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Commentary

Looking for the needle in the haystack: Proteome-based identification of treatment targets in *NF2*-related nervous system tumors

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With an incidence rate of 7.86% per year, meningiomas are the most frequent tumors within the central nervous system (CNS) in the US. The majority of schwannomas arises from the vestibular branch of the eighth cranial nerve within the CNS and represents nearly all nerve sheath tumors found within the CNS (Ostrom et al., 2015). Schwannomas are slow-growing low grade tumors. Around 80% of meningiomas are also low grade. However either due to difficult localization or tumor re-growth as a consequence of incomplete resection, tumors may cause considerable morbidity to the patients. Unfortunately, treatment options in these patients with complicated clinical course are restricted to radiotherapy, as systemic therapy has failed to deliver clear benefit so far. The key molecular aberration found in both meningiomas and schwannomas affect the Neurofibromatosis type 2 gene (*NF2*), with more than 50% of sporadic meningiomas harboring *NF2* alterations (Ruttledge et al., 1994). Most schwannomas harbor mutation of both alleles or allelic loss of one allele and mutation of the other (Agnihotri et al., 2016). The essential role of *NF2* is evident from the frequent occurrence of meningiomas and vestibular schwannomas in patients suffering from germline mutations in *NF2* (Fong et al., 2011). The protein product of the *NF2* gene is merlin (also referred to as schwannomin), and is a critical regulator of contact-dependent inhibition of tumor cell proliferation. Thus, loss of merlin contributes to both tumor growth, tumor cell invasion, and metastasis (Petrilli & Fernandez-Valle, 2016).

Clinical trials taking *NF2* alterations into account have been rarely undertaken. In one trial, the mTOR inhibitor Everolimus was able to delay the time to tumor progression in *NF2*-associated vestibular schwannomas, while tumor growth itself was not affected significantly (Goutagny et al., 2015). The dual mTORC1/mTORC2 inhibitor AZD2014 is currently being tested in patients with progressive or symptomatic *NF2*-related meningiomas (NCT02831257). However, there is a clear need to identify additional targets active and treatable in *NF2*-related meningiomas and schwannomas. The paper from Bassiri et al. (2017) contributes an important step forward to fill this gap. Using proteome and phospho-proteome approaches, they analyzed both primary cells from merlin deficient meningiomas and schwannomas in comparison to non-tumorous Schwann cells and meningeal cells. One of a number of proteins upregulated in both tumor cell types was PDZ and LIM domain protein 2 (PDLIM2), and the authors nicely confirmed its upregulation in primary tumor samples. Downregulation of PDLIM2 by shRNA reverted the increased tumor cell proliferation, suggesting that targeting PDLIM2 might be beneficial in treating aggressive *NF2*-associated tumors. Thus, one important finding is the identification of potential merlin-interacting proteins which can be targeted. The link between merlin and PDLIM2 is facilitated by the function of PDLIM2 as an adaptor protein of several cytoskeleton proteins (actinin, filamin A, myosin) (Torrado et al., 2004). PDLIM2 suppression acts as a tumor-inhibiting factor in other cancers (Kang et al., 2016). Moreover, PDLIM2 suppresses NFkappaB-mediated inflammation (Ono et al., 2015), suggesting that drug-based targeting of PDLIM2 might have a positive function in cancer, inflammation, or even tumor-associated inflammatory processes. One idea to modulate PDLIM2 was recognized by the observation that vitamin D induces demethylation of the PDLIM2 promoter (Vanoirbeek et al., 2014). However, a more detailed analysis of PDLMI2 is necessary in the context of *NF2*-related animal tumor models, as well as other *NF2*-associated tumor cells lines, such as mesothelioma cells. Given the pleiotropic function of PDLIM2, drug-based modulation of this protein is challenging.

Disclosure

The author declared no conflicts of interest.

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