Wiskott–Aldrich syndrome: another piece in the puzzle

L. D. Notarangelo and L. Mori
Department of Pediatrics and A. Nocivelli Institute for Molecular Medicine, University of Brescia, Italy

Keywords: B lymphocytes, leucocyte trafficking, T lymphocytes, Wiskott–Aldrich syndrome

During the past 15 years, major advances in molecular genetics have led to the identification of several primary immune deficiency (PID) genes. In many cases, unravelling the genetic defect has been essential to disclose the molecular and cellular pathophysiology of PID. However, for Wiskott–Aldrich syndrome (WAS), whose gene was identified in 1994 [1], we are still waiting for a comprehensive understanding of the mechanisms that lead to immune deficiency, thrombocytopenia and eczema.

During past decades, investigation of patients with WAS had led to the recognition of a variety of morphological, numerical and functional abnormalities in several haematopoietic cell lineages. After cloning of the WAS protein (WASP) gene, many groups have tried to understand the role of WAS protein (WASp) in both the haematopoietic and the immune systems; while doing so, they have also attempted to provide a biochemical and molecular basis for the abnormalities previously reported in patients with WAS.

At the same time, the identification of the WASP gene has also allowed a more detailed investigation into the clinical phenotypes associated with WASP mutations. As a result of this process, it has been shown that the spectrum of disorders associated with WASP defects may range from typical and severe WAS to a milder phenotype characterized by persistent thrombocytopenia with minimal or no signs of immune deficiency [2], and even to intermittent thrombocytopenia [3]. Moreover, and surprisingly, it has also been shown that activating mutations of WASP are responsible for X-linked thrombocytopenia or myelodysplasia [4,5]. The identification of such a broad spectrum of clinical manifestations associated with WASP mutations has further indicated the need for a clear understanding of the functional role of WASp in the haematopoietic and immune systems, and has also prompted attempts at genotype–phenotype correlations [6]. The latter is particularly important in view of the severe outcome of typical forms of WAS, and of the difficulties associated with haematopoietic stem cell transplantation (HSCT). In fact, while optimal results can be obtained with HSCT from HLA-identical family donors, experience with matched unrelated donors (MUD) has shown that good results can be achieved only if the transplant is performed within the first 5 years of life [7], once again indicating the need for accurate prediction of the clinical phenotype. Finally, the lack of suitable therapeutic options in a large proportion of WAS patients has prompted investigations into alternative forms of treatment, especially gene therapy.

With such a scenario, a detailed characterization of the defects associated with WAS, and an investigation into the contribution of WASP mutations to such abnormalities, represents an essential goal.

For many years, researchers have focused their attention on T cell abnormalities in WAS, demonstrating abnormal morphology and defective T cell proliferation in response to CD3 ligation [8,9]. More recently, these defects have been interpreted more effectively following the discovery that WASp plays a crucial role in cytoskeletal remodelling downstream of T cell receptor engagement, and contributes substantially to immune synapse formation between T lymphocytes and antigen-presenting cells [10]. There is no doubt that defects in these functions represent an essential part of the immunodeficiency of WAS, and that proof of their correction will also be part of future clinical trials based on gene therapy. Even within the T cell compartment, however, there is still room for surprising findings. In fact, the early recognition that the number of T lymphocytes decreases progressively with age [11] has recently been challenged by the group of Remold-O’Donell, who have found that T cell lymphopenia is already present early in life in patients with WAS [12]. In the same study, the authors also reported previously unidentified abnormalities in the distribution of T cell
subsets, with an increased proportion of effector memory T lymphocytes among adults with WAS [12].

A few groups, including ours, have recently looked at natural killer (NK) cell distribution and function in WAS. Defective NK cell-mediated cytotoxicity has been demonstrated in WAS patients [13,14]; once again, this defect reflects abnormalities at the immunological synapse, this time between NK and target cells.

The involvement of WASp in cytoskeletal reorganization has prompted many groups to investigate in detail the morphology and function of macrophages, neutrophils and dendritic cells in WAS patients. Indeed, severe defects have been reported in the ability of WAS macrophages to form podosomes, which are important for adhesion and cell motility [15], thus explaining the defective chemotactic responses reported previously for WAS monocytes and macrophages [16,17]. Similar abnormalities have been reported recently for dendritic cells, namely defective podosome and lamellipodia formation, impaired polarization, poor translocation and defective cell adhesion [18–21].

Surprisingly, the function of B lymphocytes in patients with WAS has received little attention, even if aberrant distribution of serum immunoglobulins, impaired antibody production to polysaccharide antigens and defective maturation of antibody responses to T-dependent antigens (such as bacteriophage φX174) have been well known for many years (reviewed in [22]). Controversial results have been reported on the efficiency of signal transduction following engagement of the B cell receptor in B lymphocytes and Epstein–Barr virus (EBV)-transformed B cell lines from patients with WAS. We and others have reported on defective cytoskeletal reorganization both in vitro and in vivo [23–25]. Moreover, we have shown that these defects are accompanied by profound architectural abnormalities of secondary lymphoid tissues, as revealed by a ‘burn-out’ morphology of germinal centres and a markedly reduced thickness of the marginal zone [24]. Importantly, such defects have been recently confirmed also in WASp-null mice [25].

In this issue of Clinical and Experimental Immunology, Park et al. report on phenotypic abnormalities of B cells in patients with WAS [26]. Their novel findings extend a previous report from the same authors, in which they had identified a selective B cell lymphopenia in WAS that was more prominent among infants [12]. In the most recent study, the authors have shown that a substantial proportion of circulating B cells from WAS patients fail to express CD21 and CD35, two complement receptors that are involved in antigen capture and presentation by B lymphocytes. While this may compromise the ability to elicit and sustain adequate antibody responses, it may also contribute to breakage of tolerance and to autoimmunity, because down-regulation of CD21 and CD35 has been reported in several autoimmune diseases in humans, as well as in murine models of autoimmunity [27,28]. Taken together, these data shed new light on the pathophysiology of autoimmune manifestations of Wiskott–Aldrich syndrome [29].

Moreover, Park et al. also report on the decreased proportion of CD27+ post-germinal centre B cells, and on the increased frequency of CD10+CD27+CD38bright germinal centre B cell progenitors among WAS adults [26]. According to the authors, these data may reflect either the failure of normal germinal centre reactions to occur or the aberrant migration of patients’ B cells due to the underlying cytoskeletal defect. In keeping with this hypothesis, our unpublished observations indicate that while in healthy individuals the proportion of somatically mutated B cell clonotypes increases after the first few years of life, such an increase is not observed among WAS patients. Furthermore, the defective migration of WASp-deficient B cells has been reported by Westerberg et al. both in humans and mice [25]. As a whole, these data confirm that WAS is characterized by impaired maturation of B cell responses, possibly as the result of defective B cell migration and defective organization of specialized lymphoid structures.

Interestingly, many abnormalities identified in T and B lymphocytes from WAS patients (including the increased proportion of effector memory T cells, and the reduced number of CD27+ memory B cells) are also observed in patients with warts, hypogammaglobulinaemia, infections and myelokathexis (WHIM) syndrome, a disorder of altered leucocyte trafficking due to mutations in the chemokine receptor CXCR4 [30]. Chemokines and chemokine receptors are crucial in regulating lymphoid development and the maturation of the immune response, including trafficking through and within the germinal centre [31]. Surprisingly, the distribution and function of chemokine receptors expressed on the surface of T and B lymphocytes from patients with WAS has not been investigated in detail until now. In view of the crucial role of WASp in regulating cytoskeletal reorganization, it is likely that chemokine-mediated lymphoid trafficking will be altered significantly in WAS, thus adding to the idea of WAS as a disease of altered cellular trafficking [32].

While the observations by Park et al. on B cell phenotypic disturbances add another piece to the puzzle of WAS, it is important that studies on these patients continue. Indeed, WASp-null mice mimic only partially the clinical phenotype of WAS patients. A complete picture of the cellular and biochemical abnormalities associated with WAS is therefore essential before novel forms of treatment, possibly based on gene therapy, come into practice.

References

Wiskott–Aldrich syndrome: another piece in the puzzle


20 Burns S, Hardy SJ, Buddle J, Yong KL, Jones GE, Thrasher AJ. Maturation of DC is associated with changes in motile characteristics and adherence. Cell Motil Cytoskeleton 2004; 57:118–32.


