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Commentary

p53 and merlin tumor suppressors: Two of a kind

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In *EBioMedicine*, Chen and colleagues [1] showed that more than 85% of sporadic vestibular schwannomas have at least one somatic mutation affecting the *NF2* gene and that the "two-hits" *NF2* gene status is associated with larger tumor size and with loss of merlin protein expression. This situation is associated with a significant decrease of p53 protein level and functions, due to enhanced nuclear accumulation of MDM2 and consequent nuclear export of p53 for degradation. The authors correlate this discovery with the relevant role of MDM2 as mediator of merlin and p53 interaction: in the normal Schwann cells they are both regularly present and reciprocally stabilized, while in Schwannoma p53 is rapidly degraded because of a higher presence of MDM2 in the absence of merlin expression. Importantly, the authors demonstrated that the combined inhibition of MDM2 and proteasome by the two drugs Nutlin-3 and MG-132 was able to restoring p53 and merlin normal level and normal biological activity (apoptosis induction and cell cycle blockade) and to efficiently reduce the growth of schwannoma in vivo. Their findings offer new opportunities both for preclinical and clinical research.

Currently, the preferred treatment of fast-growing sporadic vestibular schwannomas is surgery or radio-surgery [2], with severe implications on the sensorineural hearing capability, that still pose the preserving or restoring of hearing highly challenging [3]. Under this clinical point of view, a possible pharmacological reduction of the tumor progression and growth would be a strategy to improve the success of preservation or rehabilitation of hearing. Moreover, considering that the only drug proposed to (selected) NF2 patients is bevacizumab [4], and that this treatment has important long term adverse events, there is still a high need to find efficient pharmacological treatment for this tumor type. As for other tumors, it has to take in consideration also for schwannomas that monotherapy will rarely work on long-term because of the emergence of drug resistances, so that the most appropriate treatments would rely on combination therapies. For these reasons, the combination treatment proposed by Chen and colleagues [1] based on Nutlin-3 and MG-132 to restore the "tumor suppressor" capability of schwannoma's cells opens new clinical future perspectives for the management of schwannoma.

The cancer literature is reach of preclinical and clinical research about pharmacological combinations. Nutlin-3 and other non-genotoxic MDM2 inhibitors, used for the activation of p53-MDM2 axis, have been preclinical investigated as essential component of divalent combinational therapies for several tumor types with positive results in solid tumors as well as in hematological cancers [5,6]. In particular, it has been demonstrated by Lee et colleagues [7] that Nutlin-3 is able to enhance the sensitivity of p53-defective cancer cells to the proteasome inhibitor bortezomib by inducing paraptosis, suggesting that pharmacological combinations including Nutlin-3 can be efficient also on p53-defective tumors and reinforcing the concept for the use of the combination "inhibitor of MDM2" plus "inhibitor of proteasome". Of note, both p53 and merlin are tumor suppressor molecules that share the ability of cell cycle control and can potentiate each other in inhibiting tumor growth. The progress in the understanding of the molecular pathways underlying sporadic schwannomas development can help the advancement also of other merlin-deficient tumors, such as malignant mesothelioma that is still a therapy-resistant cancer [8], melanoma, breast cancer and glioblastoma.

Certainly some questions still remain unanswered from both preclinical and clinical sides. Limitations of the proposed approach include possible negative effects of altering merlin to levels able to cause cytoskeleton rearrangements [9] and unpredictable consequences (such as spreading of tumoral cells instead of killing them?) and other molecular effects due to altered p53 signaling cascade that deserve further considerations. Nevertheless, this study offers a strong rational to continue investigating the mutual relationship between the two tumor suppressor p53 and merlin.

Conflict of interest

The author declares no financial and non-financial conflict of interest.

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