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Repurposing of pexidartinib for microglia depletion and renewal

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Abstract

Pexidartinib (PLX3397) is a small molecule receptor tyrosine kinase inhibitor of colony stimulating factor 1 receptor (CSF1R) with moderate selectivity over other members of the platelet derived growth factor receptor family. It is approved for treatment of tenosynovial giant cell tumors (TGCT). CSF1R is highly expressed by microglia, which are macrophages of the central nervous system (CNS) that defend the CNS against injury and pathogens and contribute to synapse development and plasticity. Challenged by pathogens, apoptotic cells, debris, or inflammatory molecules they adopt a responsive state to propagate the inflammation and eventually return to a homeostatic state. The phenotypic switch may fail, and disease-associated microglia contribute to the pathophysiology in neurodegenerative or neuropsychiatric diseases or long-lasting detrimental brain inflammation after brain, spinal cord or nerve injury or ischemia/hemorrhage. Microglia also contribute to the growth permissive tumor microenvironment of glioblastoma (GBM). In rodents, continuous treatment for 1-2 weeks via pexidartinib food pellets leads to a depletion of microglia and subsequent repopulation from the remaining fraction, which is aided by peripheral monocytes that search empty niches for engraftment. The putative therapeutic benefit of such microglia depletion or forced renewal has been assessed in almost any rodent model of CNS disease or injury or GBM with heterogeneous outcomes, but a tendency of partial beneficial effects. So far, microglia monitoring e.g. via positron emission imaging is not standard of care for patients receiving Pexidartinib (e.g. for TGCT), so that the depletion and repopulation efficiency in humans is still largely unknown. Considering the virtuous functions of microglia, continuous depletion is likely no therapeutic option but short-lasting transient partial depletion to stimulate microglia renewal or replace microglia in genetic disease in combination with e.g. stem cell transplantation or as part of a multimodal concept in treatment of glioblastoma appears feasible. The present review provides an overview of the preclinical evidence pro and contra microglia depletion as a therapeutic approach.

Keywords: Brain injury; Colony stimulating factor 1 receptor; Glioblastoma; Mental disease; Microglia; Neurodegenerative disease; Pain; Receptor tyrosine kinase.