Cell. Mol. Life Sci.
DOI 10.1007/s00018-014-1641-0

Cellular and Molecular Life Sciences

LETTERS AND COMMENTS

Source of iron overload in multiple sclerosis

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Received: 7 April 2014 / Accepted: 29 April 2014

Sir,

We read with great interest the reflection by Bamm and Harauz [1] in this journal, in which they propose that a local iron overload, due to chronic subclinical blood extravasation and hemoglobin (Hb) release, could be involved in the pathogenesis and neurodegeneration of multiple sclerosis (MS). The authors raise an interesting subject, highlighting that MS could be additionally considered a degenerative disorder rather than strictly an autoimmune disease. Iron is undoubtedly an essential element in the brain, being a key co-factor in several functions as myelination, respiration and neurotransmitter biosynthesis. However, brain iron overload is also involved in several neurodegenerative diseases. Increased iron deposition has been implicated in the pathophysiology of MS and experimental autoimmune encephalomyelitis (EAE), but the mechanisms leading to brain iron overload in these diseases and its pathophysiological role are till now totally unclear. In their reflection, Bamm and Harauz [1] first underline the relationship between cerebral vasculature and MS lesions. Second, they highlight the observations of abnormal iron accumulation in MS lesions. Finally, they propose that the major source of this iron overload can be a long-term release and degradation of Hb. Hb release could in turn result in oxidative stress, inflammation and consequent tissue damage due to (1) the intrinsic oxidant activity of Hb, (2) the oxidant activity of the released heme and (3) the reactivity of free iron released from heme. The authors do not affirm that this scenario must be considered the main cause of the disease. In any case, the derived oxidative stress could be responsible for an exacerbation of inflammation and finally for neurodegeneration in MS.

In addition, the authors interestingly suggested that further risk factors could contribute to MS progression. Among them, haptoglobin (Hpt) genotype could be of great importance. Hpt deficient mice have more severe EAE disease and serum Hpt levels are altered in MS patients. Hpt binds free Hb in the circulation. Hpt/Hb complex formation is extremely important to reduce the oxidative stress derived from Hb release from erythrocytes. In humans, the Hpt gene is polymorphic, existing as two different alleles, Hpt1 and Hpt2, and the decreased antioxidant capabilities of Hpt2 protein are responsible for the increased risk of developing vascular complications in homozygous Hpt2/2 patients suffering from diabetes. We would like to briefly report here our own unpublished observation in a restricted number of Italian MS patients ($n = 11$). Patients were diagnosed with MS in the Multiple Sclerosis Center of the Civic Hospital of Brescia. Blood samples were taken with written informed consent of the patients or their relatives for the use of the material for research purpose. We chose these patients from a large cohort of MS patients under investigation since they presented with a severe cognitive deficit, therefore iron dysregulation could be implicated. We found Hpt allele frequencies similar (Hpt1 = 36.3 %; Hpt2 = 63.7 %) to the values observed in a healthy Italian population from the same area (Hpt1 = 37.5 %; Hpt2 = 62.5 %); however, the Hpt2/2 genotype was more

Bamm VV, Harauz G (2014) Hemoglobin as a source of iron overload in multiple sclerosis: does multiple sclerosis share risk factors with vascular disorders? *Cell Mol Life Sci*. doi: 10.1007/s00018-014-1570-y

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Published online: 16 May 2014

frequent (45.5 vs. 39 %) than the Hpt1/2 genotype (36.4 vs. 47 %) compared to the same healthy population [2]. We are obviously conscious that our observation is restricted to a very low number of patients and it would be tempting to make a statistical evaluation. However, we suggest that the hypothesis of a correlation between the Hpt genotype and MS should be further investigated in a larger cohort of patients, with special attention to those MS patients with evident cognitive deficit.

Furthermore, we would underline alternative explanations to the role of oxidative stress derived from the release of Hb, proposed by Bamm and Harauz [1].

An interesting alternative was recently advanced by Mehta et al. [3]. The authors investigated the cellular iron localization in chronic active MS lesions and observed iron deposition in a subset of macrophages with pro-inflammatory M1 phenotype. Different immunological signals can polarize macrophages to pro-inflammatory iron-enriched macrophages (M1), in which the blockade of iron release seems to be due to the interaction between the acute phase protein hepcidin (the master regulator of systemic iron homeostasis) and the cellular iron exporter ferroportin (Fpt), or alternatively to anti-inflammatory macrophages (M2) that actively export iron through Fpt and are implicated in the resolution phase of inflammation [4]. Metha and coworkers [3] suggested that similarly to that observed in chronic venous leg ulcers, macrophages could phagocytose locally extravasated erythrocytes also in MS, leading to intracellular iron accumulation and polarization to the pro-inflammatory M1 phenotype, then propagating chronic and neurotoxic inflammation and compromising the switch to anti-inflammatory M2 macrophages. Altered M1/M2 activation patterns of monocytes in EAE rat model of MS were also recently described by Mikita et al. [5], who demonstrated that the administration of activated M2 monocytes suppressed ongoing severe EAE. Regenerative properties of M2 macrophages in MS were further suggested by Miron et al. [6].

Furthermore, several genes and proteins relevant to iron metabolism are expressed not only in macrophages but also in other cells of the immune system and MS is a disease strictly related to immunity. Lymphocyte activation depend on the expression of transferrin receptor 1 [7], the main protein implicated in iron uptake, as transferrin-bound iron, from the extracellular milieau. T lymphocytes can acquire iron also as non-trasferrin bound iron (NBTI) [8]. Lymphocytes synthesize ferritin, the cellular iron storage protein, and Fpt, the cellular iron exporter. After activation, T lymphocytes increase the expression of hepcidin, which in turn acts in an autocrine/paracrine way to decrease Fpt expression at the cytoplasmic membrane and then reducing iron export [9]. T lymphocytes could, therefore, also act as mobilizing iron-storage compartments and could be of physiological relevance as modifiers of tissue iron overload in MS.

Finally, the acute phase protein hepcidin, which is the main regulator of iron systemic homeostasis, has also a role in innate immunity [10]. Although chiefly produced in hepatocytes and macrophages, hepcidin expression occurs also in other tissues such as the heart [11], the brain [12], and the T lymphocytes [9]. Hepcidin is induced by IL-6 and interestingly high IL-6 production by peripheral lymphocytes has been found to be correlated with poorer cognitive performances in relapsing remitting MS patients [13]. Then, a role for hepcidin in brain iron overload and cognitive deficit in MS, possibly linked either to local IL-6 production in the brain or alternatively to systemic IL-6 production with effect on the brain, could be postulated.

In conclusion, in addition to the role of iron in the pathogenesis and neurodegeneration of MS, proposed by Bamm and Harauz in this journal [1], we would propose that (1) macrophages could be also involved in the clearance of iron derived from blood extravasation, and, as a consequence, they could be driven towards the pro-inflammatory phenotype M1 and perpetuate the inflammation; (2) T lymphocytes could also contribute to iron-mediated toxicity, being activated by excessive iron, possibly derived from blood extravasation; (3) systemic or local hepcidin induction by IL6 could play a further role in the retention of iron in macrophages, T lymphocytes or alternatively also other brain cells in MS, contributing to the observed iron overload in this neurodegenerative disease.

Acknowledgments We are grateful to Dr. R. Capra (Multiple Sclerosis Center, Civic Hospital of Brescia) for the blood samples and to I. Bianchi, P. Camossi and L. Piccioni for their technical assistance.

Ethical standards The experiments comply with the Italian current laws.

Conflict of interest The authors declare that they have no conflict of interest

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