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Abstract 941: TAM receptors as potential therapeutic targets in NF2-related schwannomas and meningiomas

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Abstract

Background: Mutations in the NF2 gene, which codes for the tumor suppressor Merlin, is responsible for the development of all Neurofibromatosis Type 2 (NF2)-related tumors including schwannomas and meningiomas. These tumors can also occur spontaneously in non-NF2 patients. The only available treatments for this group of tumors are surgery and radiosurgery/radiotherapy. Therefore, in a search of effective drug-based treatments for NF2-mutated schwannomas and meningiomas, we are investigating TYRO3, AXL and MERTK (TAM) receptors as new therapeutic targets.

Methods: The expression and activation of TAM receptors were investigated using human Merlin-deficient meningioma and schwannoma tissues compared to control by Western blotting. Infiltration of tumor associated macrophages and their correlation to TAM family receptors were investigated using immunofluorescence double staining and flow cytometry. To understand the role of TAM receptors in the pathogenesis of schwannomas and meningiomas, in vitro shRNA knock-down and pharmacological inhibition analysis were conducted using patient-derived schwannoma and meningioma cells.

Results: The results revealed overexpression and hyper-activation of AXL, MERTK, TYRO3 in human Merlin-deficient meningiomas and schwannomas. Meningiomas and schwannomas show a varied level of infiltration by M2 macrophages (CD163+) and TAM receptors are expressed on these CD163+ macrophages in addition to the tumor cells. The expression of MERTK correlates to the level of infiltrated CD163+ macrophages. MERTK forms a complex with TYRO3 in both meningioma and schwannoma tissues, and its expression is mandatory to maintain AXL and TYRO3 levels in both cell types. MERTK and AXL contribute to the increased proliferation and survival of schwannoma and meningioma primary cells in vitro. Pathological proliferation and survival of both cell types were successfully reversed by AXL inhibitor BGB324 (BerGenBio, FDA approved for AML) and MERTK inhibitor UNC2025 (preclinical) in vitro, with UNC2025 being more effective. TYRO3 did not affect the proliferation of either schwannoma or meningioma primary cells.

Conclusion: Our findings suggest that TAM receptors are aberrantly expressed and activated in human Merlin-deficient meningiomas and schwannomas. Infiltration of M2 macrophages may contribute to an overall increase in the expression of TAM receptors in these tumors. AXL and MERTK are important in schwannoma and meningioma pathogenesis and are potentially good therapeutic targets. MERTK inhibitor UNC2025 has the potential to be used as a common candidate for the treatment of NF2-related tumors.

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