A large body of data indicates that multiple sclerosis (MS) is an autoimmune disease which is initiated by CD4+ T-helper 1 (Th1) and Th17 cells that are reactive against proteins in the myelin sheath. MS typically begins with a relapsing-remitting course, punctuated by clinical exacerbations associated with the development of focal inflammatory lesions in central nervous system white matter, followed by a secondary progressive (SP) phase, characterized by a gradual accumulation of neurological disability associated with widespread microglial activation and axonal loss. The molecular and cellular basis for this transition is unclear, and the role of inflammation during the SP stage is a subject of active debate. As of now, no immunological biomarkers have been identified in MS that are predictive of the clinical course or therapeutic responsiveness to disease-modifying agents, or that correlate with new lesion development, cumulative lesion load, or degree of disability. The discovery of such biomarkers would greatly facilitate clinical management and provide power for smaller and shorter clinical trials. In this article, we discuss the literature on immunological biomarkers in MS with a focus on stage-specific differences and similarities.

Introduction

Multiple sclerosis (MS), a multifocal demyelinating disease of the central nervous system (CNS), is the most common cause of nontraumatic disability among young adults in the Western hemisphere. It typically presents with a relapsing remitting course, in which discrete episodes of neurological symptoms (relapses) are separated by clinically quiescent periods (remissions). Relapses correlate with the formation of perivascular inflammatory lesions, or plaques, in the CNS. There has been no consistent evidence of an active viral or other microbial infection in the CNS of individuals with MS that would justify a local immune response. In fact, it is widely believed that relapsing remitting multiple sclerosis (RRMS) is initiated by an aberrant autoimmune attack directed against proteins embedded in the myelin sheath. An autoimmune etiology of MS is supported by extensive circumstantial evidence from animal models and gene-wide association studies (GWAS) (Steinman and Zamvil 2006; Sawcer and others 2011), and by the putative mechanism of the action of disease-modifying agents (DMA) that suppress clinical relapses by targeting lymphocytes (Stuve 2008; Kowarik and others 2011). Early in the disease course, peripheral blood leukocytes cross the blood–brain barrier (BBB) and infiltrate the brain, spinal cord, and optic nerves to drive plaque formation. Neurological deficits emerge when plaques occur in “eloquent” areas. Natural history studies have shown that the incidence of relapses and periodic breaches in the BBB decrease with disease duration. However, the majority of individuals with RRMS ultimately enter a secondary progressive (SP) stage, characterized by a gradual, inexorable accumulation of neurological disability that occurs independent of clinical relapses. The molecular and cellular basis for this transition is unclear, and the role of inflammation during the SP stage is a subject of active debate.

Clinical trials of DMA in RRMS frequently use annualized clinical relapse rates and magnetic resonance imaging (MRI) parameters that correlate with new lesion formation as primary outcome measures. The expanded disability status scale (EDSS) is the most commonly employed measure of clinical progression. However, the EDSS has been criticized for its poor intra- and inter-rater reliability and low sensitivity once patients develop difficulty with ambulation (Noseworthy and others 1990). As of now, no serological or peripheral blood mononuclear cell (PBMC)-based biomarkers have been identified that reproducibly correlate with clinical or radiological disease activity or progression. Furthermore, no immunological assays have been developed that are predictive of the subsequent clinical course or responsiveness to individual DMA. The discovery of such biomarkers would greatly facilitate the clinical management
of individuals with MS and provide power for smaller and shorter clinical trials in the future.

In this article, we discuss the literature on immunological biomarkers in MS with a focus on stage-specific differences and similarities. There is accumulating evidence that the nature of immune dysregulation evolves during the course of MS. The presence of widespread microglial activation in macroscopically normal appearing white matter (Kutzelnigg and others 2005) and lymphoid follicles in the leptomeninges (Serafini and others 2004) of secondary progressive MS (SPMS) brains suggests an ongoing participation of neuroinflammation in the pathogenic process, perhaps via pathways that are distinct from those dominant in the relapsing-remitting (RR) phase. The relative importance of different immune cell subsets and proinflammatory mediators during RRMS and SPMS holds important implications regarding strategic approaches to biomarker discovery and drug development across patient cohorts.

The Immunopathogenesis of RRMS

Histological trademarks of acute MS lesions include perivascular inflammatory infiltrates with adjacent demyelination and axonal transections (Adams and others 1989; Lassmann 2010). The perivascular infiltrates are composed of CD4+ and CD8+ lymphocytes and myeloid cells. GWAS implicate CD4+ T cells in the development of MS. The genetic locus that correlates most strongly with disease susceptibility encodes major histocompatibility complex (MHC) Class II molecules which govern CD4+ T-cell activation (Sawcer and others 2011). Other genetic polymorphisms associated with susceptibility to MS encode receptors that drive T-cell proliferation and survival, namely the interleukin-2 receptor α chain and IL-7 receptor α chain (Zuvich and others 2010; Wang and others 2011). The animal model, experimental autoimmune encephalomyelitis (EAE), provides further support for a critical role of CD4+ T cells in autoimmune demyelination. EAE has striking immunological and clinical similarities with MS. It has been induced in a wide variety of mammalian species by vaccination against MHC Class II restricted myelin epitopes. EAE can also be transferred from myelin-vaccinated mice to syngeneic naïve hosts using purified CD4+ T-cell lines or clones (Sakai and others 1986; Fallis and others 1989). Encephalitogenic myelin-specific CD4+ T cells invariably fall within the Th1 or Th17 lineage and produce the proinflammatory cytokines interferon γ (IFNγ) and IL-17, respectively (Kronke and others 2008).

Perhaps the most direct demonstration of the autoimmune basis of RRMS comes from clinical trials of immunomodulatory agents. Martin and colleagues treated RRMS patients with an altered peptide ligand (APL) of myelin basic protein (MBP) with the intention of tolerizing MBP-reactive T cells or deflecting their differentiation toward an immunosuppressive, regulatory, or an innocuous Th2 phenotype. Unexpectedly, administration of the APL was temporally associated with the expansion of circulating MBP-reactive Th1 cells and clinical worsening in a subgroup of patients (Bielekova and others 2000). Conversely, drugs that impede lymphocyte trafficking to the CNS (Polman and others 2006; Cohen and others 2010), block growth factor signaling into T lymphocytes (Gold and others 2013), or deplete lymphocytes from the periphery (Coles and others 2012) suppress MS relapse rates and the accumulation of MRI lesions.

Dysregulation of Adaptive Immunity in RRMS: The Myelin-Reactive T-Cell Repertoire

Earlier studies on the frequency of myelin-reactive T cells in MS are conflicting; some investigators report a significantly higher incidence of myelin-specific PBMC in individuals with MS compared with age- and gender-matched healthy controls (HC), while others report no significant difference (de Rosbo and Ben-Nun 1998; Diaz-Villoslada and others 1999; Moldovan and others 2003; Bielekova and others 2004; Moldovan and others 2005; Grau-López and others 2009). Many of the earlier studies that found no differences between patients and HC used proliferation as a measure of T-cell reactivity, and nonhuman myelin proteins for antigenic stimulation. In contrast, Hedegaard and others (2008) found that human MBP-reactive PBMC from untreated RRMS patients produced larger quantities of IFNγ and TNFα, and lower amounts of IL-10, than analogous PBMC from HC. The production of IL-5 and IL-17 correlated with the number of active plaques on MRI. Consistent with these results, Moldovan and others (2003) detected relatively high frequencies of PBMC in RRMS patients who produced IFNγ on ex vivo stimulation with libraries of overlapping 9-mer peptides spanning the length of human MBP. IFNγ responses to proteolipid protein (PLP) peptides correlated with the level of clinical disability. However, not all discrepancies can be attributed to technical and methodological inconsistencies. Hence, Hellings and others (2001) found no significant difference between MS patients and HC in IFNγ responses to human myelin oligodendrocyte protein (MOG), MBP, or myelin peptides, despite using the same immunological assay (enzyme linked immunosorbent spot, or ELISPOT) as the former 2 studies.

A relatively small number of longitudinal analyses have been performed in which fluctuations in cytokine production were compared with radiological and/or clinical disease activity. Calabresi and others (1998) followed 8 clinically active RRMS patients with 6 monthly MRI scans and concomitant ELISPOT assays. Changes in phthoemaglutatin-stimulated IL-2 production correlated strongly with the appearance of gadolinium-enhancing lesions. There was a weaker association between enhancing MRI lesions and the frequency of IFNγ or Lymphotoxin-α secreting cells. Arbour and others (2003) used a flow cytometry assay to monitor the activities of T cells that are reactive to myelin-associated oligodendrocytic basic protein (MOBP) in 10 untreated RRMS patients over 18 months. MOBP-specific T-cell proliferation and IFNγ production correlated with clinical relapses and enhancing lesions. Hellings and others (2002) monitored T-cell reactivity to 3 myelin proteins (human MBP, PLP, and MOG) in 7 patients with RRMS every 2 months over an 18 month period. In some patients, the appearance of gadolinium-enhancing MRI lesions concurred with increased reactivity to one or more myelin antigens as measured by IFNγ ELISPOT (Correale and others 1995). Increases in the secretion of IL-6, TNFα, and IFNγ by PBMC in response to challenge with MOG or MBP (measured in culture supernatants by ELISA) generally coincided with MRI activity and preceded clinical relapse. In contrast, a decrease in IL-10 production consistently preceded the occurrence of a clinical
attack. Of note, 6 of the 7 patients were treated with IFNβ-1a during the study, which might have altered cytokine responses. More recently, Moldovan and others (2005) collected blood samples from 14 RRMS patients and 15 age- and sex-matched HC every 3 months over 1 year. MRI scans were obtained at each visit. ELISPOT assays were performed using MBP and PLP peptides spanning the whole molecule as the antigenic stimulus. The majority of MS patients showed recurrent spikes in the frequency of MBP- and PLP-reactive IFNγ producers. This was particularly true for patients who had gadolinium-enhancing lesions on serial MRI scans. In contrast, IFNγ responses were relatively stable in the HC cohort. Periodic surges of anti-myelin T-cell reactivity in PBMC from RRMS patients have also been reported by other groups (Pender and others 2000).

**Increased Frequencies of IL-17+IFNγ+ Co-Expressing T Cells in MS**

Shortly after the IL-23 p19 chain was cloned in 2000 (Oppmann and others 2000), IL-17-producing cells were detected in the CNS of animals with EAE and humans with MS (Langrish and others 2005; Tzartos and others 2008). Subsequently, IL-23-modulated Th17 cells received a great deal of attention as putative effectors in autoimmune demyelinating disease. More recently, IL-17+IFNγ+ double producers have been implicated in the pathogenesis of EAE and MS (Hirota and others 2011). The frequency of IL-17+ T cells in human PBMCs is very low to undetectable when measured by intracellular staining and flow cytometry directed ex vivo or after short-term activation in the absence of polarizing factors. In order to enumerate CD4+ T cells in the circulation with the potential to produce IL-17, investigators have taken to activating PBMC under Th17 polarizing/stabilizing conditions for several days before analysis. Kebir and others (2009) isolated CD4+CD45RO+ memory T cells from peripheral blood of female RRMS patients and HC, and incubated them with recombinant IL-23 and neutralizing antibodies against IL-4 and IFNγ. After 6 days, the cells were harvested and subjected to flow cytometric analysis. The frequency of IL-17+ and of IL-22+ lymphocytes, as well as the percentage of cells simultaneously producing IL-17 and IL-22, was elevated in T cell lines derived from RRMS patients during a clinical exacerbation when compared with patients in remission or HC. Similarly, the frequency of CD4+ T cells co-expressing IL-17 and IFNγ was higher in RRMS patients in relapse. In contrast, there was no difference in the frequency of IFNγ single producers between the groups. Darlington and others (2013) employed a similar approach to measure Th responses in individuals with aggressive RRMS before and after treatment with ablative chemotherapy and autologous hematopoietic stem cell transplantation. PBMC were cultured for 6 days with anti-CD3 antibodies, with or without recombinant IL-23, anti-IFNγ, and anti-IL-4, before surface and intracellular staining and flow cytometry. The investigators found that a favorable clinical response to treatment was associated with a diminution in the frequency of circulating Th17, but not Th1, cells.

**Changes in Cytokine Expression After Treatment with DMA**

A number of studies have documented alterations in serum cytokine levels after the initiation of disease-modifying therapy (Navikas and Link 1996). Dhib-Jalbut and others (2013) measured cytokine responses in patients with clinically isolated syndrome and recent onset RRMS (less than 12 months from diagnosis) before and after the initiation of high-dose beta interferon therapy. Samples of sera and/or anti-CD3/CD28-stimulated PBMC culture supernatants were analyzed for expression of a panel of pro-inflammatory and regulatory cytokines by ELISA. Levels of IFNγ (in both sera and culture supernatants) and TNFα (in serum) fell after initiation of the DMA. Conversely, there were significant increases in IL-10 (in serum) and TGF-β (in serum) over the 12-month study period. Expression of the Th2-associated cytokine IL-13 rose in culture supernatants. Surprisingly, IL-17 levels remained stable in culture supernatants after the initiation of beta interferon. However, IL-17 levels were higher in patients who had breakthrough relapses compared with those who were relapse free throughout the study. Several independent laboratories have similarly detected systemic elevations in IL-10 expression in individuals with RRMS after the administration of beta interferon (Rudick and others 1998; Waubant and others 2001; Kvarnström and others 2013). Recently, Ayers and others (2013) showed that lipopolysaccharide (LPS)-stimulated CD14+ monocytes up-regulate IL-10 within hours of the first dose of glatiramer acetate.

**Evidence of a Role of Inflammation in SP Phase**

As mentioned earlier, the formation of gadolinium-enhancing MRI lesions, indicative of local BBB breakdown and associated perivascular inflammation, decreases in frequency with disease duration and is less common in individuals with SPMS than RRMS (Filippi and others 1997). Furthermore, immunomodulatory DMA tend to lose efficacy after transition to a SPMS stage (Paolillo and others 1999; Panitch and others 2004). Such observations have led to the proposal that the gradual accumulation of disability in SPMS is driven by neurodegeneration, manifested as neuronal cell death, Wallerian degeneration, and astrocytosis, independent of the autoimmune assault which predominates earlier in the disease course (Trapp and Nave 2008). Conversely, a substantial body of data indicates that inflammation is still relevant, and contributes to CNS tissue damage, during the SP stage. We and others have found increased frequencies of circulating Th1 and Th17 cells in individuals with SPMS as well as RRMS compared with age- and sex-matched HC (unpublished data (Becher and others 2013)). Neuropathological studies demonstrate widespread microglial activation and diffuse lymphocyte infiltration in the cerebral white matter of individuals with SPMS, as opposed to the multifocal, lymphocyte-rich perivascular infiltrates that are characteristic of the RR stage (Kutzelnigg and others 2005; Frischer and others 2009). Prineas originally documented the presence of perivascular infiltrates “...organized in a manner similar to the antibody-producing medullary region of lymph nodes” in the brains of individuals with progressive MS (Prineas 1979). More recently, Serafini and others (2004) discovered lymphoid follicles in the sulci of brain specimens from patients with SP, but not RR, MS. The earlier observations indicate that the nature of the aberrant immune response evolves over the disease course and might explain why the efficacy of individual DMA differs between the RR and SP phases.
**Dysregulation of the Innate Immune System in SPMS**

Multiple studies point to dysregulation of the innate arm of the immune system (and in particular, cells of the myeloid/granulocyte lineage) as a distinctive feature of SPMS. Hence, Filion and others (2003) found increased expression of costimulatory molecules on peripheral blood monocytes from SPMS patients compared with those from RRMS or HC. Freshly isolated monocytes from SPMS patients secreted 10-fold more IL-12 than monocytes from either RRMS patients or HC. Karni and others (2006) detected an increased percentage of monocytes expressing IL-12, CD80, and TNFα in the blood of SPMS patients. PBMC from SPMS patients, by comparison to PBMC from RRMS patients or HC, also produced larger amounts of the myeloid chemokine, IL-18, in response to polyclonal stimulation with αCD3 and αCD28 (Karni and others 2002). Elevated IL-18 production was dependent on the interaction between antigen-presenting cells and activated T cells via CD40-CD40 ligand engagement. Within the SPMS cohort, IL-18 levels correlated with disease duration. More recently, it was shown that purified myeloid dendritic cells from SPMS patients secrete larger quantities of IL-12 than monocytes from either RRMS patients or HC. Karni and others (2006). Myeloid dendritic cells from SPMS patients were particularly efficient at priming naïve T cells to produce proinflammatory cytokines. Collectively, these data suggest that the transition from RR to SPMS is mirrored by a shift from adaptive to innate immunity (Weiner 2008). In a recent study, an increased frequency of IL-23 receptor expressing CD4+ T cells was detected in peripheral blood from SPMS patients when compared with RRMS patients (Christensen and others 2013). IL-23 receptor is a marker of Th17 cells. The accumulation of Th17 cells during SPMS could, potentially, drive innate immune dysregulation, as a major function of IL-17 is to induce the production of chemokines and growth factors that mobilize and activate myeloid cells (Iwakura and others 2011).

**Lymphoid Chemokines and Progressive MS**

The discovery of lymphoid follicle-like structures in the meninges of autopsied brain tissue from individuals with SPMS has prompted renewed interest in the role of neuroinflammation during the SP phase. The lymphoid aggregates, found in ~40% of SPMS autopsy specimens, contained proliferating B cells, T cells, and plasma cells, and a reticulum of CD35+ stromal cells and follicular dendritic cells expressing the lymphoid chemokine, CXCL13 (Serafini and others 2004; Magliozzi and others 2007). Follicular plasma cells and plasmablasts expressed surface immunoglobulin. Similar structures were not found in a series of brains from individuals with RRMS and primary progressive MS. The presence of meningeal follicles was associated with a younger age of MS onset, a more aggressive clinical course, more pronounced demyelination, microglial activation, and loss of neurites in the cerebral cortex. Each meningeal follicle was located adjacent to a large subpial cortical lesion. The authors hypothesized that the meningeal follicles have a direct role in cortical injury, possibly by releasing soluble factors that diffuse into the underlying cortex and have toxic effects on glia and neurons/axons (Magliozzi and others 2007).

Substances produced by leukocytes in meningeal follicles, such as lymphoid chemokines, are candidate biomarkers in MS. In fact, CXCL13 is expressed at elevated levels in cerebrospinal fluid (CSF) from patients with SPMS, as well as from patients with RRMS in relapse, when compared with patients with noninflammatory neurological diseases (Krumholz and others 2006; Festa and others 2009; Sellebjerg and others 2009; Piccio and others 2010; Khademi and others 2011; Ragheb and others 2011; Bielekova and others 2012; Alvarez and others 2013; Romme Christensen and others 2013). CSF CXCL13 levels reproducibly correlate with leukocyte count and IgG index (Krumholz and others 2006; Sellebjerg and others 2009; Ragheb and others 2011). In one study, CSF CXCL13 levels correlated with levels of the neurofilament light chain (a marker of axonal damage), specifically in the progressive MS cohort (Romme Christensen and others 2013). When CSF samples were collected from SPMS patients 1 year apart, CXCL13 levels tended to be stable (Romme Christensen and others 2013).

T-follicular helper (Tfh) cells are a subset of CD4+ T cells that interact with B cells in lymphoid follicles and participate in germinal center formation. Flow cytometric studies revealed an increased percentage of CD4+ T cells with a cell surface phenotype consistent with activated Tfh (ie, CXCR5+ ICOS+) in PBMC from patients with progressive MS (Christensen and others 2013). Interestingly, the frequency of circulating Tfh cells and DC-SIGN+ B cells correlated with accumulation of disability in SPMS patients (defined by a significant increase in EDSS score over the previous 2 years). Whether Tfh cells migrate to the CNS and participate in the development of meningeal follicles remains to be elucidated.

**Challenges to the Discovery of Biomarkers in MS**

Despite the advances that have been made in our understanding of MS pathogenesis, it has been difficult to translate that knowledge into the discovery of clinically useful biomarkers. There are many explanations for this. First and foremost, biomarker discovery is hindered by the inaccessibility of nervous system tissues for cellular and molecular analysis. The inflammatory molecules and immune cells present in CSF do not necessarily reflect pathological processes in the CNS parenchyma. Furthermore, it is impractical to obtain multiple CSF samples for serial monitoring. Serum assays and PBMC analyses are even further removed from immune responses within the CNS. In addition, peripheral immune parameters are vulnerable to a multitude of extraneous factors (such as infections, vaccinations, and allergies) that could complicate data interpretation.

The ideal biomarker would be specific for CNS autoimmunity. Based on our understanding of MS pathogenesis, it would involve a measurement of myelin antigen-specific T-cell responses. However, the identification of a dominant myelin epitope that is targeted in a majority of MS patients is far from trivial. There is likely to be considerable intersubject variability even within subpopulations bearing the same MHC Class II haplotype. With the advent of epitope spreading, the myelin-reactive repertoire might evolve...
within individuals over time. Finally, autoreactive T cells in the periphery could differ in phenotype and/or antigenic reactivity from the effector cells that are actually responsible for neuroinflammation and CNS tissue damage, if the latter are sequestered behind the BBB.

Drawing correlations between immune parameters and disease activity poses additional challenges. MRI studies have shown that the majority of MS lesions form silently. Therefore, imaging is a more accurate barometer of new lesion formation than clinical signs or symptoms. However, even MRI may be insufficient. The sensitivity of MRI in detecting new lesions depends on the magnet strength, the dose of gadolinium administered, and the time lapse between administration of gadolinium and image acquisition (Uysal and others 2007; de Graaf and others 2012). Magnetization transfer and MR spectroscopy have revealed pathological changes in regions of MS brains that resemble “normal appearing white matter” on conventional MRI. The use of imaging modalities as a gold standard for validating biomarkers is particularly problematic in progressive MS, as cortical lesions, axonal changes, and meningeal follicles are the most difficult to visualize.

Future progress will likely be advanced by longitudinal studies with large cohorts of demographically uniform patients followed over long periods of time with multimodal imaging and clinical assessment tools (including cognitive testing). It is essential that the subject populations be rigorously characterized with regard to clinical, radiological, and genetic characteristics as well as treatment history. Autotantigen-specific assays should involve libraries of overlapping peptides that span the length of several candidate myelin proteins. When possible, serum and CSF parameters should be assayed in parallel. Novel assays in proteomics (including secretomics), flow cytometry, genomics, and epigenetics will hopefully yield more reliable and clinically meaningful biomarkers.

Conclusion

Based on the immunological and neuropathological studies summarized earlier, we would argue that the collective data support a persistent role of inflammation across the clinical stages of MS. However, the cytokine/chemokine networks, leukocyte subsets, and anatomical staging of the autoimmune response appear to evolve over time. In early stages after initial clinical presentation, pathology is driven by an immune assault mounted from the periphery. Lymphocytes and myeloid cells infiltrate CNS white matter from the circulation and trigger an inflammatory cascade that, ultimately, results in numerous defined areas of demyelination and axonopathy, centered around parenchymal venules. During this period, systemic administration of agents that hinder lymphocyte egress from lymph nodes (ex. fingolimod), block lymphocyte/monocyte trafficking across the BBB (ex. natalizumab), or deplete circulating lymphocytes (ie, alemtuzumab) is effective in suppressing clinical relapses.

In contrast, in the SP phase of disease, the “headquarters” of the autoimmune assault shift to the target organ itself, manifested by widespread microglial activation and astrogliosis and the development of meningeal lymphoid follicles in the deep recesses of the brain. The mechanism underlying this transformation is poorly understood. To some extent, the immunopathology of SPMS resembles an amplification of the dysregulation that occurs in the earlier RR stage. Innate immune cells that are activated by, and act downstream of, myelin-reactive T cells show striking abnormalities in SPMS. IL-17- as well as IFNγ-producing T cells have been implicated in pathogenesis throughout the disease course. IL-17 induces the production of chemokines and growth factors that activate myeloid cells and trigger their mobilization into the circulation (Ouyang and others 2008). In addition, myelin-reactive Th17 cells induce ectopic follicle-like structures in the CNS in mice with adoptively transferred EAE (Peters and others 2011). Interestingly, the frequency of circulating IL-23 receptor expressing CD4+ T cells, suggestive of a Th17 phenotype, associates with MS disease duration and is preferentially elevated during SPMS (Christensen and others 2013). Consistent with this observation, a high frequency of circulating RORγt+ CD4+ T cells was recently found in individuals with SPMS, but not RRMS (Gironi and others 2013). It will be interesting to reproduce these studies in independent cohorts and to examine, in greater detail, the relative importance of autoreactive Th1 and Th17 cells, and downstream innate immune factors, during the different stages of MS. The discovery of serological and CSF biomarkers that reflect CNS disease activity, and predict future clinical phenomenology and responsiveness to DMA, is an immediate goal for advancing MS therapeutics to the next level. Perhaps most important will be the identification of candidate therapeutic targets for progressive forms of MS.

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