesicular body pathway. The Journal of Cell Biology. 2009;**185**(3):493-502

[43] Deng L, Wang C, Spencer E, Yang L, Braun A, You J, Slaughter C, Pickart C, Chen ZJ. Activation of the IκB kinase complex by TRAF6 requires a dimeric ubiquitin-conjugating enzyme complex and a unique polyubiquitin chain. Cell. 2000;**103**(2):351-361

[44] Deng L, Wang C, Spencer E, Yang L, Braun A, You J, Slaughter C, Pickart C, Chen ZJ. Activation of the IkappaB kinase complex by TRAF6 requires a dimeric ubiquitin-conjugating enzyme complex and a unique polyubiquitin chain. Cell. 2000;**103**(2):351-361

[45] Groettrup M, Pelzer C, Schmidtke G, Hofmann K. Activating the ubiquitin family: UBA6 challenges the field. Trends in Biochemical Sciences. 2008;**33**(5):230-237

[46] Xu GW, Ali M, Wood TE, Wong D, Maclean N, Wang X, Gronda M, Skrtic M, Li X, Hurren R. The ubiquitin-activating enzyme E1 as a therapeutic target for the treatment of leukemia and multiple myeloma. Blood. 2010;**115**(11):2251-2259

[47] Liu X, Sun L, Gursel DB, Cheng C, Huang S, Rademaker AW, Khan SA, Yin J, Kiyokawa H. The non-canonical ubiquitin activating enzyme UBA6 suppresses epithelial-mesenchymal transition of mammary epithelial cells. Oncotarget. 2017;**8**(50):87480-87493

[48] Rosner K, Mehregan DR, Kirou E, Abrams J, Kim S, Campbell M, Frieder J, Lawrence K, Haynes B, Shekhar MP. Melanoma development and progression are associated with Rad6 upregulation and β-catenin relocation to the cell membrane. Journal of Skin Cancer. 2014;**2014**:10. Article ID:` 439205. https://doi.org/10.1155/2014/439205

[49] Ohh M. pVHL's kryptonite: E2-EPF UCP. Cancer Cell. 2006;**10**(2):95-97

[50] Jung C-R, Hwang K-S, Yoo J, Cho W-K, Kim J-M, Kim WH, Im D-S. E2-EPF UCP targets pVHL for degradation and associates with tumor growth and metastasis. Nature Medicine. 2006;**12**(7):809

[51] Liu S, Yamauchi H. p27-associated G1 arrest induced by hinokitiol in human malignant melanoma cells is mediated via down-regulation of pRb, Skp2 ubiquitin ligase, and impairment of Cdk2 function. Cancer Letters. 2009;**286**(2):240-249

[52] Hershko DD. Oncogenic properties and prognostic implications of the ubiquitin ligase Skp2 in cancer. Cancer. 2008;**112**(7):1415-1424

[53] Ma J, Guo W, Li C. Ubiquitination in melanoma pathogenesis and treatment. Cancer Medicine. 2017

[54] Gregori L, Poosch MS, Cousins G, Chau V. A uniform isopeptide-linked multiubiquitin chain is sufficient to target substrate for degradation in ubiquitin-mediated proteolysis. The Journal of Biological Chemistry. 1990;**265**(15):8354-8357

[55] Aydin IT, Melamed RD, Adams SJ, Castillo-Martin M, Demir A, Bryk D, Brunner G, Cordon-Cardo C, Osman I, Rabadan R, et al. FBXW7 mutations in melanoma and a new therapeutic paradigm. Journal of the National Cancer Institute. 2014;**106**(6):dju107

[56] Sato M, Rodriguez-Barrueco R, Yu J, Do C, Silva JM, Gautier J. MYC is a critical target of FBXW7. Oncotarget. 2015;**6**(5):3292-3305

[57] Fujii Y, Yada M, Nishiyama M, Kamura T, Takahashi H, Tsunematsu R, Susaki E, Nakagawa T, Matsumoto A, Nakayama KI. Fbxw7 contributes to tumor suppression by targeting multiple proteins for ubiquitin-dependent degradation. Cancer Science. 2006;**97**(8):729-736

[58] Richards MW, Burgess SG, Poon E, Carstensen A, Eilers M, Chesler L, Bayliss R. Structural basis of N-Myc binding by aurora-A and its destabilization by kinase inhibitors. Proceedings of the National Academy of Sciences of the United States of America. 2016;**113**(48):13726-13731

[59] Rajabi P, Karimian P, Heidarpour M. The relationship between MDM2 expression and tumor thickness and invasion in primary cutaneous malignant melanoma. Journal of research in medical sciences: the official journal of Isfahan University of Medical. Sciences. 2012;**17**(5):452

[60] Luo Z, Zhang X, Zeng W, Su J, Yang K, Lu L, Lim CB, Tang W, Wu L, Zhao S. TRAF6 regulates melanoma invasion and metastasis through ubiquitination of Basigin. Oncotarget. 2016;**7**(6):7179

[61] Feng H, Lopez GY, Kim CK, Alvarez A, Duncan CG, Nishikawa R, Nagane M, A-JA S, Auron PE, Hedberg ML. EGFR phosphorylation of DCBLD2 recruits TRAF6 and stimulates AKT-promoted tumorigenesis. The Journal of Clinical Investigation. 2014; **124**(9):3741-3756

[62] Linares JF, Duran A, Yajima T, Pasparakis M, Moscat J, Diaz-Meco MT. K63 polyubiquitination and activation of mTOR by the p62-TRAF6 complex in nutrient-activated cells. Molecular Cell. 2013;**51**(3):283-296

[63] Wang B, Jie Z, Joo D, Ordureau A, Liu P, Gan W, Guo J, Zhang J, North BJ, Dai X. TRAF2 and OTUD7B govern a ubiquitin-dependent switch that regulates mTORC2 signalling. Nature. 2017;**545**(7654):365

[64] Arimoto K, Takahashi H, Hishiki T, Konishi H, Fujita T, Shimotohno K. Negative regulation of the RIG-I signaling by the ubiquitin ligase RNF125. Proceedings of the National Academy of Sciences of the United States of America. 2007;**104**(18):7500-7505

[65] Yang L, Zhou B, Li X, Lu Z, Li W, Huo X, Miao Z. RNF125 is a ubiquitin-protein ligase that promotes p53 degradation. Cellular Physiology and Biochemistry. 2015;**35**(1):237-245

[66] Jia X, Zhou H, Wu C, Wu Q, Ma S, Wei C, Cao Y, Song J, Zhong H, Zhou Z, et al. The ubiquitin ligase RNF125 targets innate immune adaptor protein TRIM14 for ubiquitination and degradation. Journal of Immunology. 2017;**198**(12):4652-4658

[67] Tenorio J, Mansilla A, Valencia M, Martinez-Glez V, Romanelli V, Arias P, Castrejon N, Poletta F, Guillen-Navarro E, Gordo G, et al. A new overgrowth syndrome is due to mutations in RNF125. Human Mutation. 2014;**35**(12):1436-1441

[68] Kim H, Frederick DT, Levesque MP, Cooper ZA, Feng Y, Krepler C, Brill L, Samuels Y, Hayward NK, Perlina A, et al. Downregulation of the ubiquitin ligase RNF125 underlies resistance of melanoma cells to BRAF inhibitors via JAK1 deregulation. Cell Reports. 2015;**11**(9):1458-1473

[69] Lito P, Pratilas CA, Joseph EW, Tadi M, Halilovic E, Zubrowski M, Huang A, Wong WL, Callahan MK, Merghoub T, et al. Relief of profound feedback inhibition of mitogenic signaling by RAF inhibitors attenuates their activity in BRAFV600E melanomas. Cancer Cell. 2012;**22**(5):668-682

[70] Hernandez MA, Patel B, Hey F, Giblett S, Davis H, Pritchard C. Regulation of BRAF protein stability by a negative feedback loop involving the MEK-ERK pathway but not the FBXW7 tumour suppressor. Cellular Signalling. 2016;**28**(6):561-571

[71] Wan L, Chen M, Cao J, Dai X, Yin Q, Zhang J, Song SJ, Lu Y, Liu J, Inuzuka H, et al. The APC/C E3 ligase complex activator FZR1 restricts BRAF oncogenic function. Cancer Discovery. 2017;**7**(4):424-441

[72] Chakraborty A, Diefenbacher ME, Mylona A, Kassel O, Behrens A. The E3 ubiquitin ligase Trim7 mediates c-Jun/AP-1 activation by Ras signalling. Nature Communications. 2015;**6**:6782

[73] Delmas A, Cherier J, Pohorecka M, Medale-Giamarchi C, Meyer N, Casanova A, Sordet O, Lamant L, Savina A, Pradines A, et al. The c-Jun/RHOB/AKT pathway confers resistance of BRAF-mutant melanoma cells to MAPK inhibitors. Oncotarget. 2015;**6**(17):15250-15264

[74] McClurg UL, Robson CN. Deubiquitinating enzymes as oncotargets. Oncotarget. 2015;**6**(12):9657

[75] Wilkinson KD. DUBs at a glance. Journal of Cell Science. 2009;**122**(14):2325-2329

[76] Carbone M, Yang H, Pass HI, Krausz T, Testa JR, Gaudino G. BAP1 and cancer. Nature Reviews Cancer. 2013;**13**(3):153

[77] Machida YJ, Machida Y, Vashisht AA, Wohlschlegel JA, Dutta A. The deubiquitinating enzyme BAP1 regulates cell growth via interaction with HCF-1. The Journal of Biological Chemistry. 2009;**284**(49):34179-34188

[78] Shembade N, Harhaj EW. Regulation of NF-κB signaling by the A20 deubiquitinase. Cellular & Molecular Immunology. 2012;**9**(2):123

[79] Shembade N, Ma A, Harhaj EW. Inhibition of NF-κB signaling by A20 through disruption of ubiquitin enzyme complexes. Science. 2010;**327**(5969):1135-1139

[80] Honma K, Tsuzuki S, Nakagawa M, Tagawa H, Nakamura S, Morishima Y, Seto M. TNFAIP3/A20 functions as a novel tumor suppressor gene in several subtypes of non-Hodgkin lymphomas. Blood. 2009;**114**(12):2467-2475

[81] Giordano M, Roncagalli R, Bourdely P, Chasson L, Buferne M, Yamasaki S, Beyaert R, Van Loo G, Auphan-Anezin N, Schmitt-Verhulst A-M. The tumor necrosis factor alpha-induced protein 3 (TNFAIP3, A20) imposes a brake on antitumor activity of CD8 T cells. Proceedings of the National Academy of Sciences. 2014;**111**(30):11115-11120

[82] Bignell GR, Warren W, Seal S, Takahashi M, Rapley E, Barfoot R, Green H, Brown C, Biggs PJ, Lakhani SR. Identification of the familial cylindromatosis tumour-suppressor gene. Nature Genetics. 2000;**25**(2):160-165

[83] Brummelkamp TR, Nijman SM, Dirac AM, Bernards R. Loss of the cylindromatosis tumour suppressor inhibits apoptosis by activating NF-κB. Nature. 2003;**424**(6950):797-801

[84] Ke H, Massoumi R. The role of CYLD in blocking oncogenic cell signaling in melanoma. Journal of Cancer Therapy. 2013;**4**(06):32

[85] Qiu H, Yuan S, Lu X. miR-186 suppressed CYLD expression and promoted cell proliferation in human melanoma. Oncology Letters. 2016;**12**(4):2301-2306

[86] Zhang K, Guo L. MiR-767 promoted cell proliferation in human melanoma by suppressing CYLD expression. Gene. 2018;**641**:272-278

[87] Staal J, Driege Y, Bekaert T, Demeyer A, Muyllaert D, Van Damme P, Gevaert K, Beyaert R. T-cell receptor-induced JNK activation requires proteolytic inactivation of CYLD by MALT1. The EMBO Journal. 2011;**30**(9):1742-1752

[88] Alameda J, Fernandez-Acenero M, Moreno-Maldonado R, Navarro M, Quintana R, Page A, Ramirez A, Bravo A, Casanova M. CYLD regulates keratinocyte differentiation and skin cancer progression in humans. Cell Death & Disease. 2011;**2**(9):e208

[89] Ke H, Augustine CK, Gandham VD, Jin JY, Tyler DS, Akiyama SK, Hall RP, Zhang JY. CYLD inhibits melanoma growth and progression through suppression of the JNK/AP-1 and beta1-integrin signaling pathways. The Journal of Investigative Dermatology. 2013;**133**(1):221-229

[90] Miliani de Marval P, Lutfeali S, Jin JY, Leshin B, Selim MA, Zhang JY. CYLD inhibits tumorigenesis and metastasis by blocking JNK/AP1 signaling at multiple levels. Cancer Prevention Research (Philadelphia, Pa.). 2011

[91] Reiley WW, Jin W, Lee AJ, Wright A, Wu X, Tewalt EF, Leonard TO, Norbury CC, Fitzpatrick L, Zhang M. Deubiquitinating enzyme CYLD negatively regulates the ubiquitin-dependent kinase Tak1 and prevents abnormal T cell responses. The Journal of Experimental Medicine. 2007;**204**(6):1475-1485

[92] Trompouki E, Hatzivassiliou E, Tsichritzis T, Farmer H, Ashworth A, Mosialos G. CYLD is a deubiquitinating enzyme that negatively regulates NF-κB activation by TNFR family members. Nature. 2003;**424**(6950):793

[93] Stegmeier F, Sowa ME, Nalepa G, Gygi SP, Harper JW, Elledge SJ. The tumor suppressor CYLD regulates entry into mitosis. Proceedings of the National Academy of Sciences. 2007;**104**(21):8869-8874

[94] Tsunoda K, Oikawa H, Tada H, Tatemichi Y, Muraoka S, Miura S, Shibazaki M, Maeda F, Takahashi K, Akasaka T. Nucleus accumbens-associated 1 contributes to cortactin deacetylation and augments the migration of melanoma cells. The Journal of Investigative Dermatology. 2011;**131**(8):1710-1719

[95] Wickström SA, Masoumi KC, Khochbin S, Fässler R, Massoumi R. CYLD negatively regulates cell-cycle progression by inactivating HDAC6 and increasing the levels of acetylated tubulin. The EMBO Journal. 2010;**29**(1):131-144

[96] Sanchez-Tillo E, Liu Y, de Barrios O, Siles L, Fanlo L, Cuatrecasas M, Darling DS, Dean DC, Castells A, Postigo A. EMT-activating transcription factors in cancer: Beyond EMT and tumor invasiveness. Cellular and Molecular Life Sciences: CMLS. 2012;**69**(20):3429-3456

[97] Massoumi R, Kuphal S, Hellerbrand C, Haas B, Wild P, Spruss T, Pfeifer A, Fassler R, Bosserhoff AK. Down-regulation of CYLD expression by snail promotes tumor progression in malignant melanoma. The Journal of Experimental Medicine. 2009;**206**(1):221-232

[98] Pharoah PD, Guilford P, Caldas C. Incidence of gastric cancer and breast cancer in CDH1 (E-cadherin) mutation carriers from hereditary diffuse gastric cancer families. Gastroenterology. 2001;**121**(6):1348-1353

[99] Risinger JI, Berchuck A, Kohler MF, Boyd J. Mutations of the E–cadherin gene in human gynecologic cancers. Nature Genetics. 1994;**7**(1):98

[100] Hsu M-Y, Meier FE, Nesbit M, Hsu J-Y, Van Belle P, Elder DE, Herlyn M. E-cadherin expression in melanoma cells restores keratinocyte-mediated growth control and down-regulates expression of invasion-related adhesion receptors. The American Journal of Pathology. 2000;**156**(5):1515-1525

[101] Li G, Satyamoorthy K, Herlyn M. N-cadherin-mediated intercellular interactions promote survival and migration of melanoma cells. Cancer Research. 2001;**61**(9):3819-3825

[102] Lade-Keller J, Riber-Hansen R, Guldberg P, Schmidt H, Hamilton-Dutoit SJ, Steiniche T. E-to N-cadherin switch in melanoma is associated with decreased expression of phosphatase and tensin homolog and cancer progression. The British Journal of Dermatology. 2013;**169**(3):618-628

[103] Kuphal S, Palm HG, Poser I, Bosserhoff AK. Snail-regulated genes in malignant melanoma. Melanoma Research. 2005;**15**(4):305-313

[104] Rotte A, Martinka M, Li G. MMP2 expression is a prognostic marker for primary melanoma patients. Cellular Oncology. 2012;**35**(3):207-216

[105] Mueller BM. Different Roles for Plasminogen Activators and Metalloproteinases in Melanoma Metastasis. In: Günthert U, Birchmeier W, editors. Attempts to Understand Metastasis Formation I. Current Topics in Microbiology 213/I and Immunology. Vol. 213/1. Berlin, Heidelberg: Springer; 1996. pp. 65-85

[106] Howard JD, Moriarty WF, Park J, Riedy K, Panova IP, Chung CH, Suh KY, Levchenko A, Alani RM. Notch signaling mediates melanoma-endothelial cell communication and melanoma cell migration. Pigment Cell & Melanoma Research. 2013;**26**(5):697-707

[107] Golan T, Messer AR, Amitai-Lange A, Melamed Z, Ohana R, Bell RE, Kapitansky O, Lerman G, Greenberger S, Khaled M, et al. Interactions of melanoma cells with distal keratinocytes trigger metastasis via notch signaling inhibition of MITF. Molecular Cell. 2015;**59**(4):664-676

[108] Krepler C, Xiao M, Samanta M, Vultur A, Chen HY, Brafford P, Reyes-Uribe PI, Halloran M, Chen T, He X, et al. Targeting notch enhances the efficacy of ERK inhibitors in BRAF-V600E melanoma. Oncotarget. 2016;**7**(44):71211-71222

[109] Zhang K, Wong P, Salvaggio C, Salhi A, Osman I, Bedogni B. Synchronized targeting of notch and ERBB signaling suppresses melanoma tumor growth through inhibition of Notch1 and ERBB3. The Journal of Investigative Dermatology. 2016;**136**(2):464-472

[110] Wang L, YR Dent S. Functions of SAGA in development and disease. Epigenomics. 2014;**6**(3):329-339

[111] Luise C, Capra M, Donzelli M, Mazzarol G, Jodice MG, Nuciforo P, Viale G, Di Fiore PP, Confalonieri S. An atlas of altered expression of deubiquitinating enzymes in human cancer. PLoS One. 2011;**6**(1):e15891

[112] Liu YL, Yang YM, Xu H, Dong XS. Increased expression of ubiquitin-specific protease 22 can promote cancer progression and predict therapy failure in human colorectal cancer. Journal of Gastroenterology and Hepatology. 2010;**25**(11):1800-1805

[113] Didier R, Mallavialle A, Ben Jouira R, Domdom MA, Tichet M, Auberger P, Luciano F, Ohanna M, Tartare-Deckert S, Deckert M. Targeting the proteasome-associated deubiquitinating enzyme USP14 impairs melanoma cell survival and overcomes resistance to MAPK-targeting therapies. Molecular Cancer Therapeutics. 2018

[114] Potu H, Peterson LF, Kandarpa M, Pal A, Sun H, Durham A, Harms PW, Hollenhorst PC, Eskiocak U, Talpaz M. Usp9x regulates Ets-1 ubiquitination and stability to control NRAS expression and tumorigenicity in melanoma. Nature Communications. 2017;**8**:14449

[115] Kapuria V, Peterson LF, Fang D, Bornmann WG, Talpaz M, Donato NJ. Deubiquitinase inhibition by small-molecule WP1130 triggers aggresome formation and tumor cell apoptosis. Cancer Research. 2010;**70**(22):9265-9276

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