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Exosomes in lungs of patients with sarcoidosis: a contributor to immune pathogenesis or just another by-product of heightened immune activity?

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The concept that cells can directly communicate with, and influence the function of other cells by transfer of particulate complexes or cell surface proteins (eg, antigen-bound MHC-II, integrin, ATPase channels)^{1–3} rather than soluble factors like cytokines and chemokines has excited cell biologists for decades. Extensive efforts have been made to prove the existence of this phenomenon and understand the mechanisms by which cells (especially immune cells) transfer proteins between each other. There is now evidence for at least four ways that this transfer could occur⁴—proteolytic cleavage of the protein from one cell with attachment to another, formation of tubules between two cells, direct cell membrane fusion and transfer of enclosed membrane vesicle (figure 1). An exosome

is an example of such a membrane vesicle and is significant in that it can contain the contents of both intracellular endosomes and proteins expressed on the cell membrane of its parent cell. Therefore, it could be viewed as a ‘mini-cell’, but with the added capacity to transfer the cell content or surface proteins onto another cell.

With the acknowledgement that exosomes exist and can transfer cellular material, the focus has shifted to showing that this phenomenon has functional consequences. Interest was roused when several investigators began showing that peptide–MHC complexes on exosomes can be captured by dendritic cells, which then trigger CD4 and CD8 T-cell responses.^{5–7} Depending on the kind of T cells engaged by these complexes, the result could be amplification of the T-cell response or suppression, for example, if regulatory T cells were involved. Therefore, exosomes could also influence the net outcome of a lymphocytic response during infection or inflammation. The ability of

exosomes to trigger immune response has been utilised in the field of tumour immunology. At least two phase I clinical trials have been carried out using exosomes to enhance the body’s own immune response against tumour cells.^{8,9} Morse *et al*⁹ purified autologous, dendritic cell-derived exosomes expressing MHC-II and used these as platforms for loading of tumour-specific antigen. They showed that infusion of these autologous exosomes was safe and resulted in detectable tumour-specific T-cell response.

However, it is widely acknowledged that the role of exosomes in vivo requires further clarification. Production of exosomes is widespread and the factors controlling its relative concentration in one inflammatory setting compared to another are poorly understood. In this edition of *Thorax*, Qazi and colleagues¹⁰ (*see page 1016*) show that exosomes can be purified from the bronchoalveolar lavage fluid of sarcoidosis patients and that they are enriched compared to healthy controls. The study utilised multi-imaging modalities to show their presence and, more significantly, demonstrate that these exosomes were able to induce production of cytokines from peripheral mononuclear cells and epithelial cells. This finding forms the first step in explorations of exosomal function in lung disease. Many questions can now be raised—what is/are the parent source(s) of these exosomes? Does increased amount of exosomes contribute to amplification of the CD4 T-cell response observed in sarcoidosis? Is this a sarcoidosis-specific finding or are lungs of patient with asthma, COPD and idiopathic pulmonary fibrosis also enriched with exosomes? And do different diseases have exosomes that bear different cellular proteins? Do

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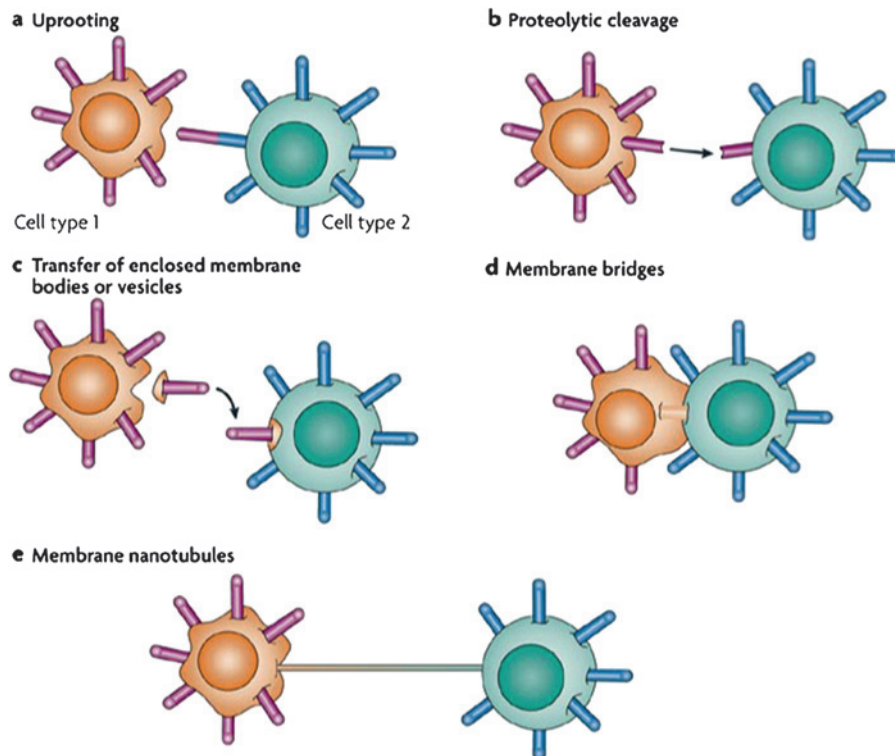


Figure 1 Potential mechanisms for intercellular protein transfer. (A) Proteins could be uprooted from the membrane of cells. (B) Proteolytic cleavage could facilitate intercellular transfer of protein ectodomains. (C) Transfer could be mediated by enclosed membrane bodies, vesicles or larger organelles at intercellular contacts. This process could involve the secretion of specialised vesicles such as exosomes. (D) Intercellular membrane fusion could produce small membrane bridges that allow protein transfer. (E) Membrane nanotubes, perhaps derived from membrane fusion or membrane bridges at the site of intercellular contact, could facilitate protein transfer between distal cells. Reprinted with permission from Macmillan Publishers Ltd. Davis DM. *Nature Reviews Immunology* 2007;7:238–43, copyright (2007).

different sarcoidosis patients with different outcomes have different composition of exosomes? It is possible to envisage, for example, that membrane-bound TGF β from dendritic cell-derived exosomes are enriched in sarcoidosis

patients who show a higher propensity for pulmonary fibrosis? Qazi and colleagues provide firm evidence for the presence of functional (albeit, in vitro) exosomes in sarcoidosis and pave the way for further questions which could show that these

exosomes contribute to immune pathogenesis of sarcoidosis.

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