The ‘best’ basic science paper on multiple sclerosis in 2012

Don Mahad

The productivity of basic science researchers working in the multiple sclerosis (MS) field has never been more evident, with several hundred peer-reviewed articles published in 2012. This makes the task of selecting the ‘best’ basic science paper on MS by one individual both an arbitrary one, and one destined to upset all but a few authors. Having acknowledged the highly subjective nature of this process, a large number of papers are worthy of consideration although only a few are summarized here.

The positive outcome of clinical trials that therapeutically target the B cell antigen, CD20, in MS patients has undoubtedly inspired the bench work of both basic and clinician scientists. Choi and colleagues investigated meningeal inflammation in primary progressive MS (PPMS) cases. They detected B cell and T cell aggregates in the meninges of a subset of PPMS cases although ectopic lymphoid-like structures, previously described in secondary progressive MS (SPMS), were absent in PPMS cases: approximately 30% of PPMS cases versus 52% of SPMS contained meningeal lymphocytic aggregates. Meningeal inflammation correlated with the extent of grey matter (GM) demyelination and damage to neurites. A pathogenic role for B cells was also suggested by the lower age at death and disease duration in the subset of cases with substantial meningeal inflammation. The detection of immunoglobulin-independent secretory products of B cells that were cytotoxic to oligodendrocytes by Lisak and colleagues raised interesting avenues for further exploration of the contribution of B cells to the GM pathology of MS. Having proposed a potential role for B cells in GM pathology, the next challenge in translating the findings to patients that attend MS clinics is to develop relatively non-invasive techniques to identify MS patients with B cell aggregates. In this respect the contribution by Von Büdingen and colleagues, who investigated immunoglobulin heavy chain variable region genes by PCR amplification of paired polymerase chain reaction (PCR) and peripheral blood (PB) samples from MS patients and other neurological disorders (OND), is of interest. They identified B cell clones in PB that were closely related, in terms of their IgG-VH sequences, to those isolated from cerebrospinal fluid (CSF) from MS patients as well as those with OND: IgG-VH sequences were found to be the same in the CSF and PB indicating that, at least in the case of a minority of central nervous system (CNS) B cell clones (approximately 8.7%), antigen-experienced B cells are shared between the CNS and PB. In MS patients, deep sequencing of IgG-VH repertoires confirmed previous findings of B cell activation in the CNS in MS and identified this approach as a potential method to monitor clonally-expanded populations of B cells in the CNS. It would be interesting to see whether such an approach may be useful to distinguish patients with B cell aggregates from those without. Furthermore, deep repertoire sequencing of IgG-VH of PB may be a way to monitor treatment response in the CNS following interventions, such as intrathecal rituximab, that target CNS B cells in MS patients.

The effector mechanisms of activated immune cells in MS include non-immune pathways. For example, reactive oxygen and nitric oxide species generated by the oxidative burst in activated microglia and macrophages resulted in diffuse mitochondrial injury, driving tissue destruction in so-called pattern III and Balo’s type acute MS lesions. In these lesions, oligodendrocytes degenerate through a dying-back process and undergo apoptosis. Capriariello and colleagues modelled oligodendrocyte apoptosis by expressing a chemically inducible analogue of caspase-9, which selectively ablated mature oligodendrocytes. This non-autoimmune method, also distinct from gliotoxin-induced myelin loss, caused oligodendrocyte loss and focal demyelination while sparing oligodendrocyte progenitor cells (OPCs). The proliferation of OPCs and endogenous repair were enhanced as a result, possibly due to the phagocytosis of myelin debris by activated microglia. In terms of the inflammatory response to oligodendrocyte apoptosis, microglial response occurred rapidly and early whereas T cell infiltration was delayed. Such a T cell response was absent when oligodendrocytes were ablated by tamoxifen-inducible diphtheria toxin-A in previous studies. This new model is a valuable tool to understand the signalling pathways of the secondary immune response.

University of Edinburgh, UK.

Corresponding author:
Don Mahad, Centre for Neuroregeneration, University of Edinburgh, Chancellor’s Building, 49 Little France Crescent, Edinburgh, EH16 4SB, UK. Email: don.mahad@ed.ac.uk
Following oligodendrocyte loss, myelin sheath tends to be restored to the axon (remyelination) as evident in MS and following experimental demyelination. In the GM, Chang and colleagues observed remyelination to a greater extent in so-called type-I or leucocortical GM lesions, where part of the adjacent white matter (WM) is also demyelinated. Molecules that inhibited remyelination were upregulated in the WM portion of these cortical lesions. Assuming that GM and WM components of type-I lesions were formed at the same time, these findings suggested enhanced endogenous remyelination in the GM relative to WM. The failure of remyelination in MS has been well-documented in the WM and continues to be a focus of intense research. The age-related decline in remyelination following experimental demyelination has provided a valuable opportunity to further explore factors that limit remyelination in MS. In an elegantly designed experimental study, Ruckh and colleagues identified enhanced CNS remyelination in an older animal physically joined to a young partner (heterochronic parabiosis), both with a shared circulation. In the older animal with an experimentally demyelinating lesion, they observed increased angiogenesis at the lesion site, OPC proliferation and differentiation and increased level of remyelinating oligodendrocytes. The positive outcome in the older animals, carried out by the endogenous OPCs, was due to the recruitment of blood-derived monocytes from the younger partner into the circulation and CNS of the older animal. The younger monocytes augmented the clearance of myelin debris following experimental demyelination, thus, minimising the inhibitory effects of myelin debris on OPC differentiation. Importantly, this study indicated that the aged OPCs residing in older subjects have the potential to remyelinate when encouraged by exogenous factors.

Together, these contributions highlight the need to better understand the cellular, subcellular and molecular basis of this acquired, inflammatory demyelinating neurodegenerative disease. Due to the fundamental implications of the findings of the impressive work by Robin Franklin’s group for strategies to enhance remyelination in MS, their contribution deserves to be the best basic science paper on MS in 2012.

Conflicts of Interest
The author declares that there are no conflicts of interest.

References