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Review

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A BID-MTCH2 love story: Energizing mitochondria until apoptosis do them part?

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Summary

Mitochondrial carrier homolog 2 (MTCH2) is currently one of the most enigmatic mitochondrial proteins. MTCH2's ligand is the pro-apoptotic BID protein, and the love story between these two proteins involves the regulation of diverse cellular processes including apoptosis, energy metabolism, mitochondrial dynamics, and protein insertion into the mitochondrial outer membrane. This review offers an updated progress report of these two proteins, and describes our hypotheses regarding their joint mechanism of action.

Mitochondrial carrier homolog 2 (MTCH2) was first identified as a putative ORF obtained from CD34+ hematopoietic stem/progenitor cells and was named after the single conserved mitochondrial carrier domain it contains (Zhang et al 2000). MTCH2 is predicted to carry six transmembrane α-helical domains, and shares sequence homology to members of the mitochondrial carrier protein (mtCP) family (Robinson et al 2012; Ruprecht et al 2020). However, unlike the classical mtCP members which are localized to the mitochondrial inner membrane (mtIM), MTCH2 is localized to the mitochondrial outer membrane (mtOM).

My group was among the first laboratories to identify MTCH2. In the early 2000, our studies were focused on BCL-2 family members, major regulators of mitochondrial apoptosis (Gross et al 1999a; Czabotar et al 2023). At that time the function of BCL-2 family members was largely unknown (actually this is true until today), and our studies focused on the pro-apoptotic BID protein. As a young postdoc in the laboratory of the late *Stanly Korsmeyer*, we were among the first three labs to demonstrate that BID connects the extrinsic and the intrinsic pathways of apoptosis (Gross et al 1999b; Li et al 1998; Luo et al 1998). In response to death receptor activation (i.e., Fas/TNFα), activated caspase-8 cleaves cytosolic full-length p22 BID (FL-BID) to generate truncated p15 tBID (Figure 1, right panel). This cleavage triggers tBID-mtOM-insertion and activation of its downstream

effectors pro-apoptotic BAX/BAK. Importantly, we, at the *Korsmeyer* laboratory, were the first to demonstrate that BID-deficient mice are resistant to Fas-induced hepatocellular apoptosis (Yin et al 1999).

Of note, it was also reported that FL-BID is cleaved by caspase-8 within a native complex on the mitochondrial membrane (Jalmar et al 2013; Schug et al 2011), arguing that FL-BID may play a role at the mitochondria prior to being cleaved (discussed further below). My group has previously reported of two functions for FL-BID. The first was that the non-cleavable BID^{D59A} mutant is a potent inducer of apoptosis in the DNA damage pathway (Sarig et al 2003). Several years later, the *Prehn* group published similar findings in neurons (Konig et al 2007). The second function was related to a non-apoptotic function in the response of cells to DNA damage. We found that FL-BID is phosphorylated by one of the most important DNA damage kinases, the ataxia telangiectasia-mutated kinase (ATM; (Kamer et al 2005; Zinkel et al 2005); Figure 1, middle panel). BID is the only reported BCL-2 family member to be phosphorylated by the ATM kinase, arguing that BID plays a pivotal role in the DNA damage response (DDR). What is special about BID? Why was it selected from all the BCL-2 family members to be phosphorylated by ATM? Is it due to its interaction with MTCH2?

These ATM phosphorylation sites in mouse BID are serines 61 and 78, whereas in human BID it is only serine 78. Strikingly, the *Korsmeyer* group and my group have independently found that this phosphorylation is critical for DNA damage-induced S-phase arrest and protection from apoptosis (Kamer et al 2005; Zinkel et al 2005). One of the interesting questions, that remains unsolved, is how does BID^{P} execute its S-phase arrest function. In 2007, the *Strasser* group published a paper in *Cell* in the "Matters Arising" section arguing that BID is dispensable to the DDR (Kaufmann et al 2007), but surprisingly did not check the involvement/effect/importance of BID phosphorylation to the DDR.

To assess whether ATM-mediated BID phosphorylation plays a role in the DDR *in vivo*, we generated a non-phosphorylatable $BID^{S61A/S78A}$ knock-in mouse, and succeed to demonstrate that these mice are hypersensitive to lethal doses of whole-body irradiation (Maryanovich et al 2012). In my opinion, these finding together with all the other findings reported in our paper, should have brought to an end the controversy regarding the importance of BID for the DDR, and thus should attract scientists to further explore the remaining open questions (Gross et al 2016). One of these open questions relates to another finding showing that in the $BID^{S61A/S78A}$ and $ATM^{-/-}$ cells, more BID is localized to mitochondria, arguing that BID phosphorylation may inhibit its mitochondrial localization (Maryanovich et al 2012). Since BID's interaction with MTCH2 most likely holds it at the mitochondria, ATM-mediated BID phosphorylation may inhibit BID-MTCH2 interaction, resulting in a change in cellular metabolism that aids the DDR process (discussed further below).

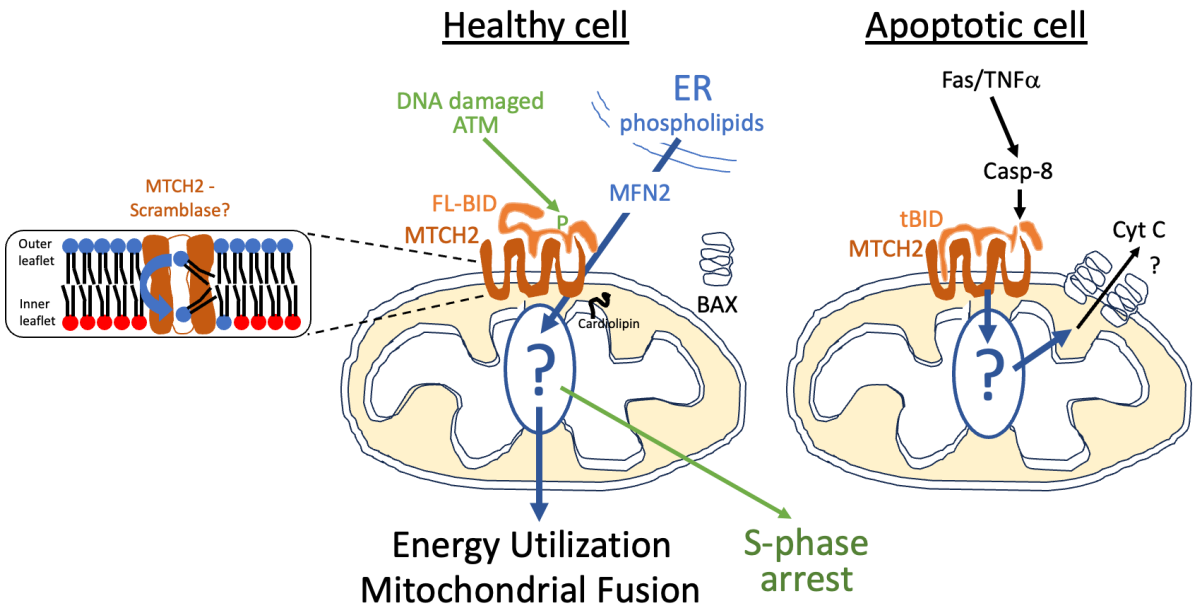

Figure 1. A BID-MTCH2 love story. Middle and left panels: MTCH2 is an integral mtOM protein. MTCH2, probably in cooperation with MFN2, is involved in phospholipid transfer from the ER to mitochondria (blue arrows), and may function as an insertase or as a scramblase (left panel) or both. Cardiolipin, a phospholipid in the mtIM, may also be regulated by the BID-MTCH2 pair. MTCH2's activity plays a critical regulatory role in mitochondria Energy Utilization and in Mitochondrial Fusion. We envision that cytosolic p22 FL-BID continuously interacts with MTCH2. In response to DNA damage, the ATM kinase phosphorylates FL-BID, which in turn regulates S-phase arrest and survival (green arrows). This phosphorylation affects FL-BID's mtOM localization, suggesting that this phosphorylation affects BID-MTCH2 interaction. Right panel: in response to Fas/TNFα-receptor activation, activated caspase-8 cleaves p22 FL-BID to generate p15 truncated tBID. This cleavage leads to tBID-membrane insertion, BAX activation and Cyt *c* release. We envision that BID cleavage also leads to a change in BID-MTCH2 interaction, resulting in a change in MTCH2 activity, which is likely involved in regulating Cyt *c* release.

tBID interaction with pro-apoptotic BAX/BAK leads to their conformational change and homo-oligomerization, resulting in the release of cytochrome *c* (Cyt *c*) from the intermembrane space (Gross et al 1999b; Li et al 1998; Luo et al 1998). The accepted notion in the field for many years is that BAX and BAK homo-oligomers form pores in the mtOM which enable Cyt *c* release (Cosentino et al 2017) (Figure 1, right panel), however, in my mind, this notion has not been fully proven. Release of Cyt *c*, which activates cytosolic caspase-9 as part of the apoptosome, is one of the most prominent events in apoptosis (actually one of the most prominent in cell biology; (Liu et al 1996)) and is believed to be a "point of no return". Thus, determining how exactly tBID triggers Cyt *c* release is one of the most important but still unresolved questions in cell biology. In an attempt to address this question, my group set up a cross-linking experiment back in 2000 to screen for the mitochondrial partner(s) of tBID and identified MTCH2 (Grinberg et al 2005).

We could later demonstrate that MTCH2 is critical for the mitochondrial targeting of tBID (perhaps a tBID mitochondrial receptor (Zaltsman et al 2010); Figure 1, middle panel) but it remained unclear whether MTCH2 has another function and whether tBID interaction affects/regulates this other function. It is now well-established that many, if not all, BCL-2 family members possess a non-apoptotic function (what we like to name "day jobs" (Gross et al 2017)). For example, pro-apoptotic BAX and BAK were found to possess a non-apoptotic function which involve mitochondrial pro-fusion activity (Hoppins et al 2011; Karbowski et al 2006). I actually believe that these "day jobs" were actually their primary jobs and later in evolution were recruited to their secondary "night jobs". Notably, the *Martinou* group reported that cardiolipin, a lipid unique to mitochondria localized to the mtIM, also functions as a tBID mitochondrial receptor (Raemy et al 2016).

One of my group's first strategies to determine MTCH2's day job was to generate a MTCH2 knockout mouse, which was not successful due to embryonic lethality at E7.5 (Zaltsman et al 2010). This finding indicates that MTCH2 is essential for embryonic development/survival. We have recently reported that MTCH2 is required to drive the exit of mouse embryonic stem cells (mESCs) from naïve pluripotency (The E5.5 stage in mice) (Bahat et al 2018). These studies were performed in cultured mESCs so it is not clear whether a defect in the exit from naïve pluripotency is the cause for embryonic lethality. Ten years earlier my group generated a MTCH2-conditional knockout mouse, and this mouse model turned out to be our most productive approach in the attempt to decipher MTCH2's exact function.

We first knocked out MTCH2 in the liver since, as described above, BID knockout mice are resistant to the lethal effect of Fas-Ab injection (the lethal effect is due to live damage) (Yin et al 1999). If MTCH2 acts as a down-stream effector of BID-induced apoptosis then MTCH2 liver-conditional knockout mice should be less sensitive to Fas-induced death, and that was indeed the case (Maryanovich et al 2015). However, the MTCH2 liver-conditional knockout mice were not resistant to Fas-induced death, as like the BID knockout mice, possibly due to the finding that cardiolipin can also act as a BID receptor or due to the fact that BID knockout mice are missing BID in the whole body (Raemy et al 2016).

In 2009, a genome-wide association study (GWAS) connecting the MTCH2 locus to obesity was published (Willer et al 2009). This study has identified single nucleotide polymorphisms (SNPs) that might modify MTCH2 expression/function/activity in obese people. Thus, we wanted to determine whether MTCH2 itself acts as a metabolic regulator and whether its deregulated expression leads to metabolic diseases, we knocked out MTCH2 in skeletal muscle. Strikingly, conditional knockout of skeletal muscle MTCH2 protected mice from diet-induced obesity (Buzaglo-Azriel et al 2016). The mice also showed an increase in energy expenditure (i.e., body temperature/heat), which was due to an increase in whole-body energy utilization.

As in the MTCH2 bone marrow-conditional knockout (Maryanovich et al 2015), deletion of skeletal muscle MTCH2 also increased mitochondrial respiration and mass. In addition, muscle MTCH2 deletion triggered conversion from glycolytic to oxidative fibers, increased capacity for endurance exercise, and increased heart function. Moreover, metabolic profiling of the muscle MTCH2 knockout mice revealed a preference for carbohydrate utilization and an increase in mitochondria and glycolytic flux in muscles (Buzaglo-Azriel et al 2016). In addition, the *Tsarfaty* group showed that MTCH2

transgenic mice develop fatty livers and kidneys, and high-fat diet-fed MTCH2 transgenic mice exhibit high blood glucose levels (Bar-Lev et al 2016). The connection of MTCH2 and obesity/lipid homeostasis was also reported by other groups (Fischer et al 2023; Kulyte et al 2011; Rottiers et al 2017). Moreover, metabolic diseases are not the only diseases that involve deregulation of MTCH2 expression, and MTCH2 was found to be involved in multiple forms of cancer (Arigoni et al 2013; Khan et al 2020; Leibowitz-Amit et al 2006; Li et al 2023b; Yuan et al 2021).

The findings described above suggest that MTCH2 is an important regulator of both apoptosis and energy utilization, perhaps even acting as a "double agent". In 2018, we reported that MTCH2 knockout also results in mitochondrial fragmentation suggesting that MTCH2 plays a role in mitochondrial fusion (Bahat et al 2018). Mitochondrial fusion and fission (i.e., mitochondrial dynamics) are intimately related to the metabolic state of the cell (Giacomello et al 2020; Picard et al 2022), and thus it is logical that MTCH2 will be involved in both. But how are these two programs related to apoptosis? The two proteins regulating mtOM fusion are mitofusin 1 and 2 (MFN1 and MFN2) which possess a GTPase/fusion activity. Notably, MFN2 also acts as a molecular tether between mitochondria and the endoplasmic reticulum (ER), which is independent of MFN2's GTPase activity (de Brito et al 2008). Interestingly, ectopic expression of MFN2 rescues the mitochondrial fragmentation in the MTCH2 knockout cells, and ectopic expression of MTCH2 rescues the mitochondrial fragmentation in the MFN2 knockout cells (Bahat et al 2018).

The fact that MTCH2 rescues the MFN2 knockout phenotype and that MTCH2 does not possess GTPase/fusion activity argues that MTCH2 is rescuing the non-GTPase activity of MFN2. Moreover, it argues that the non-GTPase activity of MFN2 is possibly the important activity for mitochondrial fusion and not its GTPase activity. In contrast to MFN2, MFN1 does not rescue the mitochondrial fragmentation in MTCH2 knockout cells, and MTCH2 does not rescue the mitochondrial fragmentation in MFN1 knockout cells (*Goldman et al, EMBO R accepted*). These results suggest that MTCH2 and MFN2 act in parallel to each other, whereas MFN1 acts downstream of them. In line with these findings, it was recently proposed that MTCH2 regulates mitochondrial fusion by modulating the pro-mitochondrial fusion lipid lysophosphatidic acid (LPA) (Labbe et al 2021). LPA synthesis is the first product of de-novo phospholipid biosynthesis. In this paper, the *Nunnari* group reported that MTCH2 monitors flux through the lipogenesis pathway and transmits this information to the mitochondrial fusion machinery to promote mitochondrial elongation, enhance energy production and cellular survival, under homeostatic and starvation conditions.

In our *Goldman et al* new paper, we report that MTCH2 cooperates with MFN2 and LPA synthesis at the ER to sustain mitochondrial fusion (Figure 1, middle panel). We found that MFN2 rescues the loss of MTCH2 partially independent of its GTPase activity and of its mitochondrial localization. Thus, MFN2's localization to the ER and its GTPase-independent activity rescue MTCH2. We also found that pharmacological inhibition of glycerol-phosphate acyl transferases (GPATs), the enzymes generating LPA at both mitochondria and ER, or silencing ER-resident GPATs, suppress MFN2's ability to rescue the mitochondrial fragmentation in MTCH2 knockout cells. These results suggest that MFN2's mitochondria-ER tethering activity plays a role in either phospholipid synthesis or phospholipid transfer between the ER and mitochondria. Importantly, loss of MTCH2 in combination with GPAT inhibition or loss of MTCH2 in combination with loss of MFN2,

impair stress-induced mitochondrial fusion. Thus, MTCH2 cooperates with ER-localized MFN2 and LPA synthesis to sustain mitochondrial fusion (*Goldman et al, EMBO R accepted*).

Thus, MTCH2 knockout affects three different cellular processes, and we believe that the common denominator is energy metabolism. Loss of MTCH2 in skeletal muscle results in a starvation-like phenotype due to an increase in whole-body nutrient utilization (Buzaglo-Azriel et al 2016). A starvation-like phenotype should lead to mitochondrial elongation and we indeed presented electron microscopy pictures of extensively long mitochondria in the MTCH2 knockout muscle tissues. However, in cultured cells, as described above, the picture was opposite: MTCH2 knockout results in mitochondrial fragmentation (Bahat et al 2018). As discussed above, perhaps the reason for this is a defect in phospholipid transfer from the ER to mitochondria that is important for mitochondrial fusion (Figure 1, middle panel). We still do not understand the reason for the differences in mitochondrial morphology between the mouse tissues and cultured cells, which will likely provide another clue to deciphering the MTCH2 puzzle.

Here is our current model regrading MTCH2's mechanism of action: based on the described above and our still unpublished data, we hypothesize that MTCH2 is a pivotal regulator of energy metabolism that is capable of sensing metabolic changes on the surface of mitochondria and transfer this information into the mitochondria. MTCH2 might bind a certain metabolite and "translate/decode" this information into the mitochondria by a certain activity. We envision a scenario similar to the one established for the serine/threonine kinase AMP-activated protein kinase (AMPK) complex that in response to low energy conditions (low ATP levels), AMPK phosphorylates specific enzymes and growth control nodes to increase ATP generation and decrease ATP consumption (Herzig et al 2018). Importantly, in the last decade multiple new targets of AMPK involved in mitochondrial homeostasis were discovered. One of the intriguing ones is the mitochondrial fission factor (MFF), a mtOM receptor for the pro-fission protein DRP1. Nonphosphorylatable and phosphomimetic alleles of the AMPK sites in MFF revealed that it is a key effector of AMPK-mediated mitochondrial fission (Toyama et al 2016). Since the MTCH2 knockout also results in low energy conditions, it is tempting to speculate that there is a functional connection between MTCH2 and AMPK.

MTCH2 looks like a mitochondrial carrier but is missing most of the classical structural properties to function as one. In addition, it is localized to the mtOM, which is thought to be permeable to all metabolites via the large voltage-dependent anion channels (VDACs). Thus, there does not seem to be a need for carriers in the mtOM. Thus, why does MTCH2 look like an MCP if it does not function like one? Notably, there are two additional non-classical MCPs that are localized to the mtOM: MTCH1, that shares ~50% identity with MTCH2 and possesses pro-apoptotic activity (Xu et al 1999), and SLC25A46, with mutants that cause optic atrophy spectrum disorder (Abrams et al 2015). Thus, there seems to be a growing sub-family of MCP-like proteins that are localized to the mtOM. Interestingly, SLC25A46 promotes mitochondrial fission, suggesting that members of this sub-family are involved in regulating both mitochondria dynamics and apoptosis.

Another important piece to the MTCH2 puzzle appeared last year when the *Voorhees* group reported in *Science* that MTCH2 is a protein insertase, which aids tail-anchored mitochondrial proteins to integrate into the mtOM (Guna et al 2022). This is a pivotal finding that sheds important light on MTCH2 and which answers a long-lasting question in mitochondria biology regarding the possible exitance of an mtOM insertase. However,

it is still unclear how this exciting data is exactly related to all the MTCH2 findings published in the past two decades. Interestingly, mutations in the central predicated "pore" region of MTCH2 led to either an increase or decrease in its insertase activity (Guna et al 2022). Notably, a recent paper proposed that insertases also function as scramblases, which flip phospholipids between the two leaflets of the membrane through their "pore" region (Li et al 2023a) (i.e., the phosphate group of the phospholipid is the negatively-charged polar head, which is hydrophilic and flipped through the watery pore region of the scramblase; Figure 1, left panel). In this paper they also showed in a well-established *in vitro* scramblase assay that MTCH2 possesses scramblase activity. Since several papers depicted above show an important involvement of MTCH2 in lipid metabolism, it seems logical that MTCH2 functions as both an insertase and a scramblase.

So how can we connect the MTCH2 metabolic/lipid/insertase/scramblase activity to its apoptotic activity? In all the many cross-linking studies my group performed in the past two decades, the MTCH2-BID pair was the most prominent, perhaps the only important interaction we revealed. Based on these findings and the published literature, we envision that FL-BID is constantly bound to MTCH2, and likely regulates MTCH2's activity. Several papers propose a connection between FL-BID/tBID and cardiolipin (Esposti et al 2003; Jalmar et al 2013; Kim et al 2004; Liu et al 2004; Raemy et al 2014; Van Mau et al 2005), and also between MTCH2 and cardiolipin (Raemy et al 2016). Cardiolipin is synthesized and localized to the mtIM, and phospholipid scramblase-3 can occasionally transport cardiolipin to the mtOM. It was previously shown that redistribution of cardiolipin serves as an 'eat-me' signal for the elimination of damaged mitochondria via mitophagy (Chu et al 2013). Based on the Cardiolipin-BID-MTCH2 triangle connection, it is tempting to speculate that BID and MTCH2 are somehow involved in this 'eat-me' or perhaps 'recognize-me' process.

Thus, if we continue with this line of reasoning, caspase-8-cleavge of BID leads to a conformation change in tBID, which exposes hydrophobic residues and enables its insertion into the mtOM (Figure 1, right panel). Perhaps MTCH2 uses its insertase activity to aid tBID's insertion. It is likely that BID's cleavage also affects its interaction with MTCH2. Interestingly, BID knockout mice are also less-sensitive to high fat-died-induced obesity (Yan et al 2022), as like the MTCH2 skeletal muscle-conditional knockout mice. One possible explanation for these results is that FL-BID acts as an activator of MTCH2; if this is the case, then loss of BID will lead to less MTCH2 activity, resulting in less sensitivity to high fat-died-induced obesity. Thus, if our assumptions are correct, then tBID may act in an opposite manner and inhibit MTCH2. Why an inhibitor? MTCH2 knockout results in an energetic crisis, and thus inhibition of MTCH2by tBID can possibly lead to low energy conditions that are more apoptosis-oriented.

Insertion of tBID into the mtOM creates a molecule that can potentially stay constantly bound to MTCH2. In contrast, the membrane localization of FL-BID solely depends on its interaction with MTCH2, and thus is reversible and may depend on post-translation modification/conformational changes that are regulated by external signals (e.g., ATM-mediated BID phosphorylation in response to DNA damage). Thus, FL-BID can be more of a sensor/sentinel as compared to tBID. In a similar manner, pro-apoptotic BAX, tBID's major effector, is known to come on and off of mitochondria under steady-state/healthy condition, and anti-apoptotic BCL-X_L is "in charge" of removing BAX from the membrane (Edlich et al 2011). Under stress conditions, the "BAX-removing activity"

of BCL-X_L is inhibited (by a BH3-only protein such as tBID), leading to BAX accumulation in the mtOM, its activation, and Cyt *c* release.

Thus, under stress/apoptotic conditions, FL-BID is cleaved to tBID, and mtOM-localized tBID activates BAX and BAK. Based on our findings, MTCH2 facilitates tBID's mitochondrial localization and its ability to activate BAX and BAK (Zaltsman et al 2010). Apoptosis is the most critical decision for cells during their lifetime and mitochondria are their energetic headquarters (perhaps brains), and thus tBID's "choice" to target mitochondria, from all organelles, and to interact with MTCH2, from all the mtOM proteins, most likely also involves a necessity to signal to mitochondria to start its metabolic/energetic reprogramming for apoptosis, which are likely involved in the release Cyt *c* (Figure 1, blue arrows in the right panel). Moreover, both BAX and BAK are regulators of mitochondrial fusion, a function that likely involves MTCH2's pro-fusion and energy-balancing activities. Thus, the tBID-MTCH2 embracement may trigger a multifunctional program, which enables the proper cellular transition from life to apoptosis.

Abbreviations

MTCH2	mitochondrial carrier homolog 2	mtIM	mitochondrial inner membrane
FL-BID	p22 full-length BID	mtOM	mitochondrial outer membrane
tBID	p15 truncated BID		

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