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REVIEW ARTICLE

MACROPHAGES - TARGETS OF MEDICATION IN MULTIPLE SCLEROSIS

***Dorota Jasinska and Jerzy Boczon**

Specialty Hospital in Gorlice, Poland

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ABSTRACT

A view that Th1/CD4 lymphocytes are responsible for inflammation in multiple sclerosis is very common. However, it was proved that destruction of the axons in the demyelination plaque correlated better with macrophages and CD4 lymphocytes activity than CD8 lymphocytes activity. Macrophages play a key role in all the multiple plaques. They are usually surrounded by lymphocytes and located around the small venous vessels. Macrophages undergo polarization that depends on the activating factors. In autoimmune disorders phenotype M1 of macrophages overbalance in acute phase of inflammation. Stimulation of PRR signaling path inducts M1 to produce inflammatory cytokine like No, ROIs that destroy the tissues, TNF-alfa, IL-beta that activate inflammatory signaling NF-kappaB, as well as IL-12 and IL-23 that induce Th1 response for antigens presented by macrophages. Cytokines with the most important one Il-17 promote inflammatory process. The latest research has pointed to a crucial role for microglia activated through TLRs in polarization of γδ T cells towards neurotoxic IL-17+ γδ T cells. We have screened a library of PubMed in order to identify M2 activating substances that could be used as the potential new medications for multiple sclerosis. Interestingly, we found one very promising recent research.

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INTRODUCTION

A view that Th1/CD4 lymphocytes are responsible for inflammation in multiple sclerosis is very common. However, it was proved that destruction of the the axons in the demyelination plaque correlated better with macrophages and CD4 lymphocytes activity than CD8 lymphocytes activity. (Bitsch *et al*., 2000) The latest data suggests that myeloid cell, e.g. dendritic cells, monocytes, macrophages and microglia have prominent roles in MS pathogenesis. (Mishra *et al*., 2016; Lussi *et al*., 2016; Brendecke and Prinz, 2015)

DISCUSSION

Classical multiple sclerosis pathogenesis scheme include:

- Activation – APC presents antigen to autoreactive lymphocytes T
- Adherence and penetration - activated T lymphocytes stick to the blood-brain barrier and penetrate it
- Reactivation – myeloid cell (e.g. Brain APC cells-dendrite cells, monocytes, macrophages and microglia) presents antigen to lymphocytes and reactivates them
- Cytokine production and cascade of inflammation that cause demyelination and axons damage.

It is clearly seen that macrophages and other antigen-presenting cells play a key role in the process of activation, reactivation and cytokine producing process. Pathomorphological view is crucial to understanding the role of macrophages in demyelinating disorders. Microscopic view of active demyelinating plaque is characterized by the infiltration caused by macrophages and T lymphocytes gathered around the vessels. Plasmatic cells are also present but occur in minority. Macrophages are even more typical for chronic active plaque, what is obvious considering that macrophages are common in the chronic inflammatory process. The chronic inactive plaque does not include inflammatory cells.

American Academy of Neurology distinguished 4 types of demyelinating plaques:

Types I and II are well limited area of the active demyelination concentrated around small venous vessels with the intensive infiltration caused by macrophages and high grade of oligodendrocytes damage in the area of active demyelination. However, in the inactive region process of remyelination is carried on. Complement system as well as immunoglobulin G presence is also typical for type II plaques. Type III plaques are

**Corresponding author: Dorota Jasinska,*
Specialty Hospital in Gorlice, Poland.

characterized by the inflammatory reaction created mainly by lymphocytes, macrophages and microglia with loss of oligodendrocytes that have the typical apoptotic feature. The regions are not well limited with very poor remyelination. Type IV plaques are distinguished by well confined areas with inflammatory reaction comprised of lymphocytes, macrophages and characterized by nonapoptotic loss of oligodendrocytes. Macrophages play a key role in all the multiple plaques. They are usually surrounded by lymphocytes and located around the small venous vessels. (Losy and Selmaj, 2007) Macrophages undergo polarization that depends on the activating factors. In autoimmune disorders phenotype M1 of macrophages overbalance in acute phase of inflammation. Stimulation of PRR signaling path inducts M1 to produce inflammatory cytokine like No, ROIs that destroy the tissues, TNF-alfa, IL-beta that activate inflammatory signaling NF-kappaB, as well as IL-12 and IL-23 that induce Th1 response for antigens presented by macrophages. Cytokines with the most important one Il-17 promote inflammatory process. The latest research has pointed to a crucial role for microglia activated through TLRs in polarization of γδ T cells towards neurotoxic IL-17+ γδ T cells. (Derkov *et al*., 2015; Nazimek and Bryniarski, 2012) Phenotype M2 is typical for inhibition of inflammation and axons damage but supported remyelination. Transition of M1 into M2 is inducted by IL-10, IL-13, TGF-beta, glycocorticosteroids and main of them is TGF-beta. Phenotype M1 is promoted by mineralocorticoids and activin A that belongs to the TGF family. The similarity in M1/ M2 macrophages ratio in multiple sclerosis juvenile, rheumatoid arthritis and Crohn disease has been established. (Nazimek and Bryniarski, 2012) We have screened a library of PubMed in order to identify M2 activating substances that could be used as the potential new medications for multiple sclerosis. Interestingly, we found one very promising recent research which showed that treatment with a urokinase receptor-derived cyclized peptide [SRSRY] improves experimental colitis by preventing monocyte recruitment and macrophage polarization. (Genau *et al*., 2016) Additional observation is that, as was previously stated, in all the multiple plaques macrophage is surrounded by lymphocytes and located around the small venous vessels. (Losy and Selmaj, 2007) The image approximates to chronic granulomatous vessel in inflammation driven primarily by macrophages, recruitment, and proliferation of which, drive plaque progression. Granuloma is an assemblage of macrophages surrounded by the cuff of lymphocytes. Granuloma occurs in many autoimmune disorders, for instance: Crohn disease, Melkersson - Rosenthal sydrome, rheumatoid arthritis, Wegener's granulomatosis, Churgh - Strauss syndrome and other vessel inflammation. (Gajewski and Szczeklik, 2016) Drugs efficient in treating these diseases should potentially be efficient in multiple sclerosis. Some, like glycocorticosteroids, methotrexate and azathioprine are indeed successfully applied in multiple sclerosis therapy, whereas others, like colchicine, cholochine, dapsone have never been tested in clinical trials. Some of them however, like dapsone, are used as a medication in other autoimmune conditions, like: Crohn disease, Melkersson - Rosenthal sydrome, rheumatoid arthritis, Wegener's granulomatosis, Churgh - Strauss syndrome and other vessel inflammation. (Gajewski and Szczeklik, 2016; Guerre – Schmidt *et al*., 2006) The mechanism of dapsone's action is inhibition of the leukocytes, therein macrophages chemotaxis. (Żychowska *et al*., 2016) These insights show the potential future directions for research.

Conclusion

To sum up, multiple sclerosis approximates to chronic granulomatous inflammation driven primarily by macrophages, recruitment and proliferation of which drive plaque progression. The substance like a urokinase receptor-derived cyclized peptide preventing monocyte recruitment and macrophage polarization and dapsone that inhibits chemotaxis point out potenial future directions for research.

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