

# The CD4–Th1 model for multiple sclerosis: a crucial re-appraisal

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**Multiple sclerosis (MS), an acquired spontaneous chronic inflammatory demyelinating disease of the human central nervous system (CNS) has features of autoimmunity to myelin, directed by CD4<sup>+</sup> T cells, which are polarized to production of type I cytokines. Similarities between MS and models of Th1-driven brain inflammation led to assumptions that the two are equivalent and that models can be used to decipher MS and predict responses to therapy. However, over decades, numerous bits of data incompatible with a simple CD4–Th1 hypothesis have accumulated. They suggest that besides Th1 cells, other immunological mechanisms and a neurodegenerative component within the target tissue might contribute to the initiation, propagation and modification of this disease. Taken together, these issues prompt reconsideration of the use of pure CD4–Th1 models in favor of a view that MS is likely to be heterogeneous and might not be strictly autoimmune.**

Multiple sclerosis (MS), the most common neurological disease affecting young adults in the Western world, is a chronic inflammatory disease of the central nervous system (CNS), resulting in the formation of focal plaques of demyelination in the brain and spinal cord [1] (Box 1). The cause of multiple sclerosis is unknown but it is widely believed to be an autoimmune disease, initiated by MHC class II-restricted CD4<sup>+</sup> T lymphocytes, which are polarized to the production of interferon- $\gamma$  (IFN- $\gamma$ ), interleukin-2 (IL-2), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and lymphotoxin (i.e. they are Th1 cells). Several lines of evidence support the view of MS as a Th1-mediated autoimmune disease (designated for convenience the CD4–Th1 model for MS).

## The CD4–Th1 model for MS makes several specific predictions

The specific predictions made by the CD4–Th1 model are:

- (i) CD4<sup>+</sup> T cells should be the predominant lymphocyte population in MS lesions. Other lymphocyte populations should be a minority accessory population.
- (ii) CD4<sup>+</sup> Th1 polarized T cells and their major effector cytokines, TNF- $\alpha$  and IFN- $\gamma$ , should be pathogenic in MS lesions.
- (iii) CD4<sup>+</sup> Th2 polarized T cells should be regulatory or anti-inflammatory in MS lesions.

- (iv) The CD4–Th1 model should encompass the observed variability in the pathological and clinical characteristics of MS.
- (v) The process should be clearly autoimmune, that is, there should be overwhelming evidence that the CNS

### Box 1. Essential clinical characteristics of multiple sclerosis (MS)

#### Clinical disease

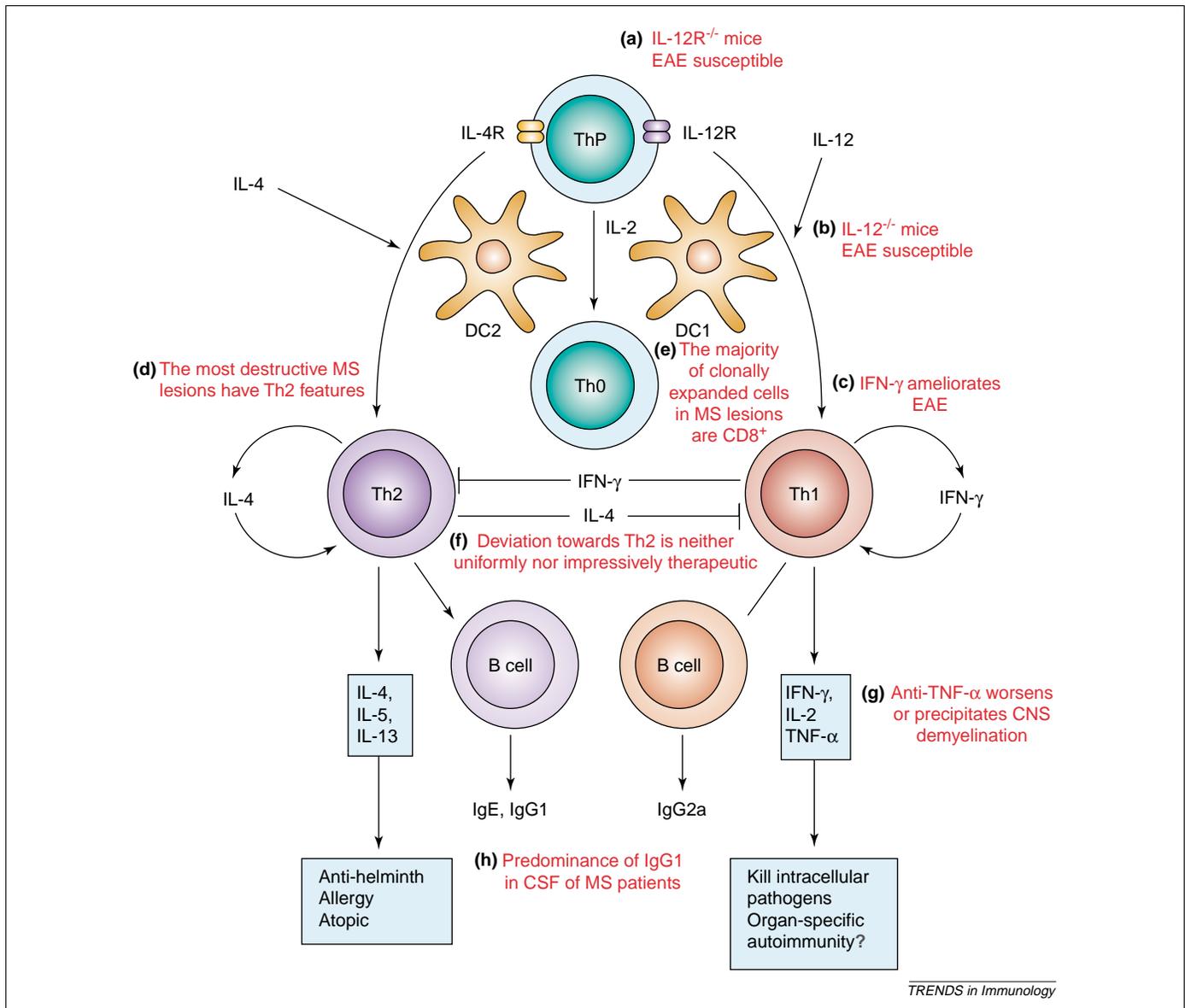
MS is a chronic disease, which can develop in different forms [1]. The most frequent form is relapsing remitting MS, characterized by bouts of the disease, which are followed by complete or incomplete remissions. After several years this relapsing disease can transform into secondary progressive MS, defined by a slow and uninterrupted course of clinical deterioration. Twenty percent of MS patients suffer from primary progressive MS. In this variant, disease starts with slow progression from the onset and relapses or remissions are absent. A small proportion of MS patients develop atypically severe disease, which leads to massive disability or even death of the patients within months [45]. Variants of this fulminate disease course are Marburg's type of acute MS (showing all typical features of chronic MS but with rapid disease evolution and more destructive lesions), Devic's type of neuromyelitis optica (a disease with dominant or exclusive involvement of spinal cord and optic nerves) and Baló's concentric sclerosis, which is characterized by the appearance of large demyelinated plaques with concentric layering of myelinated and demyelinated zones [42].

#### Genetic background

The genetic background of the patient to a large extent determines disease susceptibility [2]. Identical twins have a concordance of MS of 30%. Genomic screens disclosed that the susceptibility to develop MS is determined by multiple genes with low individual contribution. Candidate gene approaches revealed multiple possible candidates that determine disease susceptibility, severity or disease course. However, unequivocal evidence for an association with MS is so far only established for the human histocompatibility leukocyte antigen-D (HLA-D) region.

#### Imaging

The pathological alterations in the brain of MS patients can be monitored by magnetic resonance imaging (MRI) [53,54]. Conventional MRI techniques visualize the expanded extracellular space within the demyelinated plaques. With the use of a paramagnetic tracer (Gd-DTPA) blood–brain barrier damage can be seen, which reflects the change in the permeability of inflamed vessels. Gd-DTPA leakage is, thus, a good surrogate marker for active lesions. Diffuse brain injury outside plaques is documented with new imaging techniques and quantitative evaluation of signal abnormalities. Finally, the extent of neuronal and axonal damage is best visualized by magnetic resonance spectroscopy (MRS) by quantitative analysis of the concentration of N-acetyl aspartate.



**Figure 1.** Pathogenetic mechanisms proposed to be involved in the induction and propagation of inflammatory demyelinating diseases, such as experimental autoimmune encephalomyelitis (EAE) or multiple sclerosis (MS). The text in red indicates observations that contradict the propositions based on a pure Th-1 mediated inflammatory disease. Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; DC, dendritic cell; IFN-γ, interferon-γ; IL-12, interleukin-12; IL-12R, IL-12 receptor; TNF-α, tumor necrosis factor-α.

host organ was healthy before autoimmune attack by CD4–Th1-mediated mechanisms.

In this Opinion, we propose that none of these predictions fully withstands critical scrutiny in light of the neuropathological and clinical attributes of MS and findings from the widely studied animal model, experimental autoimmune encephalomyelitis (EAE) (Figure 1).

#### Evidence that MS might be mediated by autoimmune CD4<sup>+</sup>–Th1 polarized T cells

Genetic studies show an association of MS susceptibility with genes in the MHC class II region [2]. Immune surveillance of the normal brain favors the infiltration of Th1 cells [3]. MS pathology resembles that found in EAE (the animal model of Th1 mediated brain inflammation) [4]. Both diseases have a similar cellular composition of inflammatory lesions, mainly consisting of T lymphocytes

and activated macrophages, and a similar pattern of chemokine and chemokine receptor expression within the lesions, which are consistent with an inflammatory process driven by Th1 cytokines [5]. In some MS patients, immunodominant peptides of myelin basic protein (MBP) are complexed with DR2 molecules at sites of demyelination [6] and T-cell clones with receptors specific for MBP have been found in MS brain lesions [7]. Finally, therapeutic strategies, thought to induce a shift from Th1 to Th2 immune reactions, have shown beneficial effects in MS patients [8]. All these data suggest that MS develops in genetically susceptible individuals when autoimmune CD4–Th1 cells, possibly triggered by infection, invade the brain, are locally activated, and recruit and activate hematogenous macrophages and microglia cells, which destroy myelin sheaths and other tissue components through toxic effector molecules or in cooperation with

specific autoantibodies. However, many MS features are not reflected in Th1-mediated brain inflammation.

#### **CD4<sup>+</sup> T cells are not dominant in MS lesions**

CD8<sup>+</sup> T cells outnumber CD4<sup>+</sup> lymphocytes in MS lesions in all stages of their development [9,10]. In addition, PCR analysis of T-cell receptors in MS lesions (so far restricted to two cases) revealed that CD8<sup>+</sup> T cells are clonally expanded [11]. Hence, there is a prominent contribution of MHC class I-restricted T cells in MS brains, not only within lesions, but also in histologically 'normal' brain tissue. What is their function? Are they cytotoxic T lymphocytes (CTLs), which are involved in tissue injury, or regulatory cells, which limit inflammation and brain damage?

#### **CD8<sup>+</sup> T cells can be pathogenic in models of immune-mediated demyelination of the CNS**

The model of Theiler's murine encephalomyelitis virus-induced demyelinating disease, another model with similarities to MS, highlights a role for CD8<sup>+</sup> T cells in clinical disease, demyelination and axonal injury. In this model, clinical disease and tissue injury depend on an antiviral immune response, mediated by CD8<sup>+</sup> T cells [12]. Furthermore, passive transfer of autoimmune CD8<sup>+</sup> T cells induces brain inflammation and destruction of antigen containing target cells [13–15]. Thus, CTLs can induce brain inflammation, demyelination and axonal injury. Is there evidence that this occurs in MS lesions?

There is no doubt that CD8<sup>+</sup> T lymphocytes are abundant in MS lesions. In cases with aggressive disease, many of these cells express granzyme B, a cytotoxic activation marker [16]. MHC class I molecules are expressed in MS lesions on all different cell types, including glia and neurons [17]. CD8<sup>+</sup> T cells are closely apposed with oligodendrocytes and axons in MS lesions and their cytotoxic granules are polarized towards the zone of T-cell contact with the target [18]. All these data suggest that CD8<sup>+</sup> T lymphocytes can initiate brain inflammation and tissue injury in MS plaques. It remains, however, plausible that other CD8<sup>+</sup> T cells in MS lesions are regulatory, being involved – as in EAE [16] – in downregulating inflammation.

#### **CD4<sup>+</sup>–Th1 polarized T cells in MS lesions might not be purely pathogenic**

CD4<sup>+</sup> cells are also present in actively demyelinating MS lesions, primarily in perivascular spaces [10,11] and the meninges, but represent a minority of T cells in the nervous system parenchyma. There is no doubt that these cells can initiate the inflammatory process, activate effector microglia and macrophages and stimulate MHC upregulation in the CNS [19]. However, the same autoreactive CD4<sup>+</sup> lymphocytes are also potentially neuroprotective [20], producing neurotrophins, such as brain derived neurotrophic factor (BDNF) [21]; further, cognate neurotrophin receptors are expressed on glia cells and neurons in and near actively demyelinating MS lesions [22]. Class II-restricted cells, including CD4<sup>+</sup>CD25<sup>+</sup> regulatory cells, can also inhibit encephalitogenic inflammation [23]. Could it be possible that, depending on the

stage of the lesions, CD4 cells in MS also protect the nervous tissue from inflammation-induced injury?

#### **TNF- $\alpha$ and IFN- $\gamma$ , the major effector cytokines of DTH responses, have partially protective roles in inflammatory demyelination**

The concept of Th1 reactions emanated from studying host responses to intracellular pathogens, in which TNF- $\alpha$  and IFN- $\gamma$  are crucial effector molecules and deficits in their action cause susceptibility to infectious agents. Predictably, patients with genetic defects of IFN- $\gamma$  receptors, IFN-dependent STAT (signal transducer and activator of transcription) proteins or IL-12 signaling pathways or those treated with TNF neutralizing agents, demonstrate increased susceptibility to mycobacterial infection [24,25]. Thus, in host defense, the CD4–Th1 response proceeds smoothly from appropriate danger signals, to polarized dendritic cells (DCs), to polarized Th1-committed CD4<sup>+</sup> T cells, to the production of TNF- $\alpha$  and IFN- $\gamma$  and the generation of delayed type hypersensitivity (DTH) lesions (Figure 1).

In clinical or experimental inflammatory demyelination, this seamless coordinated function of effector cells and molecules has not been apparent. Consistent reports indicate that IFN- $\gamma$  is protective in rodent EAE [26–28]. Complementary results came from injecting IFN- $\gamma$  or providing the cytokine by gene therapy-mediated delivery to the affected CNS, both of which ameliorated disease [29]. The reasons why IFN- $\gamma$  reduces EAE severity are unclear [28,30] but might involve the inhibition of proliferation of pathogenetically relevant myeloid cell populations [31]. Further complexity in relating EAE with MS emerged when it was reported that injections of IFN- $\gamma$  exacerbated MS [32].

Questions about the predictive value of EAE for MS treatments intensified with the unanticipated finding that TNF neutralization worsened MS disease activity [33]. Such a result was extremely surprising because TNF blockade had been uniformly efficacious in EAE and overexpression of TNF- $\alpha$  in the CNS induces demyelination and tissue damage [34]. Additional surprises have since emerged: TNF neutralizing agents provoked inflammatory demyelination *de novo* [35]. Full mechanistic accounts of the roles played by TNF- $\alpha$  and its receptors in inflammatory demyelination are not available. However, it is now clear that IFN- $\gamma$  and TNF- $\alpha$ , the principal molecular effectors of type 1 immunity, have a far from simple part in inflammatory CNS demyelination.

#### **CD4<sup>+</sup>–Th2 polarized T cells are potentially pathogenic in EAE and MS**

Th1 (and Tc1) cells are believed to induce brain inflammation and Th2 cells are thought to be anti-inflammatory, supported by numerous detailed EAE studies [36]. In addition, patterns of chemokine receptor expression indicate a preferential homing of Th1 polarized cells into the CNS tissue [3]. However, the situation is complicated by a recent report that Th2 polarized T cells, directed against MBP, induce destructive brain inflammation in immunodeficient mice [37]. Interestingly, this model exhibited

moderate T-cell infiltration with massive accumulation of granulocytes and severe tissue destruction.

Indirect experimental evidence might implicate a role for Th2 cells in inflammatory brain lesions. EAE, induced by immunization with myelin oligodendrocyte glycoprotein (MOG), is more severe in Brown Norway rats, which favor Th2 responses, and immunization with incomplete Freund's adjuvant is equally or more effective than that with complete Freund's adjuvant [38,39]. Lesions are mainly located in the spinal cord and optic nerves, resembling Devic's neuromyelitis optica and are characterized by mild T-cell infiltration and massive recruitment of granulocytes and eosinophils [39].

In MS, patterns of inflammation are in general consistent with a Th1–Tc1-mediated immune response (see earlier). There are, however, exceptions. Devic's neuromyelitis optica (NMO) is a demyelinating disease, characterized by severe destructive lesions in the spinal cord and the optic nerves and a massive tissue infiltration of granulocytes and eosinophils [40] associated with massive deposition of immunoglobulins and activated complement. Further, T cells and eosinophils in NMO lesions frequently express CCR3, a chemokine receptor associated with Th2 responses [40]. Neuropathological studies have clearly documented transitional forms of NMO and classical MS, which show features of both disease variants, indicating that the two are related. Although a possible role for Th2 cells in the initiation or the modulation of inflammatory brain lesions is at present far from being firmly established, these data indicate that immunomodulatory strategies, which interfere with T-cell polarization in MS patients, should be pursued with a critical and cautious mind.

### **The CD4–Th1 model of MS does not account for heterogeneous mechanisms of demyelination and tissue injury in MS patient subgroups**

Heterogeneous mechanisms of demyelination are evident from comparing NMO and classical MS. This

heterogeneity is not limited to uncommon variants but is also reflected in the immunopathology of MS lesions in patients with typical disease course [41] (Box 2). This finding was interpreted as an inter-individual heterogeneity of MS pathogenesis in different patient subgroups, possibly due to differences in their genetic background. This view is supported by studies on the genetic associations of MS, which show that multiple different genes confer the risk of developing the disease or are associated with a modification of disease course or severity [2]. Thus, autoimmunity might start the disease process in some MS patients but genetic background might determine what arms of the immune system are preferentially used in tissue damage, how the CNS reacts to immunological attack and the degree of re-myelination and repair.

### **The CD4–Th1 autoimmune model of MS does not account for the neurodegenerative component of MS**

In addition to focal demyelinated plaques, MS tissues show profound diffuse damage, including massive atrophy of the white and gray matter and a widespread degeneration of nerve fibers and gliosis in uninvolved regions [termed normal-appearing white matter (NAWM)] [42]. These diffuse changes in part result from axonal degeneration in demyelinated plaques [43,44]. The transection of axons within demyelinated plaques inevitably leads to secondary degeneration of the distal and proximal portions of the affected neuron [45]. Several studies show that white matter damage in MS outside demyelinated plaques follows the anatomical arrangement of fiber tracts that traverse lesions [46,47].

However, secondary degeneration fails to explain all diffuse injury in MS brains. Profound diffuse damage of 'normal' white matter appears early in MS, when low total lesion load excludes the possibility of diffuse changes secondary to axonal degeneration within plaques [48]. Similarly, the extent of diffuse brain injury fails to correlate with the size and localization of demyelinated plaques in primary progressive MS [49]. It was thus suggested that a neurodegenerative process might develop in MS patients independently from, or even preceding, the inflammatory reaction [50,51]. This view is supported by the notorious failure of immunomodulatory or immunosuppressive treatments in patients with primary progressive MS [52]. MS could be a primary neurodegenerative disease in some patients, augmented by a secondary inflammatory response. Although this possibility cannot be ruled out, pathology suggests an alternative. All MS lesions, including focal plaques or diffuse brain injury, in all stages of the disease and in all disease variants are associated with inflammation, which is not necessarily reflected by blood–brain barrier (BBB) damage, the most prominent correlate of brain inflammation in MRI imaging [53,54]. In patients with chronic progressive MS, the inflammatory reaction appears to be compartmentalized within the CNS tissue, shielded from peripheral immune control by the repaired BBB, and might continually activate resident inflammatory cells. This compartmentalized immune response does not depend on recruitment of leukocytes from the periphery and might cause chronic diffuse tissue damage, which occurs independently of focal lesions. Finally, the

#### **Box 2. Pathology of multiple sclerosis (MS) and its variants**

MS is a chronic inflammatory disease of the central nervous system. The inflammatory reaction is associated with the formation of large plaques of demyelination with relative axonal preservation [42]. However, axons are injured and destroyed in the demyelinated areas, and axonal loss, not inflammation or demyelination, is the major correlate for permanent neurological deficit. Demyelinated plaques can in part be repaired by remyelination, in particular at early stages of the disease. In addition to focal demyelinating plaques, there is a diffuse damage in the 'normal' white matter and the cortex, characterized by some demyelination, axonal loss and microglia and astroglia activation. This diffuse brain injury is particularly pronounced in patients with primary or secondary progressive MS [45].

Recent immunopathological studies on a large sample of MS cases revealed a profound heterogeneity in the structural patterns and mechanisms of demyelination. Four patterns of demyelination were found, which were heterogeneous between patient subgroups but homogenous in multiple lesions of the same patient. The four patterns were defined as: demyelination mediated by T cells and activated microglia or macrophages alone (pattern I), antibody and complement mediated demyelination (pattern II) [55], demyelination following hypoxia-like tissue injury (pattern III) [56] and extensive oligodendrocyte destruction at the plaque edges (pattern IV) [57].

closed BBB might protect this type of inflammation against immunosuppressive medications.

### Concluding remarks

Most of the current immunological concepts on etiology, pathogenesis and therapy of MS have been developed on the basis of data obtained from EAE, induced by Th1 cells. Although this model has provided extremely valuable information about induction and control of autoimmunity, as well as on mechanisms of immune surveillance and brain inflammation, recent observations in MS patients have revealed a much more complex picture. These data suggest that many different T-cell populations can, in principle, be involved in the induction, propagation and modulation of the disease and that the same cells, which are potentially encephalitogenic, can also provide a proper environment for remyelination and repair. Thus, MS is a disease in which many different components of the immune system interact and their relative importance for the development of the lesions might depend on the stage of disease evolution, the genetic background of the patients and possibly also on concomitant environmental influences. Under these circumstances, it is not surprising that current strategies of immunotherapy, which address single mechanisms of immunoregulation or immune-mediated tissue damage, showed only limited, or no, beneficial effects.

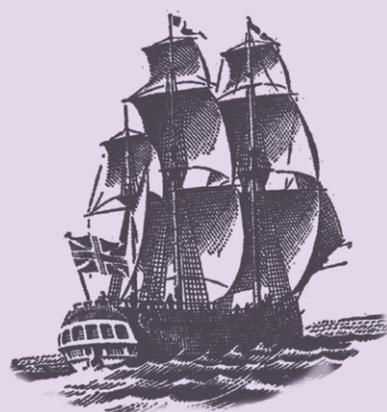
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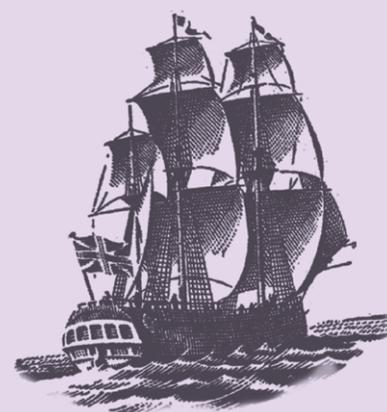
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