SIgN Immunology Seminar

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Thymus amd Myasthenia Gravis: a liaison between innate and autoimmunity

Host
Prof Paola Castagnoli
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Date
Tuesday, 19 June 2012

Time
10am – 11am

Venue
SIgN Seminar Room,
Immunos Building
Level 4
Biopolis

The thymus plays a major role in myasthenia gravis (MG) and infectious agents are possible environmental factors triggering autoimmunity. We recently demonstrated an active Epstein-Barr virus (EBV) infection in myasthenia gravis (MG) thymus, suggesting that EBV might be responsible for autoimmunity maintenance in MG patients by immortalizing intra-thymic autoreactive B-cells. The persistent EBV infection in MG thymuses, combined with data revealing a thymic pro-inflammatory state in most patients, indicate that a viral contribution to the pathogenesis of MG is likely. Transcriptional profiling by low-density array and real-time PCR showed over-expression of genes involved in inflammatory and immune response in MG thymuses. Real-time PCR for EBV genome, latent (EBER1, EBNA1, LMP1) and lytic (BZLF1) transcripts, and immunohistochemistry for LMP1 and BZLF1 proteins, confirmed an active intra-thymic EBV infection. Considerable data indicate that EBV can elicit and modulate Toll-like receptor (TLR)-mediated innate immune responses, including TLR7 and 9 signalling, reported to trigger/enhance autoimmunity. We investigated TLR7 and 9 expression in MG thymus. By real-time PCR, we found that TLR7 and 9 transcripts were significantly up-regulated in EBV-positive MG compared with EBV-negative control thymuses. By confocal microscopy, TLR7 and 9 were detected in B- and plasma cells of MG germinal centers (GCs) and medullary infiltrates, where they co-localized with EBV antigens. MG proliferating B-cells expressed TLR7 and 9, indicating that TLR7/9 stimulation might contribute to abnormal B-cell proliferation in MG thymus. TLR7 and 9 mRNA levels did not correlate with GC number; both laser microdissected GCs and GCs-free sections showed higher TLR7 and 9 transcriptional levels than control thymuses, indicating that TLR7/9 increase in MG thymuses was not due only to GCs.

Altogether, our results support a role of inflammation and EBV infection as pathogenic features of MG thymus and that EBV might activate TLR7/9 signalling in MG thymus, suggesting that EBV-associated innate immune responses might contribute to the intra-thymic pathogenesis of MG.