Immunology research in the UK: a scientific audit

Mairéad O'Driscoll, Patricia Chisholm and Joe Anderson

The Wellcome Trust has recently carried out a scientific audit of its funding of immunology research. The strategy used for the audit aimed to build on the traditional field review by the provision of quantitative, systematic analysis that could support expert opinion. This paper presents some of the findings of the Wellcome Trust audit, focusing in particular on the quantitative analysis of outputs in the field.

As a scientific organization, the Wellcome Trust is concerned that its funding policies should be based on well-researched evidence. To this end, the Unit for Policy Research in Science and Medicine (PRISM) was established in 1990 as a key resource both for the Wellcome Trust and for other organizations seeking support when reviewing their funding policies. In order to strengthen the basis for decision-making in research funding, PRISM is developing innovative approaches to evaluation and priority-setting in science based on systematic analysis of data and survey of expert opinion.

During the 1993/1994 funding year, the Wellcome Trust carried out a scientific audit of its funding of immunology research. The aim of the audit was to assess the support for this field by the Wellcome Trust and to put this support into a national and international context. The scope of the audit was restricted to the funding of basic or fundamental research in the subject: research in the immunology of infectious diseases and more derivative or strongly applied research, such as that directed to the production of diagnostics, vaccines or other therapeutic agents, was excluded.

Wellcome Trust support for basic immunology research

In 1994, commitment of the Wellcome Trust to basic immunology research was £28 million (i.e. approximately £7–10 million per annum). This represented 6% of its science-funding budget in that year. In the same year, the total UK expenditure in immunology from all funding sources was estimated to be in the region of £20 million. Since 1990, the amount of money invested in basic immunology research by the Wellcome Trust has increased, coinciding with a period of substantial increase in its funds. However, as a proportion of the science-funding budget, investment has remained constant over that period.

A key element in the public policy statement of 1992 from the Wellcome Trust was that it would increase its support of individuals in their research careers by increased provision of more senior fellowships. As a reflection of this general policy, the balance of funding by the Wellcome Trust for basic immunology has changed since 1990. A substantial proportion of the current funding is for personal (i.e. fellowship and scholarship) support, as opposed to support for projects and programme grants. In 1990, essentially equal amounts were spent on project/programme and personal support, whereas in 1994, personal support accounted for two-thirds of the total (Fig. 1). The relative commitment to senior personal awards has also increased in the same period, both in the amount of money provided and in the number of awards made.

Bibliometric analysis of immunology papers in the top journals

It is not always easy to obtain science-funding figures on a national or international scale for a particular research field, but it is relatively easy to compare international activity in the form of published papers. In order to review activity in immunology in the UK, papers published since 1988 in ten of the top immunology journals (Box 1) were analysed by address field to compare the output from different countries. In contrast to the funding data presented above, the bibliometric analysis was for all papers published and was not restricted to basic or fundamental immunology.

The results of the analysis are shown in Fig. 2. The USA dominated the publications, with over 50% of papers carrying a US address. The UK was the second most productive country, consistently publishing almost 10% of the world total. Analysis of trends over time showed that the output of the USA has declined slightly since 1988, while both Japan and the European Union have increased their share.

Immunology research in the UK

The output of immunology papers from the UK in the top ten journals from 1991 to 1994 (inclusive) was analysed by postcode to identify the main centres of activity in immunology research (Fig. 3). This analysis indicated that the most prolific centres were London, Cambridge, Oxford, Birmingham and Glasgow.

Citation analysis of 1990 papers

In addition to simple quantitative measures of research outputs, citation analysis of published papers may be used as a measure of impact. Analysis of the output of immunology papers from the UK in the top journals from 1990 to 1994 revealed that a relatively small number of researchers

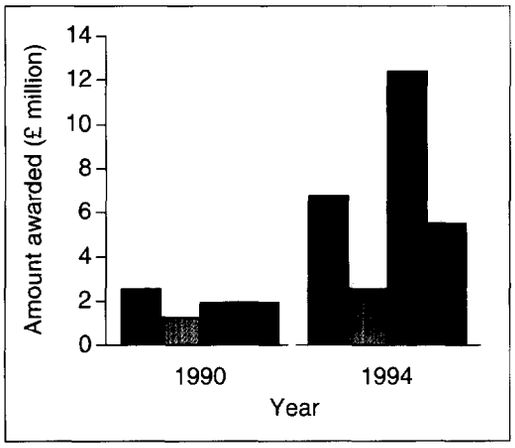


Fig. 1. *Wellcome Trust awards in basic immunology in 1990 and 1994. Coloured bars indicate: blue, project grants; yellow, programme grants; green, senior fellowships; red, training and intermediate fellowships and scholarships.*

Box 1. Journals studied in bibliometric analysis of immunology papers

Cell[a]
European Journal of Immunology
Immunogenetics
Immunology
International Immunology
Journal of Experimental Medicine
Journal of Immunology
Nature[a]
Proceedings of the National Academy of Sciences USA[a]
Science[a]

[a]Immunology papers in these journals were identified using a set of title key words.

accounted for most of the papers published. Less than 1% of authors of papers from the UK published an average of two or more papers per year in the top journals over this time period. This tiny minority included 51 individuals working in 26 different institutions, units or groups. Of these, two were commercial organizations (i.e. pharmaceutical companies), half were university departments and the remainder were institutes and units funded by research councils or charities. The distribution suggests that this substantial research output was generated fairly evenly from extramural, competitive funding (to universities) and from intramural funding (to research institutes).

To compare the performance of this relatively prolific group with immunologists as a whole, the citation rates of papers published by these 51 researchers in 1990 were analysed over the following five years (termed here 'UK-top' set). The same analysis was carried out for 19 immunologists who currently hold major and senior awards funded by the Wellcome Trust ('Trust' set). Standard citation rates were established by calculating the relevant citation norms for all papers published in the journal set ('total' set) and for all papers with at least one UK address ('UK' set). Figure 4 shows a comparison of the mean citation rates of papers published in 1990 in the years following publication (1990–1994). The UK set performed slightly less well than the total set, whereas both the UK-top set and the Trust set performed better than the norm. However, it should be noted that the mean number of citations per year is not an entirely reliable measure because of the skewed distribution of citations (i.e. because relatively large numbers of papers receive few, or no, citations, the difference between the groups may be exaggerated). It should also be noted that the sample of Trust-funded senior and major award holders is small.

A different analysis of the same data compared the numbers of papers from each group of individuals that appeared in the top decile of citations. Taking the total set as the standard, 10% of papers received more than 64 citations in the five years following publication. By contrast, 9% of papers with a UK address and 16% of papers published by the top UK researchers received more than 64 citations. The figure for papers published by holders of Trust-funded senior awards was 13%.

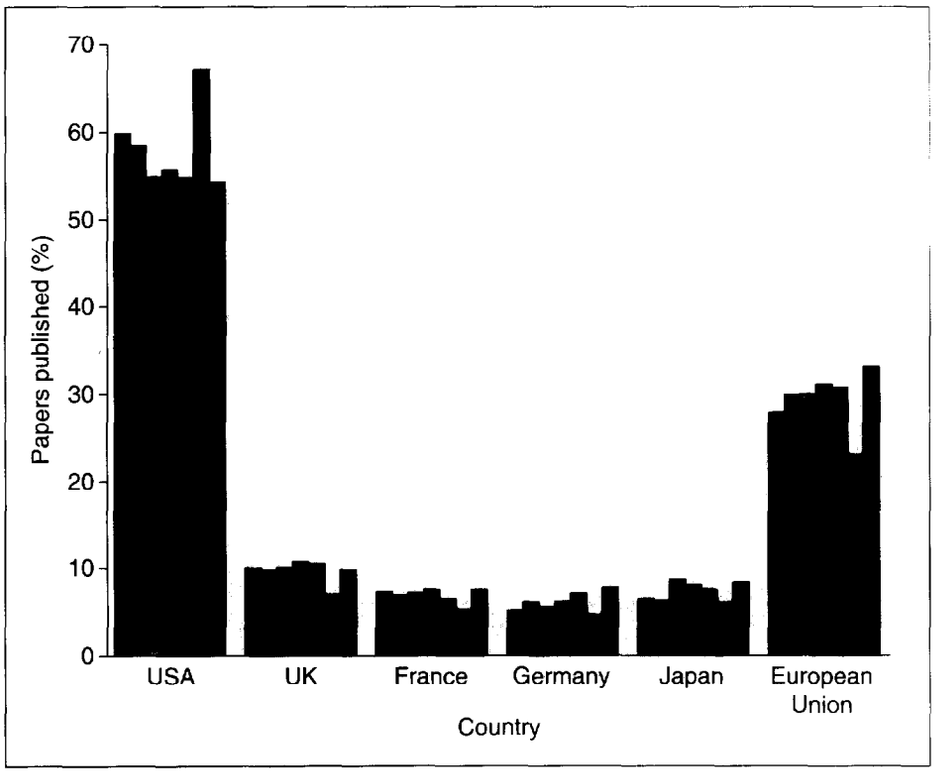


Fig. 2. *Bibliometric analysis of immunology papers published on an international scale since 1988. Consecutive bars represent consecutive years 1988–1994 as follows: red, 1988; orange, 1989; yellow, 1990; green, 1991; blue, 1992; indigo, 1993; violet, 1994.*

UK output by funding body

A new analytical technique developed by PRISM is the Research Outputs Database (ROD), which links published papers to their acknowledged source of support. The funding acknowledgements of all papers with a UK address in the specialist journal set were analysed to identify the research output from different funding bodies. The analysis was completed for the years 1989–1993.

Extramural funding was defined as support provided by a named grant or contract or by an external agency. Intramural support was indicated by the address field on the paper, provided that the source of support was a government agency or department, charity, or industrial company. Personal support referred to a fellowship, studentship or other

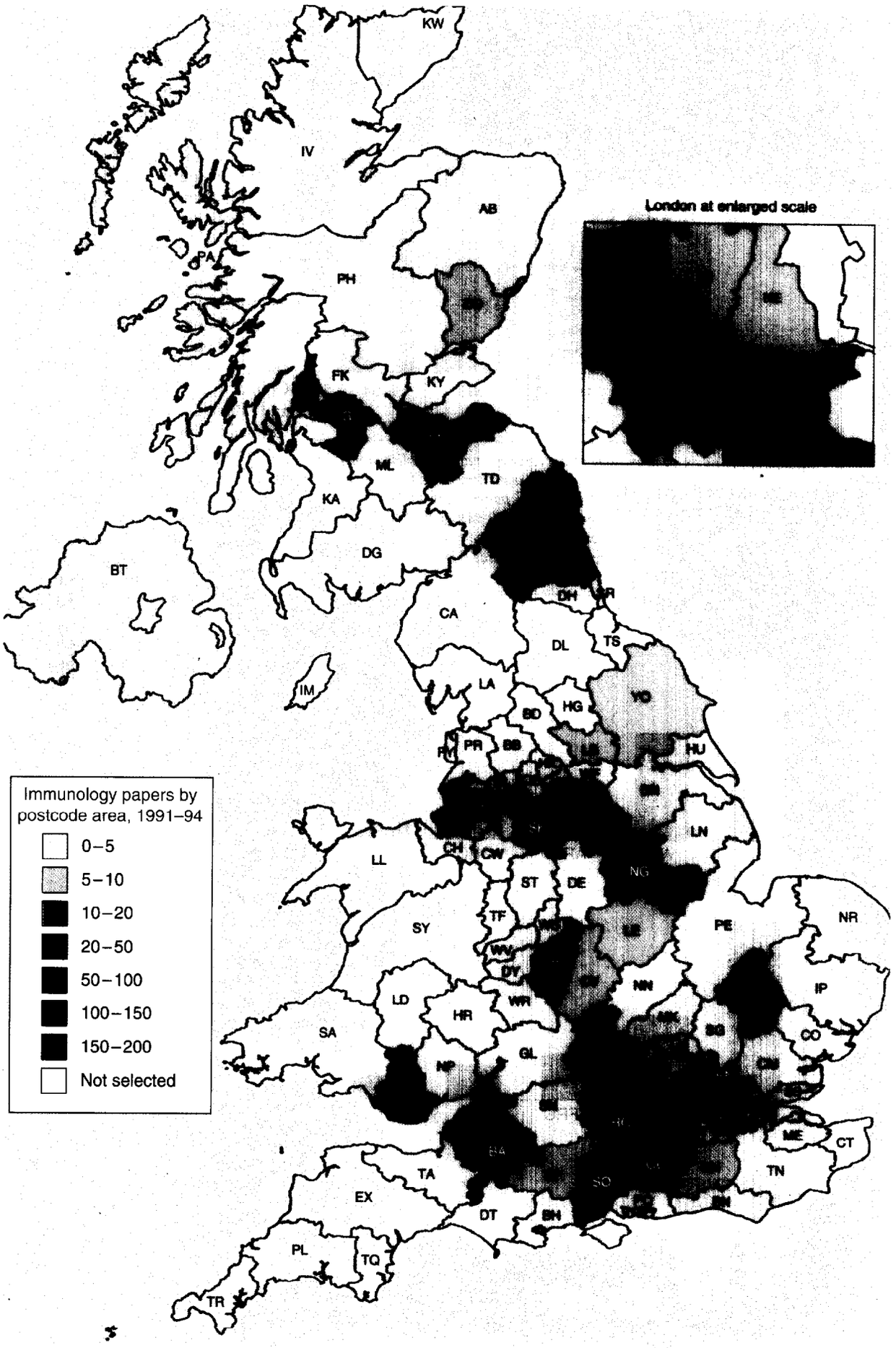


Fig. 3. *Map of the UK showing the number of papers in the top ten immunology journals (see Box 1) originating from different regions of the country.*

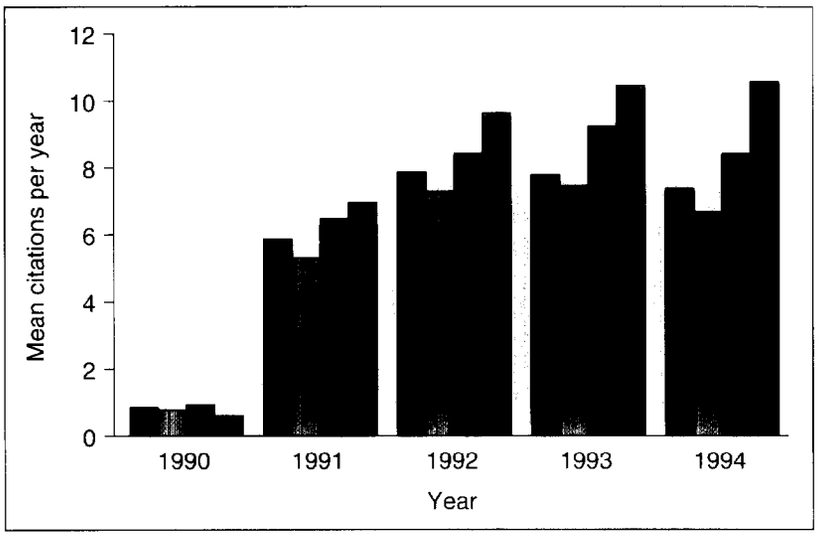
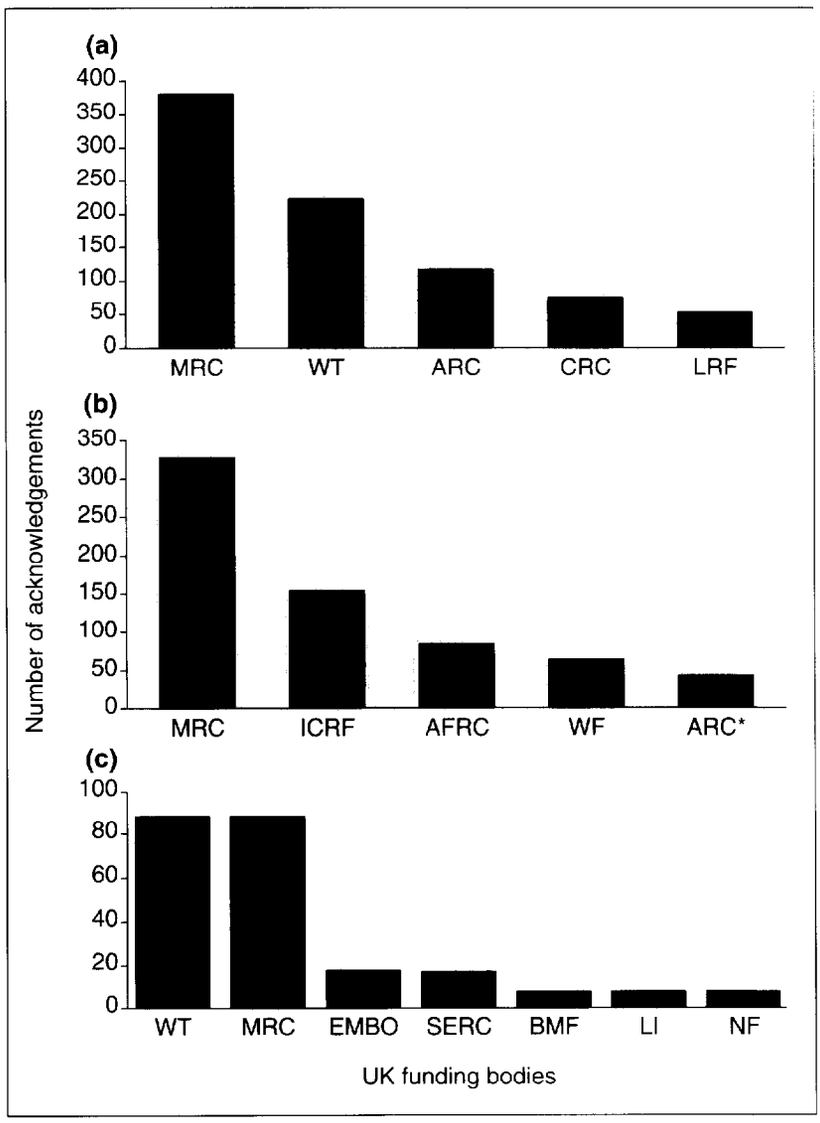


Fig. 4. *Comparison of the mean citation rates of immunology papers published in 1990 in the years following publication (1990–1994). Papers were divided as follows: red, all papers published in the journal set ('total'); yellow, all papers with at least one UK address ('UK' set); blue, all papers published by 51 individuals who published an average of two or more papers per year ('UK-top' set); green, all papers published by current holders of major and senior Wellcome Trust awards ('Trust' set).*



form of personal salary support (e.g. a professorial chair).

The total number of UK papers from the journal set was 1583. Of these, 121 (8%) did not acknowledge any source of funding. The total number of funding acknowledgements was 3499. The Medical Research Council (MRC) received more acknowledgements than any other funding body, with 22% of the total. The Wellcome Trust received 9% of the total, the Imperial Cancer Research Fund (ICRF) 4%, and the Arthritis and Rheumatism Council (ARC), the Biotechnology and Biological Sciences Research Council (BBSRC) [formerly the Agriculture and Food Research Council (AFRC)] and the Cancer Research Campaign (CRC) 3% each.

The results of the analyses are shown in Figs 5a,b,c. The largest supporters of extramural support for immunology research in the UK were found to be the MRC, the Wellcome Trust, the ARC, the CRC and the Leukaemia Research Fund (LRF). The MRC received the greatest number of acknowledgements for intramural support. Other funding agencies providing substantial intramural support were the ICRF, the BBSRC, Glaxo–Wellcome (the former Wellcome Foundation) and the ARC. As a presumed consequence

Fig. 5. *Comparison of (a) extramural acknowledgements (n = 2039), (b) intramural acknowledgements (n = 1073) and (c) personal support acknowledgements (n = 421) to UK funding bodies. Funding bodies are as follows: AFRC, Agriculture and Food Research Council; ARC, Arthritis and Rheumatism Council; BMF, Beit Memorial Fund; CRC, Cancer Research Campaign; EMBO, European Molecular Biology Organization; ICRF, Imperial Cancer Research Fund; LI, Lister Institute; LRF, Leukaemia Research Fund; MRC, Medical Research Council; NF, Nuffield Foundation; SERC, Science and Engineering Research Council; WF, Wellcome Foundation; WT, Wellcome Trust. The AFRC and SERC have now been reorganized into the Biotechnology and Biological Sciences Research Council (BBSRC) and the Engineering and Physical Sciences Research Council (EPSRC). The asterisk indicates that intramural acknowledgement of the ARC includes acknowledgement of the Charing Cross Sunley Research Centre and the Kennedy Institute of Rheumatology.*

of its deliberate policy of providing fellowship support, the Wellcome Trust was the most prominent source of personal support.

Concluding remarks

There has been substantial investment in immunology research in the UK in recent years, and this is reflected in outcome measures that show the UK second only to the USA in terms of output in the top immunology journals. A relatively small number of researchers were responsible for most of this output in the UK, and the impact of this productive group was high, as shown by citation analysis. The MRC and the Wellcome Trust were the largest financial supporters of immunology research, and the MRC received most acknowledgements for intramural support, whereas the Wellcome Trust was a major source of personal support.

As scientific research becomes progressively more expensive, there is an increasing need for funding organizations to assess the return on their investment more rigorously. This is the essence of responsible funding. However, although outcome measures and systematic analysis of trends in funding are important additions to policy debate, it must be stressed that such techniques are best used in conjunction with more traditional modes of assessment, such as peer review.

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Lactoferrin: a multifunctional immunoregulatory protein?

Jeremy Brock

Various immunoregulatory and anti-infective roles have been proposed for lactoferrin, the iron-binding protein present in external secretions and neutrophil secondary granules. A recent meeting updated current knowledge of the structure and function of this unusual protein.*

Lactoferrin is an iron-binding protein that is closely related in structure to the plasma iron-transport protein transferrin. It is found mainly in external secretions, such as breast milk, and in the secondary granules of neutrophils. Although it has been proposed to act as an anti-infective agent, a modulator of the inflammatory response and iron absorption, and an immunoregulatory protein, there is still no consensus view on the biological role of lactoferrin.

Lactoferrin structure

The structure of lactoferrin has been well worked out by crystallographic studies (E.N. Baker, Massey, New Zealand) and the development of various mutants (J.W. Tweedie, Massey). It comprises a single polypeptide chain folded into two lobes. Each lobe contains a binding site for Fe^{3+} that is located in a deep cleft, and a site for the synergistic binding of a bicarbonate anion[1]. In the absence of iron, each lobe of the molecule can flex, allowing the cleft to open and shut, but when iron is bound, the cleft is 'locked' shut (Baker). Although the overall structure of lactoferrin is very similar to that of transferrin, it is distinguished by two features that may be important functionally. First, the affinity of lactoferrin for iron is 250-fold greater than that of transferrin. Second, lactoferrin contains a strongly basic region close to the N-terminus, and hence this protein has a pI of approximately 9, compared with 5.5–6 for transferrin. According to Baker, this basic region is very flexible, and is probably responsible for the ability of lactoferrin to bind to a large number of acidic molecules.

*The 2nd International Symposium on Lactoferrin Structure and Function was held at Honolulu, HI, USA, on 19–22 February 1995.

Antimicrobial properties of lactoferrin

One of the earliest functions ascribed to lactoferrin was the inhibition of bacterial growth. It is believed that lactoferrin helps to protect breast-fed infants against infection by iron-requiring enteric pathogens, and contributes to the antimicrobial armoury of neutrophils[2]. Thus, lactoferrin is often thought of as a component of innate immunity. However, it is now clear that many microorganisms can overcome the iron-withholding effect of lactoferrin, either by secreting high-affinity low-molecular-weight iron chelators (siderophores) that can compete with lactoferrin for iron, or by expressing lactoferrin receptors, which are highly species specific (A.B. Schryvers, Calgary). Recently, a second type of antimicrobial activity has been described. It is independent of iron binding and is mediated through peptides ('lactoferricins') that contain the basic N-terminal region of lactoferrin and are obtained by proteolytic cleavage of the protein