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Review

Tyrosinase related protein 1 (TYRP1/gp75) in human cutaneous melanoma

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ABSTRACT

Melanoma prognosis is based on specific pathological features at the primary lesion. In metastatic patients, the extent of lymph node involvement is also an important prognosis indicator. Many progression markers both in tissues and serum, including circulating tumor cells, have been studied and new molecular markers are awaited from high-throughput screenings to discriminate between clinical stages and predict disease progression. The present review focuses on human tyrosinase related protein 1 also known as gp75 glycoprotein (Tyrp1/gp75), a melanosomal protein involved in the pigmentary machinery of the melanocyte and often used as differentiation marker, with a special emphasis on its emerging roles in the malignant melanocyte and melanoma progression.

1. Introduction

Tyrosinase related proteins (TYRPs) belong to a family of Cu^{++}/Zn^{++} metalloenzymes sharing several sequence homologies. They are expressed in melanocytes and mainly localized within specialized organelles called melanosomes where they play key roles in promoting melanogenesis, a biochemical complex process leading to the formation of the two types of pigments: dark eumalnins and red pheomelanins.

Three members of this family are known: 1) tyrosinase was the first to be identified (Raper, 1927) followed by 2) dopachrome tautomerase (DCT or Tyrp2) (Aroca et al., 1991) and 3) Tyrp1 (review by del Marmol and Beermann, 1996).

All three proteins share the same signaling sequence, two cystein rich and a transmembrane domains, and, most importantly, two Cu^{++}/Zn^{++} binding sites responsible of their catalytic activities (Olivares and Solano, 2009).

Human Tyrp1 is encoded by the TYRP1 gene (the human homolog of the mouse *brown* locus) (Jackson, 1988; Vijayasaradhi et al., 1990). The gene is located in chromosome 9 (9p23). Genomic sequence details are available from: http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene&cmd=Retrieve&dopt=full_report&list_uids=7306

The control of TYRP1 gene expression is achieved through regulatory elements also at the TYRP1 locus (Review by Murisier and Beermann, 2006).

The mature form of Tyrp1, also originally called gp75, is a 75 kDa transmembrane glycoprotein produced within the endoplasmic reticulum (ER) and transported through the Golgi to a specific organelles called melanosomes (Jimbow et al., 1997; Chen et al., 2001; Liu et al., 2001). Intracellular sorting of both tyrosinase and Tyrp1/gp75 is achieved by perinuclear vesicles expressing Rab7 (Gomez et al., 2001), Rab38 (Loftus et al., 2002) and Rab32 that have a key role in the biogenesis

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of melanosomes (Wasmeier et al., 2006); as well as Varp (ankyrin-repeat-containing protein) specific binding to the Rab32/38 complex that is required for proper melanosomal localization of Tyrp1/gp75 (Tamura et al., 2009). It has been also shown that the ESCRT-1 (endosomal sorting complex required for transport) pathway is necessary for such a trafficking (Truschel et al., 2009). Tyrp1 aminoacid sequence itself has a 58 kDa MW but it undergoes important post-translational modifications, mainly glycosylations and two copper ions binding, to gain 17 kDa and reach the mature active form (Zheng et al., 2010).

1.1. *Tyrp1 cellular localization*

Tyrp1 immunoreactivity is expressed both in melanosomes and on the surface of melanocytes and melanoma cells, as identified by flow cytometry (Takechi et al., 1996) and has long being identified as the most abundant glycoprotein both in normal and malignant melanocytes (Tai et al., 1983). A secretory truncated form of the protein that lacks the transmembrane region has also been described (Xu et al., 1997).

1.2. *TYRP1 role in melanocytes*

1.2.1. *Molecular mechanism of action*

TYRP1 as well as tyrosinase and DCT promoters contain a motif termed M-box that can bind to the microphtalmia transcription factor (MITF). The latter plays a central role within the melanocyte in activating pigmentation, cell proliferation and differentiation (review by Cheli et al., 2010). MITF effect on melanogenic genes appears not to affect their mRNA levels but is rather mediated through post-transcriptional processing events of the corresponding proteins (Newton et al., 2007). However, while MITF may directly affect the expression of all three proteins and unlike tyrosinase and DCT, TYRP1 expression can be independently regulated (Fang and Setaluri, 1999; Fang et al., 2002; Vachtenheim et al., 2001).

Also, it has been shown that Pax3, belonging to the paired box (PAX) family of transcription factors and expressed in melanocytes and melanomas, is able to bind the TYRP1 promoter and up-regulates its activity (Galibert et al., 1999).

1.2.2. *Role in pigmentation*

(1) Tyrp1/gp75 enzymatic activity: while tyrosinase and DCT have both well defined enzymatic functions in melanogenesis, Tyrp1 implication in this process remains largely unclear including its exact catalytic function, despite its 43% homology with tyrosinase (Jackson, 1988). A series of *in vitro* biochemical experiments suggested roles for Tyrp1/gp75 as a catalase (Halaban and Moellmann, 1990) and as a weak dihydroxyindole carboxylic acid (DHICA) oxidase (Kobayashi et al., 1994a, 1994b; Jiménez-Cervantes et al., 1994). In addition, no human TYRP1 gene polymorphism could be observed among a group of caucasians with different hair colour (Box et al., 1998).
(2) Tyrp1/gp75 regulation of tyrosinase activity: studies suggest that Tyrp1/gp75 may help stabilize tyrosinase (Kobayashi et al., 1994a, 1998) and can form a heterodimer in vivo, also of importance for intracellular trafficking of these enzymes (Luo et al., 1994; Kobayashi and Hearing, 2007), tyrosinase being the key enzyme responsible for the first step in melanin production. Tyrosinase and Tyrp1/gp75 complex may prevent the premature death of melanocytes by attenuating tyrosinase-mediated cytotoxicity.

Other studies confirm the same observations and further demonstrate that Tyrp1/gp75 decrease, negatively affects tyrosinase activity (Manga et al., 2000). Furthermore, the reexpression of the protein by transfecting human melanoma cells with a retroviral vector carrying TYRP1 cDNA, stimulated the activity of tyrosinase and promoted melanogenesis (Zhao et al., 1996).

1.2.3. *Tyrp1/gp75 is a marker of melanocyte differentiation*

In addition to its presumed enzymatic role in promoting pigment formation, Tyrp1/gp75 is associated with melanocyte differentiation (Vijayasaradhi et al., 1990) and often used in this sens as a marker until today.

1.2.4. *Tyrp1/gp75 and oxidative stress*

Abnormal synthesis and processing of Tyrp1/gp75 and its interaction with calnexin, a melanogenesis-associated chaperone, may be responsible of the early cell death of vitiligo melanocytes due to their increased sensitivity to oxidative stress (Jimbow et al., 2001). In this line, another study found that it confers melanocyte protection against oxidative stress (Manga et al., 2006).

Furthermore, several indirect proofs of Tyrp1/gp75 putative important role in melanocytes came from 1) its association with pigmentary disorders: Mutations at the *brown* locus are linked to coat-color variations in mice (Ozeki et al., 1995). Likewise, TYRP1 mutations are responsible for a moderate form of albinism in human (oculocutaneous albinism type 3, OCA3) (Boissy et al., 1996; Rooryck et al., 2006); 2) other pigmentary unrelated effects: mutations in Tyrp1 compromise cell proliferation and melanosomal maturation in mouse melanocyte cultures (Sarangarajan et al., 2000); and 3) Tyrosinase protein expression in melanocytes did not vary with ethnicity, but Tyrp1 protein was significantly elevated in darkly pigmented African and Indian skin types compared with lightly pigmented Mexican, Chinese and European skin types (Alaluf et al., 2003).

1.3. *TYRP1 in melanoma*

1.3.1. *TYRP1 gene variants and melanoma risk*

Together with the melanocortin 1 receptor (MC1R), the agouti signaling protein (ASIP), tyrosinase and through its presumed function in melanogenesis, TYRP1 variants/mutations are considered of low risk for inherited melanomas (Leachman et al., 2009). However, multiple polymorphisms of pigmentation genes including TYRP1 were found associated with a higher risk for familial melanomas (Duffy et al., 2010). An eye color variant in TYRP1 was associated with risk for melanoma (Gudbjartsson et al., 2008).

It has been also reported that mutation of TYRP1 (OCA3) can modify the OCA2 phenotype, resulting in red hair phenotype (Chiang et al., 2008) with its known associated higher risk for melanoma.

Single nucleotide polymorphisms (SNP) analysis showed TYRP1 rs1408799 and SLC45A2 1721 C > G gene variants associated with an increased risk for melanoma (Nan et al., 2009). SLC45A2 codes for a membrane associated transporter protein (MATP) that is involved in the processing and trafficking TYRP1 from the trans-Golgi.

1.3.2. *Anti-Tyrp1/gp75 antibodies*

The first monoclonal antibody raised against human Tyrp1/gp75 was a mouse IgG2a named TA99 (Thomson et al., 1985) and is still being widely used until today. Other antibodies, including polyclonals, recognizing different epitopes of the protein, such as a sequence within the 396–445 region, C- or N-termini, are also proposed nowadays for different applications (immunohistochemistry, western blotting, immunofluorescence, …) and are available from various companies.

1.3.3. *Tyrp1/gp75 as a target for therapy*

1.3.3.1. *Preclinical studies*. Tyrp1/gp75 has been first identified by an autoantibody discovered in a metastatic melanoma patient (Mattes et al., 1983). In an animal model, active xenogeneic immunization against either lysates of the human melanoma cells or against a purified human Tyrp1/gp75 protein in Freund's adjuvant induced autoantibodies that mediated rejection of B16 melanoma cells (Naftzger et al., 1996).

In C57BL/6 mice, which are tolerant to Tyrp1/gp75, it was possible to generate autoantibodies after immunization with DNA encoding human Tyrp1/gp75 (Weber et al., 1998). Likewise, immunization with an adenovirus construct containing TYRP1 cDNA induces cellular immune responses and rejection of B16 melanoma xenografts (Hirschowitz et al., 1998). Interestingly, similar animal immunization with TYRP2 cDNA generated antibodies against Tyrp1/gp75 as well (Srinivasan et al., 2002).

This implies that the antigen was presented to the immune system by different ways that are well known today such as degradation products carried by the histocompatibility complex, after melanosome transfer outside the melanocyte or after cell death that is very common in metastatic lesions.

The cloning of a cDNA that directs the expression of the shared melanoma antigen recognized by HLA-A31-restricted tumor-infiltrating lymphocytes, revealed that its sequence was almost identical to the gene encoding Tyrp1/gp75 (Wang et al., 1995).

Another original approach in this field is the design of a TYRP1 cDNA vaccine by introducing specific point mutations into the corresponding gene that create altered peptide ligands. Cross-reactive CD8+ T cell responses against multiple nonmutated epitopes of syngeneic Tyrp1 and against melanoma cells have been obtained (Guevara-Patiño et al., 2006).

^{125}I-labeled TA99 anti-Tyrp1/gp75 monoclonal antibody specifically localized to pigmented human melanoma transplants in nu/nu mice (Welt et al., 1987).

Orlow et al. (1998), checked the protein expression of tyrosinase, Tyrp1/gp75 and Tyrp2/DCT using C-terminus recognizing antibodies, in *in situ* lesions of genetically identical (C57BL/6 strain) transgenic mice. They reported a clear trend decrease of all three proteins as the tumors become amelanotic, a pigmentary change associated with ongoing malignant progression. The steepest decrease was observed for tyrosinase, an intermediate for Tyrp1/gp75 and Tyrp2/DCT had the best conserved expression.

Passive immunization with the TA99 monoclonal antibody against Tyrp1/gp75 induced protection and rejection of both subcutaneous tumors and lung metastases in syngeneic C57BL/6 mice, including established tumors (Hara et al., 1995).

Two important steps foreward has been made toward a possible use in patients: 1) Evidence of a recognition by the antibody of cell surface Tyrp1/gp75 protein (Takechi et al., 1996); and 2) the production, characterization and evaluation in B16 murine melanoma model of a human monoclonal anti-Tyrp1/gp75 (Patel et al., 2005) also for therapeutic use (Patel et al., 2007).

Of note, combining the monoclonal antibody TA99 with the TYRP1 cDNA vaccination seems to yield synergistic effects in treating B16 mouse melanoma lung metastases (Saenger et al., 2008). The same effect was also recorded in combination with an anti-VEGF receptor monoclonal antibody (Patel et al., 2008).

Furthermore, using the B16 melanoma mouse model, immunization with dendritic cells *ex-vivo* transduced with an adenovirus encoding Tyrp1/gp75 stimulates immune activation and potent tumor protection mediated by CD8 T cells, the transfer of the latter from immunized mice also leads to tumor protection (Zhang and Huang, 2008).

Based on these preclinical studies and since an immune response may influence the course of the disease and the availability of cDNA clones coding for Tyrp1/gp75, much hope has been raised as to its use as a target for immunotherapy in melanoma patients.

1.3.3.2. *Clinical trials*. A Phase II trial to study the effectiveness of peptide vaccine with or without adjuvant interleukin-2 or sargramostim in treating patients who have recurrent or refractory metastatic melanoma has been initiated by National Cancer Institute (NCI) and now completed. One of the patients groups of the trial is receiving Tyrp1 protein emulsified in Montanide ISA-51 with or without adjuvant as above (source: http://clinicaltrials.gov/ct2/show/NCT00019383).

A vaccine phase I study with TYRP1 cDNA has been initiated in 2002 and now completed in AJCC stage III/IV melanoma patients by ImClone LLC, USA company in collaboration with Memorial Sloan-Kettering Cancer Center (source: http://clinicaltrials.gov/ct2/show/NCT00034554).

An open-label, dose-escalation study using anti-Tyrp1/gp75 monoclonal fully human antibody (IMC-20D7S) has been initiated in 2010 by ImClone LLC in collaboration with different investigation centers in the USA (source: http://clinicaltrials.gov/ct2/show/NCT01137006).

1.3.4. *TYRP1 expression and melanoma progression*

There are very few studies on TYRP1 expression and melanoma progression probably due to its label/reputation as a melanogenic enzyme and a melanocyte differentiation marker.

At the primary lesion, Tyrp1/gp75 expression evaluated by immunohistochemistry seems to be present in the radial growth phase but absent from the vertical phase (Fang et al., 2001), suggesting no potential role in invasion or cell dissemination. Furthermore, the authors mention that MAP2 is expressed abundantly in a majority of melanocytic nevi and

primary melanomas, but weakly and heterogeneously in a few metastatic melanomas *in vivo*. They also observed that Tyrp1/gp75 expression was inversely correlated with markers of neuronal differentiation, MAP2 isoforms (microtubule associated protein 2), whose induction in metastatic melanoma cells is accompanied by selective extinction of Tyrp1. Interestingly, another study indicates that patients with MAP2-positive primary melanomas have a significantly improved survival (Soltani et al., 2005). Thus, we may speculate that the repression of TYRP1 gene could be concomitant with the induction of MAP2 resulting in the inhibition of melanoma cell division, a delay in tumor progression and a better survival in melanoma patients. This hypothesis is further supported by our findings summarized below, suggesting a direct correlation between TYRP1 transcript expression level and overall survival.

In metastatic tissue, Bolander et al. (2008) found by protein profiling and immunohistochemistry (IHC) that Tyrp1 is expressed in the majority of melanoma tissues and normal melanocytes, and to be inversely correlated with tumor stage but not associated with overall or disease-free survival.

In skin metastases, recent work of our group combining gene profiling microarrays, quantitative PCR, *in situ* hybridization and IHC shows a strong correlation between TYRP1 transcript—but not the protein—level of expression not only with DMFS and OS but also with Breslow thickness and Clark level at the corresponding primaries. In contrast, a very good correlation between the TYRP1 transcript and the corresponding protein was found in cultured cells (Journé et al., 2009, 2010). This strongly suggests some post-translational modifications in the sens of possible alterations in the protein processing, stability, trafficking or maturation in the metastatic tissue *in vivo* but not in *in vitro* cultured cells, thus explaining its low detection by the antibodies used in IHC in the above studies.

Another on going work based on gene knockdown experiments supports different roles for TYRP1 in morphology, proliferation and invasion of human melanoma cultured cells (Mogha et al., 2010).

2. Conclusions

There is now increasing converging evidences as to the putative roles of TYRP1/gp75 in melanoma progression. Along this process and with the concomitant increase in tumor load, it is not surprising to have more and more cells undergoing cycles of differentiation/proliferation. As a consequence and due to its relative abundance within the melanocyte as part of the pigmentary machinery, it is quite possible to observe TYRP1 expression emerging. If true, the discrepancy between tissue TYRP1 transcript versus protein levels should stimulate efforts to much further investigate the exact role of Tyrp1/gp75 at least in malignant melanocytes.

REFERENCES

Alaluf, S., Barrett, K., Blount, M., Carter, N., 2003. Ethnic variation in tyrosinase and TYRP1 expression in photoexposed and photoprotected human skin. Pigm. Cell Res. 16 (1), 35–42.

Aroca, P., Solano, F., Garcia-Borrón, J.-C., Lozano, J.A., 1991. Specificity of dopachrome tautomerase and inhibition by carboxylated indoles. Considerations on the enzyme active site. Biochem. J. 277 (2), 393–397.

Bolander, A., Agnarsdóttir, M., Strömberg, S., Ponten, F., Hesselius, P., Uhlen, M., Bergqvist, M., 2008. The protein expression of TRP-1 and galectin-1 in cutaneous malignant melanomas. Cancer Genomics Proteomics 5 (6), 293–300.

Boissy, R.E., Zhao, H., Oetting, W.S., Austin, L.M., Wildenberg, S.C., Boissy, Y.L., Zhao, Y., Sturm, R.A., Hearing, V.J., King, R.A., Nordlund, J.J., 1996. Mutation in and lack of expression of tyrosinase-related protein-1 (TRP-1) in melanocytes from an individual with brown oculocutaneous albinism: a new subtype of albinism classified as "OCA3. Am. J. Hum. Genet. 58 (6), 1145–1156.

Box, N.F., Wyeth, J.R., Mayne, C.J., O'Gorman, L.E., Martin, N.G., Sturm, R.A., 1998. Complete sequence and polymorphism study of the human TYRP1 gene encoding tyrosinase-related protein. Mamm. Genome 9, 50–53.

Cheli, Y., Ohanna, M., Ballotti, R., Bertolotto, C., 2010. Fifteen-year quest for microphthalmia-associated transcription factor target genes. Pigm. Cell Melanoma Res. 23, 27–40.

Chen, H., Salopek, T.G., Jimbow, K., 2001. The role of phosphoinositide 3-kinase in the sorting and transport of newly synthesized tyrosinase related protein-1 (TRP1). J. Investig. Dermatol. Symp. Proc. 6 (1), 105–114.

Chiang, P.W., Fulton, A.B., Spector, E., Hisama, F.M., 2008. Synergistic interaction of the OCA2 and OCA3 genes in a family. Am. J. Med. Genet. A. 146A (18), 2427–2430.

del Marmol, V., Beermann, F., 1996. Tyrosinase and related proteins in mammalian pigmentation. FEBS Lett. 381, 165–168.

Duffy, D.L., Zhao, Z.Z., Sturm, R.A., Hayward, N.K., Martin, N.G., Montgomery, G.W., 2010. Multiple pigmentation gene polymorphisms account for a substantial proportion of risk of cutaneous malignant melanoma. J. Invest. Dermatol. 130 (2), 520–528.

Fang, D., Setaluri, V., 1999. Role of microphthalmia transcription factor in regulation of melanocyte differentiation marker TRP-1. Biochem. Bioph. Res. Co 256 (3), 657–663.

Fang, D., Hallman, J., Sangha, N., Kute, T.E., Hammarback, J.A., White, W.L., Setaluri, V., 2001. Expression of microtubule-associated protein 2 in benign and malignant melanocytes: implications for differentiation and progression of cutaneous melanoma. Am. J. Pathol. 158, 2107–2115.

Fang, D., Tsuji, Y., Setaluri, V., 2002. Selective down-regulation of tyrosinase family gene TYRP1 by inhibition of the activity of melanocyte transcription factor, MITF. Nucleic Acids Res. 30 (14), 3096–3106.

Galibert, M.D., Yavuzer, U., Dexter, T.J., Goding, C.R., 1999. Pax3 and regulation of the melanocyte-specific tyrosinase-related protein-1 promoter. J. Biol. Chem. 274 (38), 26894–26900.

Gomez, P.F., Luo, D., Hirosaki, K., Shinoda, K., Yamashita, T., Suzuki, J., Otsu, K., Ishikawa, K., Jimbow, K., 2001. Identification of rab7 as a melanosome-associated protein involved in the intracellular transport of tyrosinase-related protein 1. J. Invest. Dermatol. 117, 81–90.

Guevara-Patiño, J.A., Engelhorn, M.E., Turk, M.J., Liu, C., Duan, F., Rizzuto, R., Cohen, A.D., Merghoub, T., Wolchok, J.D., Houghton, A.N., 2006. Optimization of a self antigen for presentation of multiple epitopes in cancer immunity. J. Clin. Invest. 116 (5), 1382–1390.

Gudbjartsson, D.F., Sulem, P., Stacey, S.N., Goldstein, A.M., Rafnar, T., Sigurgeirsson, B., Benediktsdottir, K.R., Thorisdottir, K., Ragnarsson, R., Sveinsdottir, S.G., Magnusson, V., Lindblom, A., Kostulas, K., Botella-Estrada, R., Soriano, V., Juberías, P., Grasa, M., Saez, B., Andres, R., Scherer, D., Rudnai, P., Gurzau, E., Koppova, K., Kiemeney, L.A., Jakobsdottir, M., Steinberg, S., Helgason, A.,

Gretarsdottir, S., Tucker, M.A., Mayordomo, J.I., Nagore, E., Kumar, R., Hansson, J., Olafsson, J.H., Gulcher, J., Kong, A., Thorsteinsdottir, U., Stefansson, K., 2008. ASIP and TYR pigmentation variants associate with cutaneous melanoma and basal cell carcinoma. Nat. Genet. 40 (7), 886–891.

Halaban, R., Moellmann, G., 1990. Murine and human b locus pigmentation genes encode a glycoprotein (gp75) with catalase activity. P. Natl. Acad. Sci. U.S.A. 87, 4809–4813.

Hara, I., Takechi, Y., Houghton, A.N., 1995. Implicating a role for immune recognition of self in tumor rejection: passive immunization against the brown locus protein. J. Exp. Med. 182 (5), 1609–1614.

Hirschowitz, E.A., Leonard, S., Song, W., Ferris, B., Leopold, P.L., Lewis, J.J., Bowne, W.B., Wang, S., Houghton, A.N., Crystal, R.G., 1998. Adenovirus-mediated expression of melanoma antigen gp75 as immunotherapy for metastatic melanoma. Gene Ther. 5 (7), 975–983.

Jackson, I.J., 1988. A cDNA encoding tyrosinase-related protein maps to the brown locus in mouse. P. Natl. Acad. Sci. U.S.A. 85, 4392–4396.

Jimbow, K., Gomez, P.F., Toyofuku, K., Chang, D., Miura, S., Tsujiya, H., Park, J.S., 1997. Biological role of tyrosinase related protein and its biosynthesis and transport from TGN to stage I melanosome, late endosome, through gene transfection study. Pigm. Cell Res. 10 (4), 206–213.

Jimbow, K., Chen, H., Park, J.-S., Thomas, P.D., 2001. Increased sensitivity of melanocytes to oxidative stress and abnormal expression of tyrosinase-related protein in vitiligo. Brit. J. Dermatol. 144 (1), 55–65.

Jiménez-Cervantes, C., Solano, F., Lozano, J.A., García-Borrón, J.C., 1994. The DHICA oxidase activity of the melanosomal tyrosinases LEMT and HEMT. Pigm. Cell Res. 7 (5), 298–304.

Journé, F., Morandini, R., Salès, F., Awada, A., Ghanem, G., 2009. Gene expression profiling to improve prognosis of cutaneous melanoma. Pigm. Cell Melanoma Res. 22 (5), 670 (OP04).

Journé, F., Id Boufker, H., Van Kempen, L., Galibert, M.D., Wiedig, M., Theunis, A., Salès, F., Nonclercq, D., Frau, A., Laurent, G., Awada, A., Ghanem, G., 2010. Gene expression profiling and RTqPCR validation in 133 melanoma metastases identify TYRP1 mRNA level as a new prognosis marker in high risk melanoma. Pigm. Cell Melanoma Res. 23 (4), e24.

Kobayashi, T., Urabe, K., Winder, A., Tsukamoto, K., Brewington, T., Imokawa, G., Potterf, B., Hearing, V.J., 1994a. DHICA oxidase activity of TRP1 and interactions with other melanogenic enzymes. Pigm. Cell Res. 7 (4), 227–234.

Kobayashi, T., Urabe, K., Winder, A., Jiménez-Cervantes, C., Imokawa, G., Brewington, T., Solano, F., García-Borrón, J.C., Hearing, V.J., 1994b. Tyrosinase related protein 1 (TRP1) functions as a DHICA oxidase in melanin biosynthesis. EMBO J. 13 (24), 5818–5825.

Kobayashi, T., Imokawa, G., Bennett, D.C., Hearing, V.J., 1998. Tyrosinase stabilization by Tyrp1 (the brown locus protein). J. Biol. Chem. 273, 31801–31805.

Kobayashi, T., Hearing, V.J., 2007. Direct interaction of tyrosinase with Tyrp1 to form heterodimeric complexes in vivo. J. Cell Sci. 120 (Pt 24), 4261–4268.

Leachman, S.A., Carucci, J., Kohlmann, W., Banks, K.C., Asgari, M.M., Bergman, W., Bianchi-Scarrà, G., Brentnall, T., Bressac-de Paillerets, B., Bruno, W., Curiel-Lewandrowski, C., de Snoo, F.A., Debniak, T., Demierre, M.F., Elder, D., Goldstein, A.M., Grant-Kels, J., Halpern, A.C., Ingvar, C., Kefford, R.F., Lang, J., MacKie, R.M., Mann, G.J., Mueller, K., Newton-Bishop, J., Olsson, H., Petersen, G.M., Puig, S., Rigel, D., Swetter, S.M., Tucker, M.A., Yakobson, E., Zitelli, J.A., Tsao, H., 2009. Selection criteria for genetic assessment of patients with familial melanoma. J. Am. Acad. Dermatol. 61 (4) 677.e1-14.

Liu, T.F., Kandala, G., Setaluri, V., 2001. PDZ-domain protein GIPC interacts with the cytoplasmic tail of melanosomal membrane protein gp75 (tyrosinase related protein-1). J. Biol. Chem. 276, 35768–35777.

Loftus, S.K., Larson, D.M., Baxter, L.L., Antonellis, A., Chen, Y., Wu, X., Jiang, Y., Bittner, M., Hammer III, J.A., Pavan, W.J., 2002. Mutation of melanosome protein RAB38 in chocolate mice. P. Natl. Acad. Sci. U.S.A. 99 (7), 4471–4476.

Luo, D., Chen, H., Jimbow, K., 1994. Cotransfection of genes encoding human tyrosinase and tyrosinase-related protein-1 prevents melanocyte death and enhances melanin pigmentation and gene expression of Lamp-1. Exp. Cell Res. 213 (1), 231–241.

Manga, P., Sato, K., Ye, L., Beermann, F., Lamoreux, M.L., Orlow, S.J., 2000. Mutational analysis of the Modulation of tyrosinase by tyrosinase-related proteins 1 and 2 in vitro. Pigm. Cell Res. 13 (5), 364–374 (11).

Manga, P., Sheyn, D., Yang, F., Sarangarajan, R., Boissy, R.E., 2006. A role for tyrosinase-related protein 1 in 4-tert-butylphenol-induced toxicity in melanocytes: implications for vitiligo. Am. J. Pathol. 169 (5), 1652–1662.

Mattes, J.M., Thomson, T.M., Old, L.J., Lloyd, K.O., 1983. A pigmentation associated, differentiation antigen of human melanoma defined by a precipitating antibody in human serum. Int. J. Cancer 32, 717–721.

Mogha, A., Primot, A., Debbache, J., Bennett, D., Ghanem, G., Dreno, B., Galiber, M.D., 2010. TYRP1 function in melanoma progression. Pigm. Cell Melanoma Res. 23 (4), e18.

Murisier, F., Beermann, F., 2006. Genetics of pigment cells: lessons from the tyrosinase gene family. Histol. Histopathol 21, 567–578.

Naftzger, C., Takechi, Y., Kohda, H., Hara, I., Vijayasaradhi, S., Houghton, A.N., 1996. Immune response to a differentiation antigen induced by altered antigen: a study of tumor rejection and autoimmunity. P. Natl. Acad. Sci. U.S.A. 93 (25), 14809–14814.

Nan, H., Kraft, P., Hunter, D.J., Han, J., 2009. Genetic variants in pigmentation genes, pigmentary phenotypes, and risk of skin cancer in Caucasians. Int. J. Cancer 125 (4), 909–917.

Newton, R.A., Cook, A.L., Roberts, D.W., Leonard, J.H., Sturm, R.A., 2007. Post-transcriptional regulation of melanin biosynthetic enzymes by cAMP and resveratrol in human melanocytes. J. Invest. Dermatol. 127 (9), 2216–2227.

Olivares, C., Solano, F., 2009. New insights into the active site structure and catalytic mechanism of tyrosinase and its related proteins. Pigm. Cell Melanoma Res. 22 (6), 750–760.

Orlow, S.J., Silvers, W.K., Zhou, B.-K., Mintz, B., 1998. Comparative decreases in tyrosinase, TRP-1, TRP-2, and Pmel 17/Silver antigenic proteins from melanotic to amelanotic stages of syngeneic mouse cutaneous melanomas and metastases. Cancer Res. 58, 1521–1523.

Ozeki, H., Ito, S., Wakamatsu, K., Hirobe, T., 1995. Chemical characterization of hair melanins in various coat-color mutants of mice. J. Invest. Dermatol. 105, 361–366.

Patel, D., Lahiji, A., Melchior, M., Ng, S., Bassi, R., Wu, Y., Bohlen, P., Hicklin, D., Kang, X., 2005. Characterization of novel human monoclonal antibodies against melanoma associated antigen gp75/TRP-1. P. Am. Assoc. Canc. Res. 46 Abstract #701.

Patel, D., Balderes, P., Lahiji, A., Melchior, M., Ng, S., Bassi, B., Wu, Y., Griffith, H., Jimenez, X., Ludwig, D.L., Hicklin, D.J., Kang, X., 2007. Generation and characterization of a therapeutic human antibody to melanoma antigen TYRP1. Hum. Antibodies 16 (3–4), 127–136.

Patel, D., Bassi, R., Hooper, A.T., Sun, H., Huber, J., Hicklin, D.J., Kang, X., 2008. Enhanced Suppression of melanoma tumor growth and Metastasis by Combined therapy with Anti-VEGF receptor and Anti-TYRP-1/gp75 monoclonal antibodies. Anticancer Res. 28, 2679–2686.

Raper, H.S., 1927. The tyrosinase-tyrosine Reaction: production from Tyrosine of 5: 6-Dihydroxyindole and 5: 6-

Dihydroxyindole-2-carboxylic acid-the Precursors of melanin. Biochem. J. 21 (1), 89–96.
Rooryck, C., Roudaut, C., Robine, E., Müsebeck, J., Arveiler, B., 2006. Oculocutaneous albinism with TYRP1 gene mutations in a Caucasian patient. Pigm. Cell Res. 19 (3), 23–242.
Saenger, Y.M., Li, Y., Chiou, K.C., Chan, B., Rizzuto, G., Terzulli, S.L., Merghoub, T., Houghton, A.N., Wolchok, J.D., 2008. Improved tumor immunity using anti-tyrosinase related Protein-1 monoclonal antibody Combined with DNA vaccines in murine melanoma. Cancer Res. 68 (23), 9884–9891.
Sarangarajan, R., Zhao, Y., Babcock, G., Cornelius, J., Lamoreux, M.L., Boissy, R.E., 2000. Mutant alleles at the brown locus encoding tyrosinase-related protein-1 (TRP-1) affect proliferation of mouse melanocytes in culture. Pigm. Cell Res. 13 (5), 337–344.
Soltani, M.H., Pichardo, R., Song, Z., Sangha, N., Camacho, F., Satyamoorthy, K., Sangueza, O.P., Setaluri, V., 2005. Microtubule-Associated protein 2, a marker of neuronal differentiation, induces Mitotic Defects, Inhibits growth of melanoma cells, and predicts metastatic potential of cutaneous melanoma. Am. J. Pathol. 166, 1841–1850.
Srinivasan, R., Houghton, A.N., Wolchok, J.D., 2002. Induction of autoantibodies against tyrosinase-related proteins following DNA vaccination: unexpected reactivity to a protein paralogue. Cancer Immun. 2, 8.
Tai, T., Eisinger, M., Ogata, S., Lloyd, K.O., 1983. Glycoproteins as differentiation markers in human malignant melanoma and melanocytes. Cancer Res. 43, 2773.
Takechi, Y., Hara, I., Naftzger, C., Xu, Y., Houghton, A.N., 1996. A melanosomal membrane protein is a cell surface target for melanoma therapy. Clin. Cancer Res. 2, 1837–1842.
Tamura, K., Ohbayashi, N., Maruta, Y., Kanno, E., Itoh, T., Fukuda, M., 2009. Varp is a novel Rab32/38-binding protein that regulates Tyrp1 trafficking in melanocytes. Mol. Biol. Cell 20, 2900–2908.
Thomson, T.M., Mattes, M.J., Roux, L., Old, L.J., Lloyd, K.O., 1985. Pigmentation-associated glycoprotein of human melanomas and melanocytes: definition with a mouse monoclonal antibody. J. Invest. Dermatol. 85 (2), 169–174.
Truschel, S.T., Simoes, S., Setty, S.R.G., Harper, D.C., Tenza, D., Thomas, P.C., Herman, K.E., Sackett, S.D., Cowan, D.C., Theos, A.C., Raposo, G., Marks, M.S., 2009. ESCRT-I function is required for Tyrp1 transport from early endosomes to the melanosome limiting membrane. Traffic 10 (9), 1318–1336.
Vachtenheim, J., Novotna, H., Ghanem, G., 2001. Transcriptional repression of the microphthalmia gene in melanoma cells correlates with the unresponsiveness of target genes to ectopic microphthalmia-associated transcription factor. J. Invest. Dermatol. 117, 1505–1511.
Vijayasaradhi, S., Bouchard, B., Houghton, A.N., 1990. The melanoma antigen gp75 is the human homolog of the mouse b (brown) locus gene product. J. Exp. Med. 171, 1375–1380.
Wang, R.F., Robbins, P.F., Kawakami, Y., Kang, X.Q., Rosenberg, S.A., 1995. Identification of a gene encoding a melanoma tumor antigen recognized by HLA-A31-restricted tumor-infiltrating lymphocytes. J. Exp. Med. 181 (2), 799–804.
Wasmeier, C., Romao, M., Plowright, L., Bennett, D.C., Raposo, G., Seabra, M.C., 2006. Rab38 and Rab32 control post-Golgi trafficking of melanogenic enzymes. J. Cell Biol. 175 (2), 271–281.
Weber, L.W., Bowne, W.B., Wolchok, J.D., Srinivasan, R., Qin, J., Moroi, Y., Clynes, R., Song, P., Lewis, J.J., Houghton, A.N., 1998. Tumor immunity and autoimmunity induced by immunization with Homologueous DNA. J. Clin. Invest. 102, 1258–1264.
Welt, S., Mattes, M.J., Grando, R., Thomson, T.M., Leonard, R.W., Zanzonico, P.B., Bigler, R.E., Yeh, S., Oettgen, H.F., Old, L.J., 1987. Monoclonal antibody to an intracellular antigen images human melanoma transplants in nu/nu mice. P. Natl. Acad. Sci. U.S.A. 84, 4200–4204.
Xu, Y., Setaluri, V., Takechi, Y., Houghton, A.N., 1997. Sorting and secretion of a melanosome membrane protein, gp75/TRP1. J. Invest. Dermatol. 109, 788–795.
Zhang, S., Huang, W., 2008. Dendritic cell based genetic immunization stimulates potent tumor protection dependent on CD8 CTL cells in the absence of autoimmunity. J. Cancer Res. Clin. 134 (9), 987–994.
Zhao, H., Eling, D.J., Medrano, E.E., Boissy, R.E., 1996. Retroviral infection with human tyrosinase-related protein-1 (TRP-1) cDNA upregulates tyrosinase activity and melanin synthesis in a TRP-1-deficient melanoma cell line. J. Invest. Dermatol. 106 (4), 744–752.
Zheng, H., Li, X., Zhou, R., Li, L., Guo, X., Kang, J., Li, D., 2010. Bioinformatics analysis of tyrosinase-related protein 1 gene (TYRP1) from different species. Front. Agric. China 4 (1), 109–115.