Journal of Neurology & Neurophysiology

Wang, J Neurol Neurophysiol 2012, 3:2
DOI: 10.4172/2155-9562.1000e104

Editorial Open Access

Microglia: A Major Player in Rett Syndrome

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Abstract

Microglia, the brain-resident macrophages of haematopoietic origin, are involved in the pathology of many neurological disorders. Microglia from mouse model of the X-linked autism spectrum disorder Rett syndrome (RTT), have been shown to cause excitotoxicity through release of abnormally high levels of glutamate. One recent study showed that transplantation of wild-type bone marrow or targeted expression of MeCP2 in myeloid attenuated the symptoms of RTT in the mouse models, indicating that wild-type MeCP2-expressing microglia within the context of RTT can arrest the disease pathology. This study thus implicates microglia as a major player in RTT, and may open up a new avenue for treatment of this autism spectrum disorder.

Rett syndrome (RTT), typically caused by mutations in the X-linked MECP2 encoding Methyl-CpG-binding protein 2 (MeCP2), is a neurodevelopmental disorder that mainly affects females [1-5]. RTT patients develop normally until 6–18 months of age but then show progressive loss of spoken language, loss of hand use, and the development of distinctive hand stereotypes. Clinical features include deceleration of brain growth, cognitive and motor abnormalities, autism, seizures, and respiratory dysfunction [6-13]. MeCP2 is a DNA-binding protein that can both activate and repress transcription [14-18]. MeCP2 also affects differential splicing [19]. Investigating the biological targets of MeCP2 may help elucidate the mechanisms underlying RTT.

Although MECP2 is widely expressed in human tissues, the disease is primarily attributed to the dysfunction of neurons. Previously, RTT is basically seen as a disease of synaptic plasticity [20-22]. Evidence from studies in recent years has implicated glia, including astrocytes and microglia, in the pathophysiology of RTT [23-27]. MeCP2-null astrocytes were unable to support the normal dendritic ramification of wild-type neurons growing in culture [23], and expression of wild-type MeCP2 protein in astrocytes of MeCP2-null hosts mice dramatically ameliorated the pathology of RTT [24]. Microglia, the resident macrophages in the central nervous system (CNS), are of haematopoietic origin [28]. These cells extend an extensive network of processes in the CNS parenchyma. Microglia actively and constantly interact with neurons and astrocytes, provide surveillance of their cellular environment [29,30]. Microglia regulate synaptic functions and synaptic turnover even without the context of inflammation [31]. MeCP2-null microglia have been reported to cause excitotoxicity through release of abnormally high levels of glutamate. The excitotoxicity may contribute to dendritic and synaptic abnormalities in RTT [26].

RTT-like neurological deficits in both immature and mature MeCP2 mutant mice can be reversed by postnatal activation of MeCP2 expression or targeted delivery of MeCP2 transgene to forebrain neurons [32-35]. These results raise the possibility that RTT might be also ameliorated by restoration of MeCP2 in microglia. To test this hypothesis, Derecki et al. [36] investigated the effect of restoration of MeCP2 in microglia in the mouse model of RTT, as reported recently in Nature. Through multiple approaches, they found that wild-type MeCP2-expressing microglia within the context of RTT arrested numerous facets of disease pathology in mouse models [36]. Their study further implicates microglia as a major player in the pathophysiology of RTT.

To study the role of microglia in RTT, Derecki et al. [36] first examined microglial function in the context of MeCP2$^{-/y}$ male mice. Males possess a single mutant X chromosome. As reported previously [37,38], the authors found that these males manifest a severe phenotype, including markedly retarded growth, apneas, tremor, impaired gait and locomotor function, and a postnatal life expectancy of approximately 8 weeks. To address the role of hematopoietically derived cells in the pathophysiology of RTT, the authors subjected MeCP2$^{-/y}$ (MeCP2$^{tm1.1Jae}$ and MeCP2^{tm2Bird}) mice to lethal split-dose irradiation at postnatal day (P) 28 (the approximate age at which neurological signs appear [37]) and then injected them intravenously with syngeneic bone marrow from C57Bl/6J mice ubiquitously expressing Green Fluorescent Protein (GFP). Control groups were injected with autologous (MeCP2$^{-/y}$) bone marrow, or left naive. The authors found that the lifespan of MeCP2-null recipients of wild-type bone marrow (wild type→MeCP2$^{-/y}$) was significantly extended compared to MeCP2$^{-/y}$ mice receiving autologous bone marrow (MeCP2$^{-/y}$→MeCP2$^{-/y}$) or to naive MeCP2$^{-/y}$. Although MeCP2$^{-/y}$ mice on the C57Bl/6J background are usually undersized [37,38], the authors found that within 4 weeks of transplantation, wild-type→MeCP2$^{-/y}$ (but not MeCP2$^{-/y}$→ MeCP2$^{-/y}$) mice approached the size of wild-type littermates. They noticed that wild-type→MeCP2$^{-/y}$ mice also exhibited an increase in brain weight, which was probably caused by general growth of the mouse, because the reduced soma size characteristic of MeCP2-null neurons was not changed by bone marrow transplantation and the brain to body weight ratio was normalized. Growth retardation is a characteristic feature of RTT pathology. Previous study has shown that treatment with Insulin-like Growth Factor (IGF)-1 benefits survival and behavioural outcomes in MeCP2-null mice [39]. Derecki et al. [36] actually found that peripheral macrophages from wild-type mice expressed significantly

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Received April 05, 2012; **Accepted** April 05, 2012; **Published** April 12, 2012

Citation: Wang H (2012) Microglia: A Major Player in Rett Syndrome. J Neurol Neurophysiol 3:e104. doi:10.4172/2155-9562.1000e104

higher levels of IGF-1 in vitro in response to immunological stimuli than macrophages from MeCP2-null ($MeCP2^{tm1.1Jae/y}$) mice. They believed that this difference may contribute to the increase of body growth seen in MeCP2-null mice after bone marrow transplantation.

Derecki et al. [36] further compared the general appearance of wild-type→$MeCP2^{-/y}$ mice to that of naive $MeCP2^{-/y}$ or $MeCP2^{-/y}$→$MeCP2^{-/y}$ mice. They found that the severe involuntary tremors normally seen in mutant mice were absent following wild-type bone marrow transplantation, and gait was improved. More interestingly, no detectable benefit on hindlimb clasping phenotype was observed. Breathing irregularities and apneas are cardinal signs of RTT. The authors used whole-body plethysmography to compare the breathing patterns of $MeCP2^{-/y}$ mice with or without bone marrow transplantation to those of control mice. They found that $MeCP2^{-/y}$ mice developed apneas progressively with age. However, wild type →$MeCP2^{-/y}$ exhibited significantly reduced apneas and fewer breathing irregularities than either naive $MeCP2^{-/y}$ or $MeCP2^{-/y}$→$MeCP2^{-/y}$ mice. Wild-type →$MeCP2^{-/y}$ mice also displayed significantly increased mobility in the open field compared with naive $MeCP2^{-/y}$ or $MeCP2^{-/y}$ →$MeCP2^{-/y}$ mice.

To confirm their findings in $MeCP2^{-/y}$ male mice, Derecki et al. [36] performed bone marrow transplantation in heterozygous female mice at 2 months of age, and these mice were examined at 9 months. The authors found that the disease in $MeCP2^{+/-}$ mice develops slowly, with behavioural abnormalities becoming clear at 4–6 months of age. The weights of treated $MeCP2^{+/-}$ mice were comparable to wild-type controls. In addition, there was significant improvement in motor function, as examined on rotarod, and time spent in the centre of the open field arena was significantly increased. They also noticed that apneas in bone marrow transplanted mice were reduced and their overall breathing patterns were improved compared to their non-treated controls.

It has been previously reported that bone marrow transplantation after whole-body irradiation results in engraftment of microglia-like myeloid cells into the brain parenchyma [40]. Derecki et al. [36] found that the peripheral immune system of $MeCP2^{-/y}$ hosts was repopulated by donor bone marrow. Indeed, GFP^+ cells in the parenchyma of bone marrow transplanted mice expressed CD11b, a specific marker for microglia, but not GFAP or NeuN, specific marker for astrocytes and neurons, respectively. Interestingly, they found that in mice in which bone marrow transplantation was performed later (P40 or P45), only slight improvements in disease pathology were observed. No microglial engraftment was evident, although substantial numbers of GFP^+ cells were found in the meningeal spaces. The authors thought that these results may suggest that when disease progression is faster than microglial engraftment, full rescue cannot be achieved. The moderate results observed, however, may have been due to a yet-unknown mechanism, perhaps through soluble factors produced by meningeal immune cells, or peripherally-expressed IGF-1. The authors also noticed that newly engrafted microglia expressed detectable levels of wild-type MeCP2 but nearby cells did not show any MeCP2 labelling. This finding argues against the possibility of protein transfer from engrafted microglia into nearby cells as an underlying mechanism for the beneficial effect of bone marrow transplantation.

To substantiate the specific role of microglia in bone marrow transplantation-mediated disease arrest, Derecki et al. [36] repeated transplantation experiments at P28, but with the addition of lead shielding to block cranial irradiation. The authors found that the transplantation with lead shielding to block cranial irradiation, results in repopulation of peripheral immunity but no parenchymal engraftment. This result is consistent with previously published work [40,41]. Finally, they found that the disease was not arrested in 'head-covered' mice. This finding suggests that peripheral immune reconstitution without microglial engraftment is insufficient to arrest pathology in $MeCP2^{-/y}$ mice.

To further confirm the role of myeloid cells in arrest of RTT pathology, Derecki et al. [36] used a genetic approach. They employed the widely used $Lysm^{Cre}$ mouse, which results in a high degree of recombination in myeloid cells, granulocytes and in significant numbers of microglia [42-44], in cross with $MeCP2^{lox-stop}$ mice. Male progeny, $MeCP2^{lox-stop/y}Lysm^{cre}$, express wild-type MeCP2 in myeloid cells on an otherwise MeCP2-null background. The authors found that these mice exhibited improvements in overall appearance and growth and their life spans were significantly increased. Apneas and inter breath irregularity of these mice were also significantly reduced compared to control mice. Additionally, the authors noticed that the open field activity of these $MeCP2^{lox-stop/y}Lysm^{cre}$ mice was not significantly different from wild-type counterparts. The authors believed that these results cannot be interpreted by cre leakiness, because no cre-mediated recombination was evident in either astrocytes or neurons in $Lysm^{cre}$ crossed to a reporter strain, in line with previous publications [43,44].

How can microglia contribute to the pathology of RTT? To address this, Derecki et al. [36] examined the function of microglia by feeding cultured microglia with pre-labelled ultraviolet-irradiated neural progenitor cells. The authors found that microglia from MeCP2-null mice were deficient in their response to immunological stimuli and in phagocytic capacity. They believed that it is possible that apoptotic debris would accumulate over time in the MeCP2-null brain, contributing to neuronal malfunction and accelerating disease progression. Unsurprisingly, supplementation of wild-type microglia could reduce debris levels and thus allow improved neuronal function. This is supported by the fact that in mice transplanted with GFP^+ bone marrow only GFP^+ parenchymal cells were consistently found containing cleaved caspase-3-positive debris within lysosomes. It has been reported that annexin V (a protein that binds phosphatidylserine on apoptotic cells and inhibits engulfment) injected intravenously can reach the CNS [45]. Intravenous injection of annexin V results in substantial blockade of phagocytic activity in the brain [46]. In this study, Derecki et al. [36] found that treatment of wild-type mice with annexin V resulted in significant accumulation of Terminal Deoxynucleotidyl Transferase (TdT)-mediated dUTP nick end labelling $(TUNEL)^+$ fragments. The authors then further inhibited brain microglia activity pharmacologically in $MeCP2^{lox-stop/y}Lysm^{cre}$ mice and compared disease progression with controls. They found that treatment of $MeCP2^{lox-stop/y}Lysm^{cre}$ mice with annexin V abolished the amelioration of the disease normally seen in these mice, whereas wild-type mice treated with annexin V were not significantly affected. These findings suggest that wild-type microglia are actively engaged in clearance of apoptotic cells or cell remnants within the context of MeCP2-null brain. MeCP2-null microglia, deficient in phagocytic function, may be unable to efficiently clear debris left behind from the normal process of neural cell death or membrane shedding. The inability of MeCP2-null microglia to clear debris as effectively as wild-type microglia may potentially contribute to the underlying neuropathology in MeCP2-null mice.

This study thus suggests the possibility of treatment of RTT through manipulation of brain microglia. Phagocytic activity per se is definitely just one aspect of microglial involvement in the pathophysiology of the disease. Future studies should be focused on understanding the connections between microglia and neuronal function, interactions between microglia and astrocytes, and alterations within microglia themselves in the context of RTT. Microglia have also been shown to be involved in the pathophysiology of other neurological disorders, such as Down syndrome [47-49], Amyotrophic lateral sclerosis [50,51], Alzheimer's disease [52-56] and Stroke [57-60]. The identification of microglia as a major player in RTT might shed light upon treatment of these neurological disorders.

Acknowledgements

This manuscript was prepared at the invitation of the Managing Editor of Journal of Neurology & Neurophysiology. Dr. Hansen Wang was formerly supported by the National Natural Science Foundation of China (NSFC, No.30200152) for the study of Rett syndrome.

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