Abstract:

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There is inconsistent neural stem cells (NSCs) differentiation in MS. Blockage of bone morphogenetic protein (BMP) is required for NSCs differentiation and remyelination, via downstream inhibition of pSMAD .
We examined the effect of BMP blockage in the MS model –R-EAE. BMP blockage was done by neutralizing Abs or blocking small molecules (SMs) that were sorted by HTS with alkaline phosphatase production in ATDC5 cells bioassay. Of 7,600 Maybridge SMs, 3 hits, SM1, SM7 and SM9, eventually demonstrated top IC_{50} values without toxic effect. R-EAE-I.V treated with anti-hBMP-2/4-5-7 or isotype controls (IC), on day 9. SMs or vehicle were IP treated: Anti-BMP-2/4,-5-7 significantly ameliorated EAE and delayed 2nd relapse. Anti-BMP-2/4 significantly ameliorated EAE during whole experiment period vs. anti-BMP-2/4,-5-7 altogether. Anti BMP-2/4 induced 2.9- and 3.5- fold of BrdU+DCX+ neuroblasts, reduced BrdU+GFAP+ NSCs in SGZ and SVZ vs. IC, and increased BrdU+O4+corpus callosum oligodendrocyte. No immunosuppression detection of anti-BMP-2/4 by H&E of infiltrates, and splenocytes proliferation with anti-CD3 or PLP. SM1 and SM9 significantly ameliorated R-EAE during 2nd, 3rd relapses vs. vehicle. A 2.5- fold induction of $BrdU^{+}DCX^{+}$ cells in SVZ in SM9- treated EAE. *In vitro*: SM1, SM7, SM9 induced P19 neuronal phenotype. These SMs inhibited pSMAD expression. Microscale Thermophoresis demonstrated: SM1 and SM7 bind to rhBMP-2.
In Conclusion, systemic blockage of BMP-2/4 signaling have therapeutic potential to induce neurogenesis and oligodendrogenesis at the expense of astrogenesis in neuro-inflammation diseases as MS.