Another case for diet restriction: TAp73-expressing medulloblastomas are stunted by glutamine withdrawal

Marco Napoli and Elsa R. Flores

Department of Molecular Oncology, Cancer Biology and Evolution Program, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida 33612, USA

Medulloblastomas are among the most common malignant brain cancers in the pediatric population and consist of at least four distinct subgroups with unique molecular and genetic features and clinical outcomes. In this issue of *Genes & Development*, Niklison-Chirou and colleagues (pp. 1738–1753) identify the *p53* family member and *p73* isoform TAp73 as a crucial factor causing glutamine addiction in aggressive medulloblastomas. Their findings pave the way for the use of glutamine restriction as an adjuvant treatment for TAp73-expressing medulloblastomas.

Medulloblastomas (MBs) are malignant brain tumors arising in the posterior fossa and typically occur in children and young adults. The current therapeutic regimen (a combination of surgery, radiotherapy, and systemic chemotherapy) allows for an 85% 5-yr survival rate but results in significantly lower neurocognitive and neuroendocrine functions (Liu et al. 2017). Therefore, several efforts are being made to obtain more effective and less toxic treatments. A pivotal breakthrough came from large-scale genomic analyses indicating that MBs comprise at least four molecular subgroups (Wingless [WNT], Sonic hedgehog [SHH], group 3, and group 4), each characterized by specific genetic alterations and clinical outcomes (Northcott et al. 2011). WNT-associated MBs have the most favorable prognosis, possibly due to their secretion of WNT antagonists that impair the blood–brain barrier, making these MBs more susceptible to chemotherapy. On the other side of the spectrum are group 3 MBs, which are the most metastatic and deadly cases (Liu et al. 2017).

It has been proposed that the four molecular subgroups of MB could be classified further based on the presence of additional mutations. The best-investigated example is mutations in the tumor suppressor *TP53* gene. Indeed, the presence or absence of mutant p53 stratifies the SHH-MBs, but not the other MBs, in cases with poor and better prognosis, respectively (Zhukova et al. 2013). The prognostic value of *TP53* in MBs prompted researchers to evaluate whether the other members of the p53 family (p63 and p73) could also be prognostic in MBs. In particular, p73 was reported to be overexpressed in MB tumors and cell lines, indicating a possible prosurvival role for p73 in these tumors (Zitterbart et al. 2007). This is in agreement with observations using mouse models indicating that p73 is required for the embryonic development of the central nervous system (Yang et al. 2000) and the maintenance of neural stem cell niches in the adult brain (Pozniak et al. 2002).

To clarify which among the several isoforms of the *TP73* gene are expressed in MBs, Niklison-Chirou et al. (2017) analyzed RNA sequencing data from 240 human MBs, showing that TAp73α is the predominant *TP73* isoform in MBs and, importantly, that its levels are higher in aggressive MBs (group 3 and group 4) compared with either the other subgroups or normal cerebella. Remarkably, the investigators demonstrated that transient or stable down-regulation of *TPp73* impairs MB cell growth and causes profound metabolic alterations, including decreased mitochondrial respiration rates and glycolytic capacity. This correlates with reduced expression of several metabolism-related TAp73 target genes, in line with the important role of TAp73 in controlling numerous metabolic processes, such as mitochondrial oxidative phosphorylation, the pentose phosphate pathway, and autophagy (Napoli and Flores 2013, 2017). Importantly, the most crucial of these down-regulated target genes is *glutaminase 2* (*GLS-2*), which encodes for an enzyme hydrolyzing glutamine in glutamate that in turn will be used as a substrate for the TCA cycle and for the production of the antioxidant glutathione. Indeed, the overexpression of *GLS-2* in *TP73* knockdown MB cells is sufficient to rescue the metabolic defects due to *TP73* down-regulation. As a consequence of this dependency on GLS-2 activity, MB

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Corresponding author: elsa.flores@moffitt.org
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cells with high levels of TAp73 are more sensitive to glutamine starvation compared with MB cells with lower levels of TAp73. Notably, this glutamine addiction is maintained in vivo, as demonstrated in a xenograft model in which MB tumor growth is decreased in mice fed with a glutamine restriction diet. More importantly, this diet synergizes with cisplatin (a chemotherapeutic drug commonly used to treat MB patients) in counteracting MB tumor growth and extending survival of the treated mice. Taken together, these data provide exciting evidence for an alternative and less toxic treatment for MB patients.

However, this tumor-suppressive effect of glutamine starvation is not observed exclusively in MBs. Indeed, it has been shown previously to be an effective treatment in other cancers, including glioblastoma multiforme, liposarcoma, and breast cancer (Still and Yuneva 2017). This broad efficacy of glutamine restriction has led to the generation of glutaminase inhibitors whose activity is currently being evaluated in early phase clinical trials in combination with either chemotherapeutic drugs (e.g., paclitaxel), inhibitors of metabolic pathways (e.g., everolimus), or immunotherapeutic agents (e.g., nivolumab) (Still and Yuneva 2017). Therefore, the data reported by Niklison-Chirou et al. (2017) may have profound implications for the management of patients with not only TAp73-expressing MBs but also other cancers overexpressing this *TP73* isoform. To guarantee the successful translation of the investigators' crucial findings into the clinic, it is important to remember the lesson learned from clinical trials of targeted therapies: Selection of the subset of patients that can benefit from such therapy is essential. Therefore, the possible functional interactions between TAp73 and the genetic alterations commonly found in the different MB subgroups should be considered. In particular, given the important role of *TP53* status on prognosis of MB, and since mutant p53 proteins are known to bind and inhibit TAp73 (Walerych et al. 2012), is the *TP53* mutation status relevant for the effectiveness of glutamine restriction? Furthermore, even though TAp73 exerts distinctive functions with respect to its family members (Napoli and Flores 2016), cellular metabolism is a process regulated by the whole p53 family at multiple levels (Napoli and Flores 2017). So, can glutamine restriction be affected by the expression of the other members of the p53 family? While the investigators provide elegant in vivo data indicating the role of TAp73 in MBs, further addressing these points will be crucial for the success of a glutamine restriction diet as an adjuvant treatment for MBs, especially those expressing TAp73.

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