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Phosphodiesterase (PDE) 4 inhibition boosts Schwann cell myelination in a 3D regeneration model

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Phosphodiesterase 4 (PDE4) inhibitors have been extensively researched for their anti-inflammatory and neuroregenerative properties. Despite the known neuroplastic and myelin regenerative properties of nonselective PDE4 inhibitors on the central nervous system, the direct impact on peripheral remyelination and subsequent neuroregeneration has not yet been investigated. Therefore, to examine the possible therapeutic effect of PDE4 inhibition on peripheral glia, we assessed the differentiation of primary rat Schwann cells exposed *in vitro* to the PDE4 inhibitor roflumilast. To further investigate the differentiation promoting effects of roflumilast, we developed a 3D model of rat Schwann cell myelination that closely resembles the *in vivo* situation. Using these *in vitro* models, we demonstrated that pan-PDE4 inhibition using roflumilast significantly promoted the differentiation of Schwann cells towards a myelinating phenotype, as indicated by the upregulation of myelin proteins including MBP and MAG. Additionally, we created an unique regenerative model comprised of a 3D co-culture of rat Schwann cells and human iPSC-derived neurons. Schwann cells treated with roflumilast enhanced axonal outgrowth of iPSC-derived nociceptive neurons, which was accompanied by an accelerated myelination speed thereby showing not only phenotypic but also functional changes of roflumilast-treated Schwann cells. Taken together, the PDE4 inhibitor roflumilast possesses a therapeutic benefit to stimulate Schwann cell differentiation and subsequently myelination, as demonstrated in the biologically relevant *in vitro* platform used in this study. These results can aid in the development of novel PDE4 inhibition-based therapies in the advancement of peripheral regenerative medicine.