Molecular characteristics of uveal melanoma and intraocular tumors (Review)

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Abstract. Malignant melanomas within the eye present different types of metabolic and metastatic behavior. Uveal melanoma (UM) affects a quarter of a million individuals in the USA; however, the molecular pathogenesis is not well understood. Although UV radiation is a risk factor in cutaneous melanomas, it is not crucial for UM progression. Apart from chromosomal abnormalities, numerous major tumorigenic signaling pathways, including the PI3K/Akt, MAPK/ERK, Ras-association domain family 1 isoform A and Yes-associated protein/transcriptional co-activator with PDZ-binding motif signaling pathways, are associated with intraocular tumors. The present review describes the current insights regarding these signaling pathways that regulate the cell cycle and apoptosis, and could be used as potential targets for the treatment of UMs.

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1. Introduction

Uveal melanoma (UM) is the most common primary malignant tumor of the eye in adults (1). Uveal, as well as cutaneous, melanomas have origins from the same precursor cell, the melanocyte, which migrates from the neural crest during embryonic development (2). UM represents 3-5% of all melanomas and it arises from proliferating atypical melanocytes situated in the choroid (85-90%), the ciliary body (5-8%) and the iris (5-8%) (1). Primary tumor location has an effect on UM progression: Melanoma originating from melanocytes in the iris is usually associated with good prognosis, while choroidal and ciliary ones have a poor prognosis, and in ≤50% of all cases lead to metastatic disease (3), which most commonly occurs in the liver (60.5%), lung (24.4%), skin (11%) and bone (8.4%) (1,4).

UM has a median diagnostic age of 62 years, with a peak between 70 and 79 years (5,6). It has been recorded to have 30% higher incidence in males; however, to the best of our knowledge, there is no known reason for this (7). Based on the Surveillance, Epidemiology, and End Results database (1973-2009), cases of UMs affect 5.1 in every million individuals (5). In Europe, the incidence varies between 2 and 8 individuals per million based on latitude according to the European Cancer Registry (1983-1994) (8). Additionally, UMs are less prevalent in Asian and black populations (9).

Similarly to other melanomas, the most common risk factors of UM are fair skin, light eyes, ocular melanocytosis, dysplastic nevus syndrome and multiple mutations (10-12). Exposure to UV radiation is a major risk factor for the development of cutaneous melanoma; however, there is little evidence regarding its role in UM progression (13). Since UVA is mainly filtered by the cornea and lens, while UVB and UVC do not reach the choroid, 'it is unlikely' that UV radiation exposure is responsible for choroidal melanoma (14,15).

The primary tumor is often difficult to diagnose as a third of the cases are asymptomatic (6). In most cases, UM

is manifested through blurred vision and a variety of other symptoms, such as elevated intraocular pressure, which causes glaucoma (16). UM is frequently misdiagnosed as glaucoma, since the latter is one of the potential side effects of the tumor (16). The median life expectancy after metastatic growth is 13.4 months with an 8% survival rate after 2 years (4).

Gene expression profiling is currently used to classify UMs into two distinct types depending on their ability to metastasize. Class 1 are tumors with a 1% chance of spreading, while class 2 are tumors that have a 25.9% chance of forming secondary tumors (17). Little is known regarding its molecular pathogenesis, and it has been considered that a variety of epigenetic alterations occur in the melanocyte to UM pathway (18). p53 and the retinoblastoma (Rb) signaling pathway are commonly inhibited, whereas the PI3K/Akt signaling pathway in mostly activated (18). The present review discusses these signaling pathways that regulate cell death and the cell cycle in UM. Increased understanding of these pathways may lead to the identification of the genetic profile of UM, enable the design of a personalized targeted therapy for the patient and, finally, an improved prognosis of patients with UM.

2. Chromosomal origin of UM

UM is often characterized by multiple chromosomal aberrations. Abnormalities on chromosomes 1, 3, 6 and 8 have been observed in 17-61% of UM cases (18). Additionally, these have been demonstrated to affect the prognosis and development of the tumor (19). The most common chromosomal aberrations result in loss of chromosome 3 and 6q, or in the gain of 6p and 8q (19). Monosomy 3 is observed in 50% of all tumors, 65% of UMs and in >70% of metastasizing UMs (20). Chromosome 3 loss results in a >50% reduction in the 5-year survival rate of patients (19). By contrast, patients with an intact pair of chromosome 3 have a 5-year survival rate of 90%, which is reduced to 37% by the loss of one sister chromatid (20). BRCA1 associated protein 1 (BAP1) is one of the genes that is mutated in 47% of all Ums, and, due to its location on chromosome 3, it is important for the understanding of the disease development (21). This also explains why monosomy 3 is associated with a poor prognosis. Furthermore, BAP1 is a single copy gene, which often results in inactivating mutations (21). In UM, this results in an earlier onset at the age of 30 to 59 years (22). Additionally, mutations in BAP1 have been associated with an 11% higher risk of secondary malignancies (22). Other genes located on chromosome 3 encode PI3K and Ras-association domain family 1 isoform A (RASSF1A), both of which are associated with essential molecular pathways that are mutated in cancer (23,24).

Other aberrations, including gain of chromosome 8, loss of chromosome 1 or polysomy 8q, have been associated with a reduced survival due to various factors, such as exposure to sun light, oculodermal melanocytosis and dysplastic nevi (25,26). Some of the genes located on chromosome 1 are associated with essential molecular pathways by encoding PI3K and Akt, or tumor suppressor genes (TSGs), such as centromere protein S (27). On the other hand, gain of chromosome 6p has been associated with good prognosis, despite the abundance of oncogenes (28).

One of the most common chromosomal abnormalities in UM is rearrangement of chromosome 8q. Copy number variations have been observed in 79% of UM cases (26). In patients with a normal 8q number the 5-year survival rate is 93%; however, with the increase of copy numbers, this rate is reduced to 67 and then 29% (20).

It has been noted that there are two distinct developmental pathways in UM. Class one exhibits disomy 3 with gain of chromosome 6p, while class 2 typically exhibits monosomy 3 and a high metastatic propensity (29,30). These chromosomal aberrations are present at early stages, while increased aneuploidy and changes in chromosome 8 are considered to be associated with later stages (31). While this two-class model is relatively simplistic, it provides a good basic understanding of the main chromosomal aberrations and their consequential effects.

3. Cell death regulation

One of the hallmarks of cancer is the ability of cells to evade death signals and proliferate indefinitely (32). Therefore, the regulation of the cell cycle and the induction of self-mediated cell death, also known as apoptosis, is vital.

The extrinsic apoptotic signaling pathway is activated when a death ligand binds to a death receptor on the cell membrane. These receptors have an intracellular death domain that recruits adapter proteins, which results in the formation of a binding site known as death-inducing signaling complex (DISC) (33). DISC assembles and activates pro-caspase-8, which initiates apoptosis by cleaving other caspases (34). Once activated, caspase 3 cleaves the caspase-activated deoxyribonuclease, which begins the process of DNA degradation (35). Finally, downstream caspases induce cleavage of protein kinases and proteins, and break down the cytoskeleton disturbing signaling pathways, which results in the typical morphological alterations of apoptosis (36).

The mitochondrial intrinsic pathway is initiated within the cell due to internal stimuli, such as genetic damage, hypoxia and oxidative stress (37). This results in the release of pro-apoptotic molecules, apoptosis inducing factor mitochondria associated 1, second mitochondria-derived activator of caspase, diablo IAP-binding mitochondrial protein, HtrA serine peptidase 2 and cytochrome *c*, which initiate apoptosis (38). Subsequently, cytochrome *c* and Apaf-1 assemble the apoptosome which activates caspase-9 (38). Alongside caspase-9 activation, caspase-3 is activated, leading to the same steps as the aforementioned extrinsic pathway (39). The Bcl-2 family proteins, which are directly controlled by p53, determine the cell fate through the balance of pro- and anti-apoptotic molecules (38).

The molecular and genetic makeup of UMs is considered to be more complicated than the aforementioned mutations. Therefore, the present review will explore the potential role of multiple molecular pathways and their role in UM development and pathogenesis.

4. G protein subunit αq and G protein subunit α11

Despite the chromosome abnormalities, most UMs are considered to be caused by point mutations in G protein α subunits, specifically in G protein subunit αq (GNAQ) and G protein subunit α11 (GNA11), regardless of tumor stage or chromosomal constellation (40). These mutations have similar effects

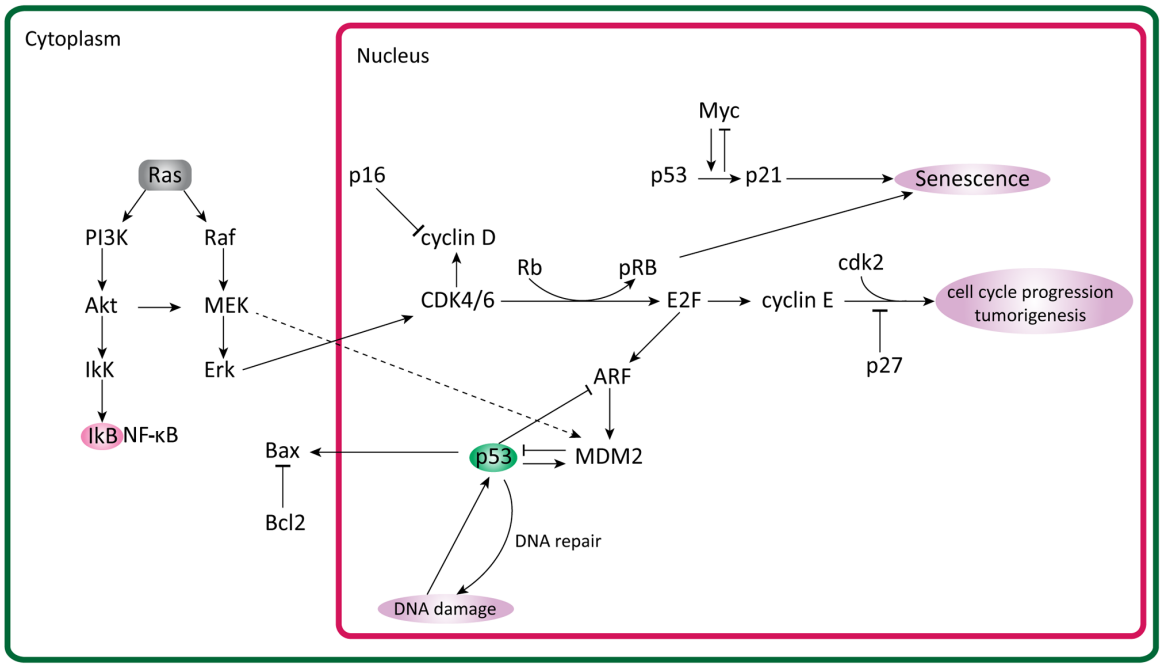

Figure 1. Outline of the key molecular signaling pathways affected in UM discussed in the present review article. The present review explored the typical UM abnormalities starting from the cytoplasm and moving to the nucleus. Firstly, RAS regulates the PI3K/Akt and Raf/MEK/ERK signaling pathways (left). Subsequently, the present review explored apoptosis involving p53/MDM2, and the regulation within the nucleus, including cyclins and cyclin-dependent kinases. MDM2, MDM2 proto-oncogene; UM, uveal melanoma.

as mutations in RAS, which are common in a number of other tumors (41). The G-α subunit is important due to its involvement in multiple essential cellular pathways, such as the MAPK (cell proliferation and apoptosis), PI3K-Akt (growth and homeostasis) and Hippo signaling pathways (42). GNAQ and GNA11 activate phospholipase C, which triggers a cascade of events resulting in the activation of protein kinase C (PKC). PKC then initiates a phosphorylation cascade, which activates Raf, MEK1/2 and ERK (43). This process results in the regulation of cell proliferation and survival (44). It has been hypothesized that these mutations are early events in the pathogenesis of UM and are necessary for tumor malignancy (45). On the other hand, mutant GNAQ and GNA11 are considered to be weak oncogenes and, therefore, cannot cause damage to melanocytes unless they are already deficient in the p53 and p16/CDK4/RB signaling pathways (46). Due to the importance of GNAQ and GNA11 in UM malignancy, the 5-oxo-ETE acid G-protein-coupled receptor 1 (GPCR) signaling pathway is a potential viable therapeutic target (42). The development of inhibitors for specific molecules, such as Gq/11 inhibitor YM-254890 and Arf6-inhibitor NAV-2729, is one of the main strategies that is currently being investigated (47,48). One such example is the inhibition of CysLT2R-L129Q, which is responsible for the constitutive activation of the Gq/11 signaling pathway in UM (47,49).

5. RAS interactions

The Ras superfamily consists of small GTPases that act as switches and modulate a vast array of cell functions by influencing signaling pathways. They are separated into six different groups of proteins, and are present in all cell types (50). One of the subfamilies, also referred to as RAS, consists of proteins that regulate cell proliferation. They have downstream effects on signaling pathways crucial to UM, such as the MAPK/ERK and PI3K/AKT/PTEN signaling pathways (51). In cancer, RAS is often mutated which affects a number of these pathways and makes them less sensitive to apoptosis triggers, thus increasing proliferation levels (Fig. 1) (52).

All three common RAS proteins in humans are highly conserved in the active regions and often undergo mutations in codons 12, 13 and 61 (53). The resulting point mutations lead to preferential binding to GTP over GDP, which in-turn leads to activation of proliferation pathways (54). Interestingly, RAS mutations are not usually associated with UM (55,56).

In general, RAS serve as activating proteins that remove GDP and allow GTP to bind its target (57). Ras-bound GTP goes on to activate Raf, which initiates the MAPK/ERK signaling pathway (58). In the case of PI3K, active Ras directly activates it without an intermediary protein (59).

6. PI3K/Akt/PTEN signaling pathway

The PI3K/Akt/PTEN is one of the main molecular pathways involved in cell proliferation. It is mutated in multiple types of cancer and is constitutively activated in most UMs (24). RAS directly activates PI3K, which then goes on to phosphorylate phosphatidylinositol 4,5-bisphosphate to produce phosphatidylinositol (3,4,5)-trisphosphate (PIP3) (60). PIP3 is dephosphorylated by PTEN to regulate PIP3 levels, which, when elevated, activates Akt. Subsequently, Akt goes on to phosphorylate a number of signaling pathways, such as the mTORC1, MDM2 proto-oncogene (MDM2), BAD and GTPase-activating protein signaling pathways (Fig. 1) (61).

Akt is an anti-apoptotic protein which serves an important role in cell survival and tumorigenesis (62). It is activated via

phosphorylation, becoming phospho-Akt which inactivates several proteins, including members of the Bcl-2 family (BAD protein) and caspase-9 (63). Phospho-Akt is involved in the protection from apoptosis, but also in other cancer development processes, such as blockage of anti-proliferative signaling, facilitation of cell replication and angiogenesis (63). Using immunohistochemical testing, it has been demonstrated that phosphorylation of Akt is associated with a poor prognosis (62).

PTEN downregulation has also been associated with various types of cancer, including breast cancer, thyroid cancer, kidney cancer, endometrial cancer, colorectal cancer and melanoma (64,65). In UMs, loss of heterozygosity of PTEN has been observed in 76% of tumors, with 11% being within the PTEN coding region (66). Loss of cytoplasmic PTEN in primary UM tumors was associated with shortened disease-free survival (67). Its decreased expression can also result in increased aneuploidy and reduced survival (45).

Overall, these findings suggest that the PI3K/Akt/PTEN signaling pathway serves a vital role in UM progression; however, more research needs to be performed to fully understand its role.

7. MAPK/ERK signaling pathway

The MAPK/ERK pathway is crucial for mediating cell-cycle progression. In multiple cancer types, it is constitutively activated, resulting in proliferation of neoplastic cells (68,69). It has also been identified to serve an important role in melanocytic neoplasia (70).

MAPK signaling, similar to the PI3K/Akt signaling pathway, begins with the activation of RAS, which then recruits RAF (68). RAFs are a group of kinases that transduce signals along the MAPK signaling pathway (68). There are three isoforms that are expressed in humans: A-Raf proto-oncogene serine/threonine kinase, BRAF and Raf-1 proto-oncogene serine/threonine kinase (cRAF) (71). cRAF was the first to be discovered and BRAF has been the most extensively studied due to its high mutation rate in various types of cancer (72,73).

Activation of BRAF by RAS results in the phosphorylation of kinases, such as MEK1/2 and ERK1/2, which induces a multitude of proliferative and survival processes (74) via the consequent activation of transcription factors, such as ETS transcription factor ELK1. In cutaneous melanomas, RAS and BRAF often undergo activating mutations (75). These also appear in benign melanocytic naevi and, alongside activation of the MAPK signaling pathway, constitute early events of melanogenesis (51,76,77). In UM, the MAPK signaling pathway is upregulated, which advocates for the presence of upstream mutations (78). It is also known that mutations in RAS and BRAF are uncommon in UM (79-81). Therefore, the constitutive activation is considered to be caused by mutations in the GNAQ family, which results in the upregulation of the pathways (82,83).

8. Yes-associated protein/transcriptional co-activator with PDZ-binding motif signaling pathway and its potential for treatment

Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ) modulate regulation of cell proliferation, migration and survival (84). They are, in turn, negatively regulated by the Hippo signaling pathway (85), which acts as a tumor suppressor to limit cell proliferation and organ size regulation (86). As previously mentioned, mutations in GNAQ and GNA11 are present in >80% of UM cases. This is essential as GPCRs activate F-actin, which targets YAP/TAZ and, therefore, could result in the upregulation of the pathway (87). When this happens, YAP is activated independently of the Hippo signaling pathway, resulting in greater resistance to contact inhibition of growth (88-90).

In contrast to MAPK-targeted therapy, which has no impact on the prognosis of patients with UM, YAP-targeted therapy is strongly associated with cancer metastasis (91) and shows promise as an ideal target (91-93). For example, focal adhesion kinase-targeted therapy reduces YAP levels and counteracts the effects of the GNAQ/GNA11 mutation (43). This may be effective in treating UMs that exhibit such mutations (94).

9. p53

p53 is one of the key apoptotic regulators, which induces cell cycle arrest and consequently apoptosis. A study by Liu and Zhou (95) explored the role of p53 in the development of UM. They observed that p53 expression and prognosis were negatively associated. The mortality rate increased with p53 expression. Additionally, inhibition of p53 has been associated with inhibited invasion in UM (95). Other studies have mentioned that mutations in the p53 gene are rare and, in fact, most causes of disruption in the pathways are due to upstream or downstream mutations (2,96,97). One such cause could be MDM2 upregulation, which is common in UMs (98). MDM2 regulates p53 and reduces its expression (98).

Protection from apoptosis is a major factor in the metastatic cascade of most types of cancer, including UM. p53 does not appear to have a significant impact on UM (99). However, a previous study demonstrated that multiplication of chromosome 8 and c-myc expression are associated, suggesting that c-myc could be used as a prognostic factor (11). C-myc alone is involved in the regulation of cell proliferation and with p53-dependent mechanisms promotes apoptosis (100). On the other hand, Bcl-2, which is vital for the intrinsic apoptotic pathway, has been reported to be upregulated in most UMs (2,101). A strong inverse relationship has been observed between c-myc (nuclear and cytoplasmic) and Bcl-2, suggesting that the latter co-operates with c-myc to immortalize UM cells (79,101).

Brantley and Harbour (2) immunohistochemically analyzed the p53 and retinoblastoma protein (pRb) pathways and found that, in UM cases, most alterations are due to mutations in other proteins.

10. CDK and cyclin kinase inhibitors

A fine balance between cyclin kinase inhibitors (CDKs) and CKIs is required for a normal cell cycle (102). If toxic chemicals, oxidative stress (reactive oxygen species), ionizing radiation and other factors induce DNA damage, the cell must repair it and reenter the cell cycle (102). When the cell fails to repair the damage, it becomes senescent and the cell cycle is arrested in G1 phase (diploid DNA) or G2 phase (tetraploid

DNA content). Deregulation of the cell cycle, especially at the G2/M phase, leads the cell to a more cancerous fate (103).

Cell cycle regulation is achieved through a family of serine/threonine kinase holoenzyme complexes consisting of regulatory cyclins that bind to and activate catalytic CDKs. The cyclins D1, D2, D3 and E are important for the G1-S cell cycle transition (104). Cyclin A is involved in DNA synthesis, S-phase completion and preparation for mitosis, while cyclins B1 and B2 control the onset, sequence of events and completion of mitosis (105). For example, the cyclin B1/CDK1 complex is a mitotic regulator that is responsible for the progression of the cell cycle (105).

On the other hand, cyclin-dependent kinase inhibitors (CDKIs) negatively regulate the kinase activity of the cyclin-CDK complexes (106). There are two known families of CDKIs: The cyclin dependent kinase inhibitor 2A (INK4) family, which includes p16/INK4A, p15/INK4B, p18/INK4C and p19 (p14)/INK4D, and the cardiac ISL1-interacting protein (CIP)/calcium and integrin binding 1 (KIP) family, which includes p21/CIP1, p27/KIP1 and p57/KIP2 (107-109).

Different CKIs have been observed to affect different CDKs. For example, p15 and p16 inhibit CDK4 and CDK6 respectively, while p21 and p27 act on G1 CDK cyclins and S-phase CDK2 complexes (110,111). Both p21 and p27 inhibit DNA replication but through different mechanisms. p21 binds to and promotes CDK1 and CDK2 with cyclin D activity, while, under certain conditions, inhibiting CDK4 and CDK6 with cyclin E activity (112). p27 promotes CDK2 cyclin E complex and CDK4/6 cyclin D complex formation (113,114).

In uveal and choroidal melanoma cell lines, the expression levels of p21 and p27 are downregulated resulting in suppressed p16-CDK interaction (110,115). This results in more CDK activity, leading to cyclin D and CDKs phosphorylating pRb, which goes on to release E2F transcription factor 1 (E2F1) (116). E2F1 is a transcriptional factor that leads to the expression of numerous necessary factors for G1 to S phase progression (117). pRb is another one of the vital molecules in the cell cycle regulation of uveal and choroidal cells. It is encoded by the Rb gene and serves an important role as a tumor suppressor (118). Deregulation and inactivation of p16 and/or overexpression of cyclin D leads to inactivation of pRb by cyclin-dependent phosphorylation (119,120). In most UMs, the Rb protein is constitutively hyperphosphorylated and functionally inactivated (120). This has been attributed to cyclin D1 upregulation in 65% of cases and has also been associated with larger tumor sizes and poor prognosis (63,76,121).

E2F transcription factors are key regulators of cell division and, among them, E2F1, E2F2 and E2F3a are potent activators of E2F-responsive genes, but their transcriptional activity is inhibited by binding to pRb (122,123). pRb is functionally inactivated at the G1-S transition by cyclin D-CDK4/CDK6 and cyclin E-CDK2-mediated phosphorylation, thus enabling E2F transcription factors to activate their target genes (124).

11. RASSF1A

RASSF1A is a TSG that is required for death receptor-dependent apoptosis (80) and can be found at the 3p21.3 locus. RASSF1A inhibits the accumulation of cyclin D1 protein without affecting its mRNA levels (81). This results in suppressed proliferation via negative regulation of the cell cycle progression at the G1/S phase transition (125). It has been reported that the endogenous inactivation of RASSF1A leads to a decrease of p27 which is a negative cell cycle regulator at the protein level (111,125). The depletion of this gene in RASSF1A mouse mutants has been noted as an early event in the senescence of uveal melanocytes and is considered to contribute to the malignancy of UM (125). RASSF1A is frequently hypermethylated in UM, which results in its downregulation (126). Additionally, in 83% of the cases in a study by Calipel *et al* (125), the RASSF1A promoter was methylated which suppressed gene expression. Overall, the downregulation of RASSF1A is most likely explained by the loss of heterozygosity typical for UM.

12. Conclusion

UM is the most common intraocular tumor in adults and is caused by multiple molecular abnormalities. The most frequent mutations in GNAQ and GNA11 are considered to be the main driving events in UM. Due to the involvement of GPCRs in multiple molecular signaling pathways, the present review explored the various downstream effects that such mutations could trigger. Additionally, the potential effects of chromosomal abnormalities, and how the loss or gain of specific regions could improve or worsen prognosis, were described. All this information allowed the authors to pinpoint potential therapeutic targets which could be used to successfully treat patients with UM. Based on the understanding of the aforementioned pathways and DNA expression profiles of UM, prediction models can be produced, and this could lead to improved prognosis for patients with UM.

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Competing interests

The authors declare that they have no competing interests.

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