Abstract #368

Regulation of Schwann cells oncotransformation by changes in *Nf2*/merlin expression, Hippo/YAP signaling and DNA methylation

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Content

Schwann cell (SC) express the Neurofibromin type 2 gene (*Nf2*), encoding the tumor suppressor protein merlin, a cytoskeleton-associated protein regulating cell proliferation and survival. *Nf2*/merlin inactivation causes protein loss and leads to SC transformation into a form of benign tumor called schwannoma. Moreover, *Nf2*/merlin is mutated in an autosomal dominant multiple syndrome, called neurofibromatosis type 2. In line with observation that physio/mechanical cues, such as environmental challenges, may be pathogenetically relevant for SC oncotransformation, we recently showed that the exposure to electromagnetic fields (EMFs) causes changes in SC *Nf2*/merlin expression, cell migration, chemotactic responsivity and cytoskeleton reorganization. We showed a downstream MAPK/Erk activation, involved in SC proliferation, as well as activation of Hippo/YAP signalling commonly altered during tumorigenesis. We also showed that some genes, known to be upstream or downstream mediators of Hippo (Amotl2, Dchs, Fat, Wnt1) were changed. Further studies on rat SC oncotransformation following acute EMF exposure (0.1 T, 50 Hz, 10 min) demonstrated that the number of cells in G1 phase was increased. Focus forming analysis, after repeated exposures, showed an increase in 3D SC growth. EMF affects also the SC epigenome, as total DNA methylation, de novo DNMT and HDAC were reduced. Furthermore, *RT2*-profile assay evidenced that genes crucial for SCs are upregulated in EMF exposed cells. Overall, we identified some mechanisms responsible of environmental-induced SC changes toward a proliferative/migrating state, which may be pathologically relevant for nerve tumor development.

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References

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