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C1q Production by Bone Marrow Stromal Cells

To the Editor

Complement components and their receptors have recently come into focus as key regulators in the clearance of apoptotic cells by human dendritic cells (DC), a subset of phagocytic cells derived from bone marrow stromal cell progenitors [1, 2]. C1q, the first component of the classical pathway of complement activation, is able to bind to the surface of apoptotic cells inducing C3b deposition and promoting the uptake of apoptotic cells by DC via the interaction with C1q receptor and other C1q binding structures (Table 1) [3]. C1q production by human DC has been reported to be restricted to immature DC *in vitro*, as it is downregulated upon DC maturation [4]. In human bone marrow, active phagocytosis of apoptotic cells and uptake of immune complexes, as well as antigen presentation to lymphocytes, are provided by stromal cells with dendritic morphology that are intermingled with haematopoietic cells. These cells, hereafter referred to as bone marrow stromal DC, contribute to the formation of the bone marrow microenvironment actively participating into the normal haematopoiesis through the constitution of maturational niches [5]. They also have a share in the composition of the bone marrow infiltrates in lymphoid malignancies, although the underlying mechanisms are still unknown [6]. We investigated the expression of C1q in bone marrow stromal cells *ex vivo* studying 17 bone marrow biopsies with normal histology or non-specific reactive changes by immunohistochemistry and fluorescent *in situ hybridization* (FISH). By immunohistochemical evaluation, C1q resulted strongly expressed by bone marrow stromal DC (Fig. 1A) and by macrophages (Fig. 1B) in all cases. These results were confirmed by double stainings with CD1a (Fig. 1A, inset) and CD68 (Fig. 1B, inset). FISH for C1q B chain mRNA confirmed that C1q expression in bone marrow stromal cells was due to direct production of C1q and not to C1q uptake (Fig. 1C). Recently, a report by Yamada *et al.* [7] demonstrated that C1q was able to suppress pro-inflammatory cytokine production (IL12p40, TNF-α) by murine bone marrow-derived DC *in vivo*. This

Table 1 C1q binding structures and their functions.

Receptor	Function
CR1 (CD35)	Binds C1q and other complement derived opsonins (C4b, C3b, iC3b, MBL); involved in immune complex transfer
Calreticulin (CD91, C1q receptor complex)	Cell surface receptor for the collagenous domains of C1q; uptake of apoptotic cells, induction of chemotaxis
gC1qbp	Binding protein for the globular head of C1q

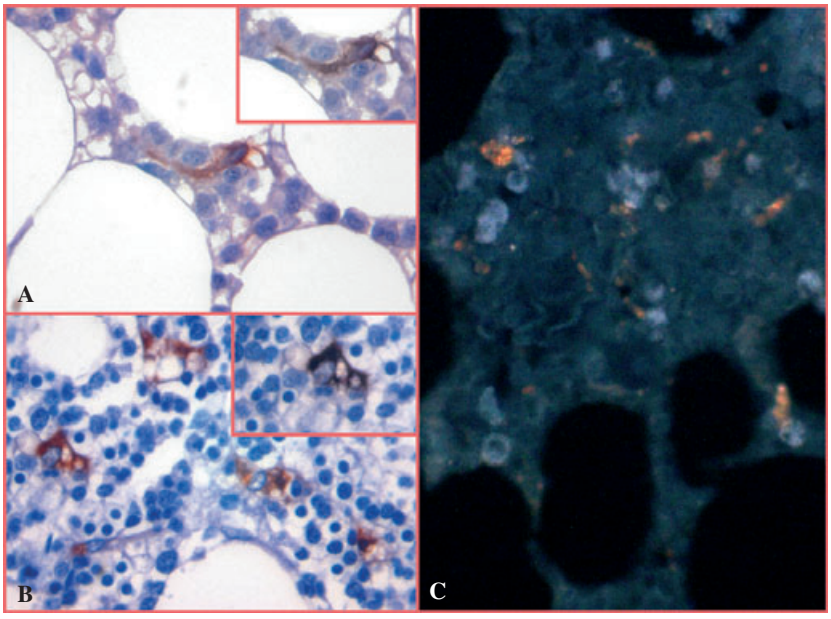

Figure 1 (A) The few bone marrow dendritic cells are positive to C1q (anti-C1q Dako, rabbit anti-human polyclonal antibody, 1:100; original magnification 400×). CD1a staining (inset) confirms their dendritic phenotype (anti-CD1a Dako, mouse anti-human monoclonal antibody, 1:50; original magnification 400×). (B) C1q is also expressed by bone marrow macrophages expressing CD68 (inset, anti-CD68 Dako, mouse anti-human monoclonal antibody, 1:50; original magnification 400×). (C) The orange signal throughout the cytoplasm of bone marrow stromal cells represents C1q B-chain mRNA expression (original magnification 400×).

finding, together with our observation of C1q production by bone marrow stromal cells, makes it possible to speculate on a role for C1q in the maintenance of bone marrow homeostasis through an autocrine feedback system. These results may add a valuable piece of information to the current figure about the interactions between human bone marrow stroma and the complement system.

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