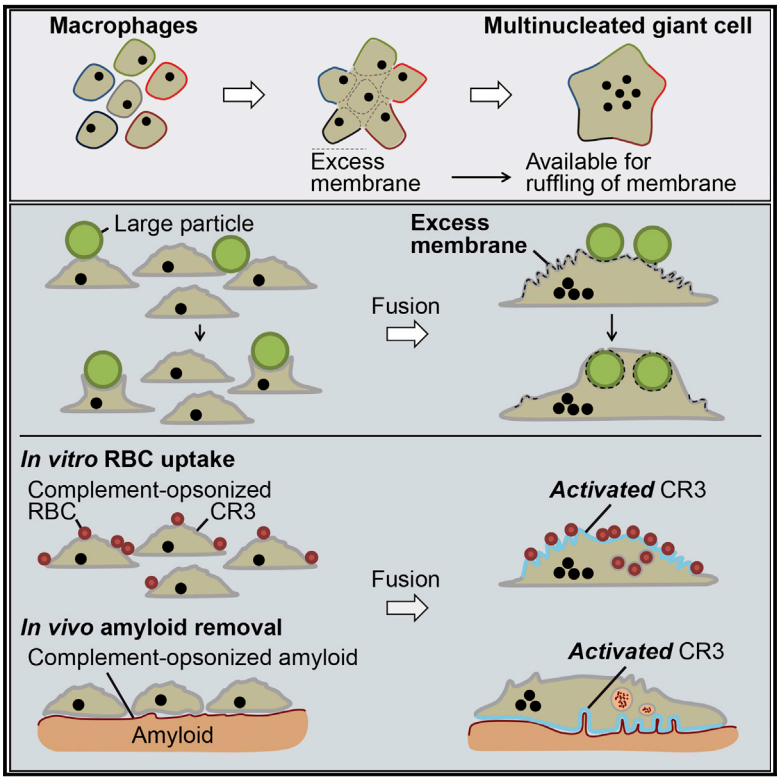
Article

Cell Reports

Multinucleated Giant Cells Are Specialized for Complement-Mediated Phagocytosis and Large Target Destruction

Graphical Abstract



Authors

Ronny Milde, Julia Ritter, Glenys A. Tennent, ..., Mark B. Pepys, Admar Verschoor, Laura Helming

Correspondence

m.pepys@ucl.ac.uk (M.B.P.), admar.verschoor@uksh.de (A.V.)

In Brief

Macrophage-derived multinucleated giant cells (MGCs) form in diverse chronic inflammatory diseases, but their functional role remains unclear. Milde et al. show that MGCs are specialized for complement-mediated phagocytosis and destruction of large targets and demonstrate their key role in the therapeutic elimination of the pathogenic amyloid deposits in systemic amyloidosis.

Highlights

- MGCs are specialized for phagocytosis of large and complement-opsonized particles
- MGCs show extensive membrane ruffles containing pre-activated complement receptor 3
- Membrane ruffles provide excess membrane for ingestion of large materials
- MGCs eliminate systemic amyloid deposits after immunotherapeutic targeting

Milde et al., 2015, Cell Reports *13*, 1937–1948
December 1, 2015 ©2015 The Authors
http://dx.doi.org/10.1016/j.celrep.2015.10.065

Cell Reports
Article

OPEN ACCESS
CellPress

Multinucleated Giant Cells Are Specialized for Complement-Mediated Phagocytosis and Large Target Destruction

Ronny Milde,[1] Julia Ritter,[1] Glenys A. Tennent,[2] Andrzej Loesch,[2] Fernando O. Martinez,[3] Siamon Gordon,[4] Mark B. Pepys,[2,6,*] Admar Verschoor,[1,5,6,*] and Laura Helming[1,6]
[1]Institute for Medical Microbiology, Immunology and Hygiene, Technische Universität München, 81675 Munich, Germany
[2]Wolfson Drug Discovery Unit, Centre for Amyloidosis and Acute Phase Proteins, Division of Medicine, Royal Free Campus, University College London, London NW3 2PF, UK
[3]Kennedy Rheumatology Institute, University of Oxford, Oxford OX3 7LD, UK
[4]Sir William Dunn School of Pathology, University of Oxford, Oxford OX1 3RE, UK
[5]Institute for Systemic Inflammation Research, Universität zu Lübeck, 23538 Lübeck, Germany
[6]Co-senior author
*Correspondence: m.pepys@ucl.ac.uk (M.B.P.), admar.verschoor@uksh.de (A.V.)
http://dx.doi.org/10.1016/j.celrep.2015.10.065
This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

SUMMARY

Multinucleated giant cells (MGCs) form by fusion of macrophages and are presumed to contribute to the removal of debris from tissues. In a systematic in vitro analysis, we show that IL-4-induced MGCs phagocytosed large and complement-opsonized materials more effectively than their unfused M2 macrophage precursors. MGC expression of complement receptor 4 (CR4) was increased, but it functioned primarily as an adhesion integrin. In contrast, although expression of CR3 was not increased, it became functionally activated during fusion and was located on the extensive membrane ruffles created by excess plasma membrane arising from macrophage fusion. The combination of increased membrane area and activated CR3 specifically equips MGCs to engulf large complement-coated targets. Moreover, we demonstrate these features in vivo in the recently described complement-dependent therapeutic elimination of systemic amyloid deposits by MGCs. MGCs are evidently more than the sum of their macrophage parts.

INTRODUCTION

Multinucleated giant cells (MGCs), first described in tuberculosis (Langhans, 1868), are also present in diverse infectious and non-infectious chronic inflammatory conditions, including schistosomiasis, atherosclerosis, sarcoidosis, and Langerhans cell histiocytosis (Helming and Gordon, 2009; Samokhin et al., 2010). MGCs also typify the foreign body reaction to macroscopic organic and inorganic materials, such as uric acid crystals and surgical implants (Helming and Gordon, 2009; Lai and Zhou, 2013). MGCs and osteoclasts are derived by cell-cell fusion of macrophages. Formation of osteoclasts, essential for bone resorption, is mediated by receptor activator of nuclear factor kappa-B ligand (RANKL) and macrophage colony-stimulating factor (M-CSF). Factors inducing MGC formation are less well defined (Helming and Gordon, 2009), but interleukin-4 (IL-4), a T_H2 cytokine of alternative (M2) macrophage activation, induces fusion in vitro and in sarcoidosis and foreign body reactions in vivo (Kao et al., 1995; Prokop et al., 2011). The role of MGCs in disease is also obscure, and it remains unclear whether they are beneficial or detrimental to disease outcome. It cannot be excluded that fused macrophages exhibit different roles depending on the nature of the disease. As they are often found under conditions where large and/or poorly degradable material is present (e.g., implants and uric acid crystals), there is speculation about specialization of MGCs for uptake of large particles (Anderson et al., 2008), but there are no rigorous quantitative studies. Indeed, reduced (Chambers, 1977; Lay et al., 2007), increased (Moreno et al., 2007; Nakanishi-Matsui et al., 2012), or unchanged (Schlesinger et al., 1984) phagocytic activity of MGCs compared to non-fused macrophages have all been reported. However, all of these studies lacked unambiguous discrimination between fully ingested particles and those loosely attached to the external cell surface. Here, we report a direct and well-controlled systematic comparison of the phagocytic activity of MGCs and M2 macrophages in vitro and characterize the cellular mechanisms underlying the unique functional behavior of MGCs.

Furthermore, we demonstrate these features in vivo in the recently described complement-dependent therapeutic elimination of systemic amyloid deposits by MGCs. This process is characterized by antibody-mediated complement activation and opsonization of amyloid deposits, triggering macrophage infiltration and formation of MGCs, which efficiently eliminate the amyloid (Bodin et al., 2010; Richards et al., 2015). We show here that this therapeutic process involves the same phenotypic features of MGCs that characterize them in vitro.

Download English Version:

https://daneshyari.com/en/article/2039121

Download Persian Version:

https://daneshyari.com/article/2039121

Daneshyari.com