CCR2 ANTAGONIST, RS 102895 MODULATES THE BEHAVIORAL, ELECTROPHYSIOLOGICAL AND PATHOLOGIC FEATURES OF SEVERE MURINE EXPERIMENTAL AUTOIMMUNE NEURITIS.

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INTRODUCTION

Severe murine experimental autoimmune neuritis (sm-EAN) is a recently characterized mouse model of GBS (AIDP variant).

There is progressive infiltration of hematogenous mononuclear leukocytes (F4/80+ macrophages > CD3+ T-cells >CD19+ B-cells) into peripheral nerves associated with demyelination and axonal loss that peaks at maximal severity.

Chemokines are the initial mediators of leukocyte migration across concentration gradients *in vitro* and to sites of inflammation *in vivo*.

Human observational studies demonstrate increased expression of chemokines CCL2 (MCP-1), CXCL10 (IP-10) and CCL5 (RANTES) and their receptors CCR2, CXCR3 and CCR1/ CCR5 respectively in patients with inflammatory demyelinating polyradiculoneuropathies (IDP).

CCR2 is expressed on >90% of circulating monocytes and on endoneurial macrophages in IDP nerves.

Chemokine receptors are G-protein coupled, making them feasible targets for therapeutic intervention.

OBJECTIVES

To determine whether selective chemokine ligand-receptor pairs seen in IDP are expressed in sm-EAN peripheral nerves and determine their cellular localization.

To determine whether CCR2 blockade modulates the behavioral, electrophysiological and pathologic features of sm-EAN.

METHODS

Sm-EAN was induced in 8-12 week old female SJL/J mice using bovine peripheral nerve myelin emulsified in complete Freund adjuvant, with pertussis toxin and recombinant mouse interleukin-12 serving as co-adjuvants.

Neuromuscular severity scores (NMSS) were obtained using published methods. Mice were weighed daily.

At expected maximal severity (Day 30 post-induction), dorsal caudal tail and sciatic motor nerve conduction studies were performed on both sides.

Sciatic nerves were harvested from the sciatic notch to the trifurcation at the popliteal fossa for pathological assessment by semi-quantitative and quantitative polymerase chain reaction.

Indirect fluorescent immunohistochemistry of 10 µm frozen sciatic nerve sections was used to determine cellular localization of selected chemokine ligands and receptors.

CCR2 antagonist, RS 102895 (5 mg/kg, Sigma-Aldrich, St Louis, Missouri, USA) was administered daily to sm-EAN affected mice by intraperitoneal injection on days 9-18 post-induction, using appropriate controls.

NMSS was performed from day 0-30, with electrophysiological and pathologic assessment performed at expected peak severity.

RESULTS

Figure 1. Chemokine ligand/ receptor expression in sm-EAN

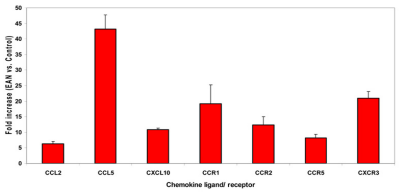


Figure 2. Chemokine ligand/ receptor expression in sm-EAN

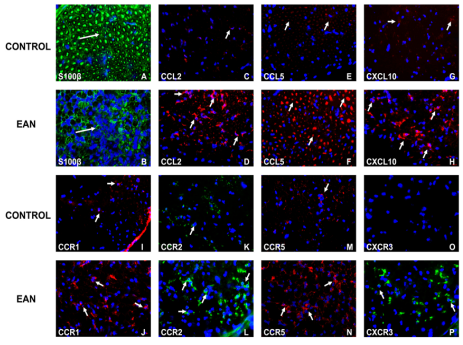


Figure 3. Cellular source of chemokines in sm-EAN

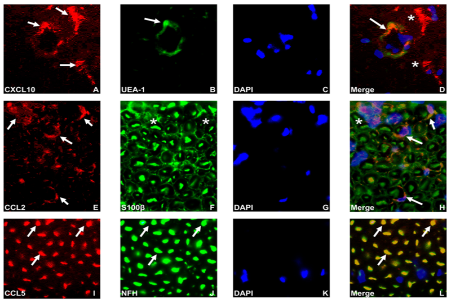


Figure 4. Anti-inflammatory treatment in sm-EAN: NMSS

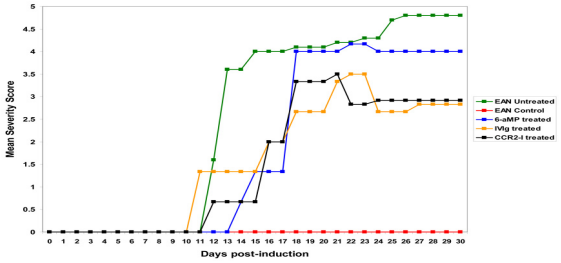


Figure 5. Anti-inflammatory treatment in sm-EAN: NCS

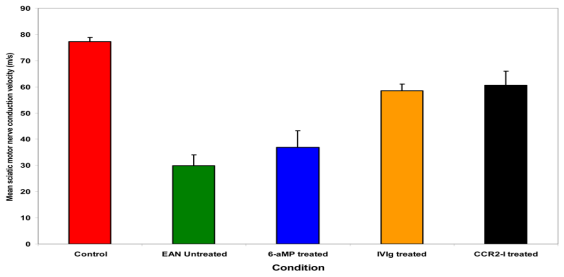
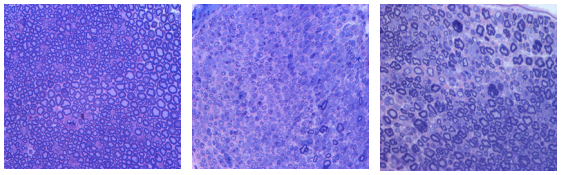


Figure 6. Anti-inflammatory treatment in sm-EAN: Histopathology



EAN control | EAN Untreated | CCR2-I treated

CONCLUSIONS

Selective proinflammatory chemokine ligand/ expression pairs are highly expressed in the sciatic nerves of sm-EAN.

CCL2 expressed by Schwann cells may attract CCR2+ monocytes/ macrophages into the endoneurium in sm-EAN.

CXCL10 expressed by endoneurial endothelium may attract CXCR3+ T-cells into endoneurium in sm-EAN

CCR2 inhibitor RS 102895 improved clinical, electrophysiological and pathologic features of sm-EAN.

Further studies are required to determine optimum dose and systemic effects of CCR2 antagonism in sm-EAN.

Sm-EAN provides a reliable model to study mechanisms of peripheral nerve inflammation and its reparative processes *in vivo*.

Further Reading:

Xia RH, Yosef N, Ubogu EE. Clinical, electrophysiological and pathologic correlations in a severe murine experimental autoimmune neuritis model of Guillain-Barré syndrome. J Neuroimmunol 2010; 219:54-63

Xia RH, Yosef N, Ubogu EE. Dorsal caudal tail and sciatic motor nerve conduction studies in adult mice. Technical aspects and normative data. Muscle Nerve 2010;41:850-856

Xia RH, Yosef N, Ubogu EE. Selective expression and cellular localization of pro-inflammatory chemokine ligand/receptor pairs in the sciatic nerves of a severe murine experimental autoimmune neuritis model of Guillain-Barré syndrome. Neuropathol Appl Neurobiol 2010 (Accepted article, on-line version: DOI: 10.1111/j.1365-2990.2010.01092.x, published May 25th, 2010).