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Review

Characteristics and function of Fc receptors on human lymphocytes

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Abbreviations: RFc, receptors for the Fc portion of immunoglobulin; RFcγ, receptors for the Fc portion of IgG; RFcμ, receptors for the Fc portion of IgM; RFcα, receptors for the Fc portion of IgA; RFcε, receptors for the Fc portion of IgE; RFcδ, receptors for the Fc portion of IgD; ORBC, ox erythrocytes; TNP, trinitrophenol; E, sheep erythrocytes; T_G, E-rosette-forming cells with RFcγ; T_M, E-rosette-forming cells with RFcμ; OKMI, mouse monoclonal antibody to monocytes; OKT3, mouse monoclonal antibody to the majority of human T cells; NK, natural killer cells; ADCC, antibody-dependent cell cytotoxicity; PHA, phytohaemagglutinin; Con A, concanavalin A; CLL, chronic lymphocytic leukaemia; ALL, acute lymphoblastic leukaemia; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

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Introduction

A wide range of cells express receptors for the Fc portion of immunoglobulin (RFc). Surface receptors for IgG (RFcγ) have been found on a variety of cells including lymphocytes (Dickler, 1976), monocytes and polymorphonuclear cells, whereas the expression of receptors for the other classes of immunoglobulin is more limited. Receptors for IgM (RFcμ) appear to be exclusively associated with lymphoid cells. Receptors for IgA (RFcα) are expressed on lymphoid cells (Gupta, Platsoucas, Schulof & Good, 1979b; Lum, Muchmore, Keren, Decker, Koski, Strober & Blaese, 1979a; Fanger, Shen, Pugh & Bernier, 1980), monocytes (Fanger *et al.*, 1980), and granulocytes (Fanger *et al.*, 1980). Originally found on mast cells and basophils,

receptors for IgE (RFcε) have now been observed on monocytes (Melewicz & Spiegelberg, 1980) and subpopulations of lymphocytes (Gonzalez-Molina & Spiegelberg, 1977). Even receptors for IgD have been found on lymphocyte subpopulations. This heterogeneity of RFc has been recently reviewed (Unkeless, Fleit & Mellman, 1981).

During the past 10 years there has been an avalanche of studies on the characteristics and functions of cells bearing these receptors. This review is an attempt to summarize the available information on the properties of RFc and their associations with human lymphocytes and to approach a clearer understanding of the functional importance of these molecules and the cells on which they are expressed.

Detection of Fc receptors

Initially, fluorescein-labelled aggregated Ig was used to identify cells expressing Fc receptors (Stout & Herzenberg, 1975). Although such assays are still used, they have been largely superceded by rosetting techniques. RFcμ and RFcγ are now routinely identified by indicator systems in which ox erythrocytes (ORBC) are sensitized with suboptimal concentrations of rabbit anti-ORBC antibody of the appropriate isotype. ORBC are used because of their poor agglutinability even with large amounts of sensitizing antibodies (Uhlenbruck, Seaman & Coombs, 1967). Indicator cells are incubated with lymphocytes and the percentage of rosette-forming cells evaluated. Specificity is determined by the ability of different Ig classes, subclasses and fragments to block rosette formation. The formation of relatively stable rosettes has permitted, in the case of cells expressing RFcγ, the isolation or removal of cell populations bearing this receptor and their subsequent functional analysis (Moretta L., Webb, Grossi, Lydyard & Cooper, 1977c). Although RFcμ and RFcα bearing cells have been subjected to similar isolation procedures and functional assays, the fragility of RFcμ and RFcα rosettes has made such studies more difficult as well as more equivocal. Potential problems associated with the contamination of IgM anti-ORBC with small amounts of IgG have been overcome in our laboratory by use of monoclonal IgM antibodies with reactivity to ORBC (Lydyard & Fanger, 1981). RFcα were first identified using TNP-coupled erythrocytes sensitized with mouse myeloma anti-TNP IgA antibodies (Gupta *et al.*, 1979b; Lum *et al.*, 1979a). A more sensitive system for identification of RFcα utilizes ORBC sensitized with secretory IgA anti-ORBC obtained from the milk of post partum rabbits which have undergone intra-mammary immunization (Fanger *et al.*, 1980). RFcε and RFcδ have been identified using rosetting assays in which RBC coated with myeloma IgE or IgD are used as indicator cells (Gonzalez-Molina & Spiegelberg, 1977; Sjöberg, 1980). It seems evident from the rapid development of cytofluorography that, in the future, RFc associations with cell populations as well as the isolation of RFc-bearing cells for biochemical and functional characterization will probably involve the use of this technology (Endoh, Sakai, Nomoto, Tomino & Kaneshige, 1981). Association of Fc receptors with different lymphocyte subpopulations.

Human lymphocytes have been classically subdivided into T, B and Null cells. In addition, a number of criteria including functional studies and Fc receptor expression have permitted recognition of subpopulations of these main groups of lymphocytes. Table 1 summarizes the organ distribution of lymphocytes bearing different Fc receptors.

T lymphocytes

Less than 5% of human thymus cells possess detectable receptors for IgG, IgM or IgA (Table 1; Moretta L., Ferrarini & Cooper, 1978a; Gupta & Good, 1978a; Lydyard & Fanger, 1981). However, some reports suggest higher numbers with receptors for IgM, especially in the population unreactive with peanut agglutinin (Musiani, Lauriola, Carbone, Maggiano & Piantelli, 1981).

Most studies on human lymphocytes in the peripheral circulation have, to date, relied on the formation

Table 1. Organ distribution of human lymphocytes bearing Fc receptors for different Ig classes*

	Percentage lymphocytes bearing receptors for				
	IgG	IgM	IgA	IgD	IgE
Thymus	1±0·5	7±3	9±4	—	
Blood: adult	22±8	63±8	55±9	3±3	1·2±0·3
neonatal	44±5	42±5	34±4	—	3±1·3
Spleen	37±7	30±3	22±4	—	5·6±4·7
Tonsils	11±7	21±16	38±20	—	4·9±4·2
Bone marrow	55±11	13±8	14±11	—	—

* Data for IgG, IgM and IgA receptors were taken from Lydyard & Fanger (1981) and except for the data for RFcα are very similar to data obtained in other laboratories. Data for IgD and IgE are from Sjoberg (1980) and Spiegelberg (1981).

Table 2. Distribution of Fc receptor bearing cells among lymphocyte subpopulations in human peripheral blood*

Lymphocytes bearing receptors for	Rosette forming cells (%)	
	T	Non-T
IgG	28±8	75±11
IgM	68±10	10±5
IgA	53±8	7±2
IgD	2±0·6	9±3
IgE	0·5	23·4

* Data were taken from Lydyard & Fanger (1981), Sjoberg (1980) and Gonzalez-Molina & Spiegelberg (1977).

of rosettes with sheep erythrocytes (E) as a definitive marker for T cells. On this basis, T-cell subpopulations expressing RFc for each of the Ig classes have been identified (Table 2). A lymphocyte subpopulation with RFcγ and with receptors for E, designated T_G, has been extensively studied because of its apparent association with suppression. Recently, however, some controversy has developed as to the identity of this subpopulation. Using a monocyte-specific monoclonal antibody, OKMI, evidence has been obtained that many T_G cells are of the monocyte lineage (Reinherz, Moretta, Roper, Breard, Mingari, Cooper & Schlossman, 1980). In addition, only 30%–40% of T_G cells reacted with a putative pan T-cell monoclonal (OKT3). Such studies may be misleading since possession of common antigens by cells of different lineages is not unprecedented. Subsequent studies by other groups using the same (Fox, Thompson & Huddlestone, 1981; Pichler & Broder, 1981), or different monoclonals (Haynes & Fauci, 1981), and perhaps more stringent methods for E rosetting, have found much higher percentages of T cells in the T_G population. Moreover, the finding that T cells from two patients with haemopoietic disorders possess both pan T antigens and RFcγ (Callard, Smith, Worman, Linch, Cawley & Beverley, 1981) supports the existence of RFcγ on some T cells.

It is interesting that RFcγ-bearing T cells enriched by E rosetting are morphologically distinct from T cells bearing RFcμ (T_M cells) and also show differences in lysosomal enzyme localization (Grossi, Webb, Zicca, Lydyard, Moretta, Mingari & Cooper, 1978). Many null cells also have the morphological and lysozomal enzyme characteristics of T_G cells and can be induced to express E receptor by neuraminidase treatment (Ferrarini, Cadoni, Franzi, Ghigliotti, Leprini, Zicca & Grossi, 1980).

Furthermore, some T_G cells may be derived from activated T_M (see section on Modulation). It seems clear, therefore, that the T_G population is heterogenous and includes (i) cells morphologically and enzymatically similar to the third population cells, (ii) 'true' T cells with RFcγ, and (iii) monocytes.

RFcα were found originally on a relatively small population of human T cells which appeared to be distinct from both T_M and T_G (Gupta *et al.*, 1979b; Lum, Beneviste & Blaese, 1980). However, work in our laboratory indicates that these receptors are present on the majority of RFcμ bearing cells (Lydyard & Fanger, 1981). The associaton of RFcγ with RFcα bearing cells is less clear. RFcε (Yodoi & Ishizaka, 1979) and RFcδ (Sjöberg, 1980), have been found on 0·5% and 2%, respectively of human T cells (Table 1).

B cells

It was initially thought that RFcγ were expressed only on B lymphocytes and that T and B cells could be separated on this basis. As the result of more sophisticated analyses, it is now clear that some T cells as well as non-T, non-B cells also express these receptors. Some B cells can express RFcμ, RFcα (Romagnani, Maggi, Biagiotti, Giudizi, Amadori & Ricci, 1977; Ferrarini, Hoffman, Fu, Winchester & Kunkel, 1977; Pichler & Broder, 1978), RFcε (Gonzales-Molina & Spiegelberg, 1977) and/or RFcδ (Sjöberg, 1980).

Null, L or third subpopulation cells

This lymphocyte subpopulation consists of cells lacking T- and B-cell markers but possessing high affinity RFcγ (Froland & Natvig, 1973; Horwitz & Garret, 1977). Human erythrocytes coated with human anti-D antibodies bind specifically to third population cells and not to B cells (Winchester, Fu, Hoffman & Kunkel, 1975). However, some T cells also react with these indicator cells suggesting similarities between null and T_G cells (Ferrarini *et al.*, 1980). The null lymphocyte population contains cells with natural killer (NK) and, in particular, RFcγ-dependent antibody-dependent cell cytotoxicity ADCC activities. Receptors for other classes of immunoglobulin on null cells have not been extensively examined, although some non-T non-B cells have been reported to express RFcα and/or RFcμ (Lum, Muchmore, O'Connor, Strobel & Blaese, 1979b; Romagnani *et al.*, 1977;

Table 3. Subclass and domain specificity of Fc receptors on human lymphocytes

Receptors for	Subclass	Domain
IgG	IgG1, IgG3 > IgG2 > IgG4	Cγ3*
IgM	—	Cμ4
IgA	IgA2 > IgA1	Cα2

* Based on studies with mouse lymphocytes and human monocytes. It seems likely that RFc for different IgG subclasses may exist and be expressed on different cell types. Thus, some RFcγ may recognize structures in the CH2 domain and/or in the hinge region of IgG.

Reaman, Lum & Poplack, 1980a). Even so, neither IgM nor IgA mediate ADCC activity (Greenberg & Lydyard, 1979; Shen, Lydyard, Roitt & Fanger, 1981; Shen & Fanger, 1981).

Biochemical properties of Fc receptors

Of the various lymphocyte Fc receptors, RFcγ have undergone the most extensive biochemical analysis. RFcμ, RFcα and RFcε have been less well characterized and no information is presently available on the properties of RFcδ.

RFcγ

These receptors bind most avidly to the human IgG1 and IgG3 subclasses (Table 3) although they may also react with IgG2 and weakly with IgG4 (Dickler, 1976). Little information is available on the possible differences among the binding specificities and affinities of these subclasses for the different human lymphocyte subgroups. Based on information from mouse systems and from studies with human monocytes, it would appear that RFcγ react primarily with structures in the CH3 domain (Ramasamy, Secher & Adetugbo, 1975; Klein, Neauport-Sautes, Ellerson & Fridman, 1977; Foster, Dorrington & Painter, 1980). However, the isolated Fc fragments and domains are less efficient than the parent molecule in binding to RFcγ. Certainly, it is possible that some RFcγ—those on different cell types, from different animals or with different Ig subclass specificity—may interact primarily with structures in the CH2 domain and/or in the hinge region. It is also noteworthy that Fc fragments from all IgG subclasses, but not their parent molecules, are capable of activating murine lymphocytes (Berman, Spiegelberg & Weigle, 1979). These observations suggest that the conformation or availability of the RFcγ binding areas in the isolated fragment are different from those in its parent Ig molecule, and may be similar to those in antigen-complexed Ig. Moreover, they emphasize the difficulties associated with interpretations of RFcγ specificity and distribution.

A wide range of properties and molecular weights have been reported for RFcγ from different sources (Fridman, Rabourdin-Combe, Neauport-Sautes & Gisler, 1981). These differences may result from the existence of fundamentally different RFcγ on different cell populations and in different species, and/or be due to proteolytic breakdown of RFcγ during isolation (Bourgois, Abney & Parkhouse, 1977). Under conditions of limited proteolysis, IgG binding proteins of 120,000 and 60,000 mol. wt have been isolated from T_G cells (Cunningham-Rundles, Lawless, Gupta, Galenos & Good, 1980) in surprisingly large amounts ($> 10^6$ RFcγ molecules/T_G cell). In addition, a 28,000 mol. wt RFcγ has been isolated from human leukaemic B cells and found to polymerize into a 115,000 mol. wt molecule (Thoenes & Stein, 1979). To some extent these findings are consistent with studies on the structure of mouse RFcγ which suggest that these receptors exist as single 120,000 mol. wt polypeptide chains which are folded into five IgG binding globular domains of 23,000 mol. wt (Bourgois *et al.*, 1977; Kahn-Perles, Sire, Boned & Bourgois, 1980). Thus, each parent RFcγ molecule appears to contain multiple IgG binding sites. Extrapolated to Fc receptors for other classes, these findings may indicate that each RFc is multivalent, and that such multiple bindings per RFc molecule may be important to the function(s) of these receptors. Some of these functions may depend on release of immunoglobulin binding factors (e.g. sRFcγ and sRFcε) by lymphocytes under appropriate conditions (Fridman *et al.*, 1981; Spiegelberg, 1981; see section on Role of Fc receptors).

RFcμ

Human peripheral lymphocytes appear to express, on average, 800 RFcμ/cell, each of which has an apparent Ka of $2{\cdot}5 \times 10^9$ M^{-1} (Hardin, Nahoka & Carboni, 1979). These receptors are more sensitive to pronase and trypsin digestion than are RFcγ but like RFcγ are resynthesized during overnight culture (Mingari, Moretta, Moretta, Ferrarini & Preud'homme, 1978; and unpublished observations). The difficulty associated with demonstration of RFcμ on fresh lymphocytes may result from their occupation with IgM or

IgM-antigen complexes and the degree of sensitization of the indicator cells (Fanger & Lydyard, 1979a). Overnight incubation in IgM-free media permits shedding and resynthesis and/or dissociation of this complex and permits their detection (Moretta L., Ferrarini, Durante & Mingari, 1975; Fanger & Lydyard, 1979a). Studies on the specificity of RFcμ indicate that these receptors bind to structures within the CH4 domain of the μ heavy chain (Table 3; Conradie & Bubb, 1977; Bubb & Conradie, 1978). Rosette inhibition studies with IgM from different patients with Waldenström's macroglobulinaemia suggest the existence of different subclasses of human IgM (Fanger & Lydyard, 1979b). Similarly, comparisons of the ability of monomeric (8S), or polymeric (19S) IgM or the Fc5μ fragment of IgM to inhibit RFcμ rosetting indicate that although monomeric IgM can inhibit IgM rosettes, it is less efficient than its Fc$_5\mu$ fragment or the native molecule (Fanger & Lydyard, 1979b). Based on the ability of native IgM to bind to RFcμ and the apparent occupation of RFcμ on freshly isolated cells, it seems likely if RFcμ are important to some function, that native IgM alone does not trigger this function. More likely, IgM-antigen complexes may be important to activation of cells through RFcμ (Lydyard & Fanger, 1980).

RFcα

Large percentages of freshly isolated human peripheral lymphocytes display receptors for IgA as well as IgM, indicating that these receptors are expressed *in vivo* (Lydyard & Fanger, 1981). Although capable of binding both human IgA subclasses (Table 3), RFcα appear to preferentially bind IgA2, a subclass localized more to the mucosal areas than to the circulation (Fanger & Lydyard, 1981). Other studies indicate that multivalent Fc display is of less importance to binding avidity than with IgM-RFcμ interactions, and that secretory component and J chain are not involved in receptor binding. Moreover, the site on IgA which interacts with RFcα is in the CH2 domain and is not dependent on H chain pairing (Fanger & Lydyard, 1981). These findings contrast with the observations on the specificity of human lymphocyte RFcμ (Conradie & Bubb, 1977), in that different Ig domains (Cα2 *vs* Cμ4) and requirements for multivalent expression of Fc regions are involved in the binding of IgM and IgA to RFcμ or RFcα, respectively.

RFcε

The properties of lymphocyte RFcε have been primarily established using the human lymphocyte cell lines WIL-2WT and RPMI-8866. Labile IgE binding glycoproteins with molecular weights of 86,000 and 47,000, have been isolated (Fritsche, Meinke & Spiegelberg, 1981; Ishizaka, 1980). As with RFcγ, a 23,000 molecular weight IgE binding molecule was observed, suggesting that RFcε on the surface of the lymphocyte may express multiple Fc binding sites. Although RFcε on functionally distinct groups of cells may be structurally related, antibody prepared against lymphocyte RFcε does not react with RFcε on basophils. Furthermore, the Ka for IgE binding to RFcε on lymphocytes *v.* basophils is quite different, $1{\cdot}2\text{–}13 \times 10^6\,\text{M}^{-1}$ and $6 \times 10^9\,\text{M}^{-1}$, respectively (Ishizaka, 1980; Spiegelberg & Melewicz, 1980). RFcε are represented on the surface of WIL-2WT and ROMI-8866 cells to the extent of $7\text{–}32 \times 10^4$ molecules/cell (Ishizaka, 1980; Spiegelberg & Melewicz, 1980; Spiegelberg, 1981). Like RFcγ bearing cells, lymphocytes, with receptors for IgE release a soluble form of RFcε (sRFcε) which appears to influence *in vitro* antibody responses (Spiegelberg, 1981; Yodoi & Ishizaka, 1980). It is an attractive possibility that factors with affinity for a particular Ig isotype (IgE, IgG, IgM or IgA) may bind to the isotype, or to isotype-antigen complexes and subsequently regulate the function of B-cell subpopulations important to the development of Ig responses of that isotype (see section on the Role of RFc). Rat IgE binding factors with potentiating or suppressive activities have both been reported (Suemura, Yodoi, Hirashima & Ishizaka, 1980; Hirashima, Yodoi & Ishizaka, 1980). That these factors appear to differ primarily in their sugar content suggests that glycosylation may be important in determining their biological function (Yodoi, Hirashima & Ishizaka, 1980, 1981; Pecond, Ruddy & Conrad, 1981).

Modulation of Fc receptor expression

Fc receptors on lymphocytes are actively synthesized and lost or shed from the cell membrane (Mingari *et al.*, 1978; Moretta L. *et al.*, 1975; Spiegelberg, 1981). The expression of these molecules can be modulated in either a positive or negative way by antigen and/or antibodies, certain drugs and other ligands or factors (Table 4). In addition, various ligands and/or culture conditions may select *in vitro* for or against an RFc bearing lymphocyte population.

Interaction of RFcγ on E-rosette-forming cells with polyclonal IgG-antigen complexes results in loss of

Table 4. Modulation of human lymphocyte RFc expression*

Treatment	RFcμ	RFcγ	RFcα	RFcε
Mitogens				
PHA	↓(1)		↓(1)	
Con A	↓(1, 2)	↑(2)		
PWM	↓(1)			
Immunoglobulins ± antigen				
IgM	↓(3)			
IgG	↑(4, 5)	↑(6)†↓(4, 5)		
IgA			↑(7)†	
IgE				↑(8)
Alloantigens	↓(9, 10†)	↑(9,10†)		
Pharmacological mediators				
Theophylline/isoproterenol	↓(11)	→(11)	→(11)	
Phenylephrine	↑(11)			
α/β-Interferons	↓(12–14)	↑(12–14)		
Other factors				
Steroids	→↓(15, 16†)	↓(15)↑(16†)		
Irradiation	→(15)	↓(15)		
Thymic factors	↑(15, 17, 18)			
β_2-microglobulin		↑(17)		

* Numbers in parentheses refer to references as follows: (1) Lydyard & Fanger, 1979; (2) Gupta, Schwartz & Good, 1979c; (3) Mingari *et al.*, 1978; (4) Moretta L. *et al.*, 1978b; (5) Pichler *et al.*, 1978; (6) Hoover *et al.*, 1981a; (7) Hoover *et al.*, 1981b; (8) Yodoi & Ishizaka, 1980; (9) Moretta L. *et al.*, 1981; (10) Bacigalupo *et al.*, 1981; (11) Gupta, 1979; (12) Platsoucas *et al.*, 1980; (13) Itoh *et al.*, 1980; (14) Fridman, Gresser, Bandu, Aguet & Neauport-Sautes, 1980; (15) Gupta & Good, 1977; (16) Haynes & Fauci, 1978; (17) Astaldi *et al.*, 1979; (18) Gupta *et al.*, 1979a; (19) Birch *et al.*, 1979. Arrows indicate increase ↑, decrease ↓, or no change → in percentage of RFc bearing cells as a result of treatment with various agents.

† *In vivo.*

RFcγ and a concomitant appearance of RFcμ (Moretta L., Mingari & Romanzi, 1978b; Pichler, Lum & Broder, 1978). On the other hand, interaction of IgM complexes with RFcμ, results in the shedding, endocytosis and reappearance of RFcμ in the lymphocyte membrane (Mingari *et al.*, 1978). Thus, decreased numbers of T_G found in patients with active systemic lupus erythematosus may be interpreted in terms of an *in vivo* effect of IgG antibody complexes (Moretta L. *et al.*, 1978b; see section on Disease States). In contrast, in patients with IgG myeloma, IgG itself appears to significantly enhance the number of T_G cells (Hoover, Gebel, Dieckgraffe, Hickman, Rebbe, Hirayama, Dravy & Lynch, 1981b). Although modulation of receptor expression may be involved in these cases, such *in vivo* changes could be the result of mobilization of different lymphocyte populations.

Direct interaction of lymphocytes with specific IgE together with allergen results in enhanced expression of RFcε by RFcγ bearing cells (Yodoi & Ishizaka, 1979). Similarly, studies with IgA myelomas in mice indicate that exposure to high concentrations of IgA alone can increase lymphocyte RFcα expression (Hoover & Lynch, 1980; Hoover, Dieckgraffe & Lynch, 1981a).

PHA, Con A and pokeweed mitogen induce a loss of expression of RFcμ and RFcα within 6 hr of addition to lymphocytes (Lydyard & Fanger, 1979, 1980). These receptors are undetectable on blast cells. Alloantigens induce an alternative mode of response which results in expression of RFcγ on T_M without necessarily altering the regulatory function of these cells (Moretta L., Moretta, Canonica, Bacigalupo, Mingari & Cerrottini, 1981; Mingari, Moretta, Canonica, Melioli, Corte & Moretta, 1981). Moreover, β_2-microglobulin, a molecule which forms part

of the transplantation antigens on normal cells, increases RFcγ bearing cells with no significant change in cells expressing RFcμ (Birch, Fanger & Bernier, 1979).

Among the pharmacological mediators which modulate RFc expression, theophylline and isoproterenol, which operate through β-adrenergic receptors, decrease *in vitro* T-cell expression of RFcμ without an alteration in RFCγ or RFcα (Gupta, 1979). In contrast, stimulation of α-adrenergic receptors by phenylephrine enhances RFcμ expression. Interestingly, isoproterenol enhances expression of RFcγ in mouse pre-B cell tumours induced by Abelson virus (Burchiel & Warner, 1980). Alpha and beta interferons have been shown to enhance RFcγ but decrease RFcμ expression on both T and non-T cells (Platsoucas, Fernandes, Kampin, Clarkson, Good & Gupta, 1980; Itoh, Inoue, Kataoka & Kumagai, 1980; Fridman *et al.*, 1980).

High concentrations of the corticosteroids prednisolone and hydrocortisone decrease T_G *in vitro* with no significant change in T_M (Gupta & Good, 1977). In contrast, 4 hr after intravenous injection of hydrocortisone, T_G were increased, while T_M decreased. Normal proportions of T_M and T_G were seen after 24 hr (Haynes & Fauci, 1978). Although seemingly contradictory, these results might be interpreted in terms of population redistribution *in vivo*. Thymic hormones, which appear to have a profound effect on immune reactivity, induced RFcμ on some thymocytes (Astaldi, Astaldi, Wymans, Groenewond, Bemmel, Van Schellekans & Eijsvoogel, 1979) but enhance RFcγ expression on peripheral blood T cells (Gupta & Good, 1977; Gupta, Kapoor, Goldstein & Good, 1979a; Fiorilli, Sisianni, Pandolfi, Quanti, Tosti, Auti & Goldstein, 1981).

Fc receptors on lymphocytes in disease states

The putative immunoregulatory role for E-rosette-forming cell populations bearing different Fc receptors (Moretta L. *et al.*, 1977c) initiated numerous investigations into the proportions, absolute numbers and functional properties of T_M and T_G cells in the blood of patients with various diseases, especially those in which defective immunoregulation could serve as a pathological basis (Table 5).

Immunodeficiency states

Patients with primary immunodeficiency do not appear to have a consistent pattern of alteration of proportions or absolute numbers of the T_M or T_G subsets (Moretta L., Mingari, Webb, Pearl, Lydyard, Grossi, Lawton & Cooper, 1977b; Gupta & Good, 1978b). In one patient with hypogammaglobulinaemia and thymoma, T_G cells in the peripheral blood were increased (Moretta L. *et al.*, 1977b). In contrast, patients with ataxia telangiectasia have fewer circulating T_M cells (Trompeter, Layward & Hayward, 1978). No consistent changes in proportions of circulatory RFcα-bearing T cells have thus far been observed in patients with selective IgA deficiency (Gupta & Good, 1980).

Lymphoproliferative disorders

Hodgkin's Disease results in a number of immunological abnormalities. Patients with this disease have an increased T_G:T_M ratio in the circulation (Romagnani *et al.*, 1978; Moretta L., Mingari & Moretta, 1979) with the reverse observed in the spleen (Gupta, 1980). Fewer T_M cells were found in the peripheral blood of these patients especially in stages III and IV of the disease which may be related to the migration characteristics of T_M and T_G (Gupta, 1980). In spite of an increased ratio of T_G:T_M, T-cell-mediated NK cell activity in Hodgkin's patients is decreased compared with normals. Similar imbalances in the ratio of T_G:T_M were seen in patients with newly diagnosed non-Hodgkin's lymphomas, although there appears to be no correlation with the stage of the disease (Beck, Wollner, Miller, Good & Gupta, 1980b).

Chronic lymphocytic leukaemia (CLL) is frequently accompanied by hypogammaglobulinaemia, a deficiency which may result from defects in B cells or helper T cells (Chiorazzi, Fu, Montazen, Kunkel, Rai & Gee, 1979). Several studies have reported high ratios of T_G:T_M cells in the circulation of these patients and correlated these findings with the stage of the disease (Kay, Johnson, Stanek & Douglas, 1979; McCaan, Whelan, Willoughby, Lawler, Creally & Tempeseley, 1980; Lauria, Foa & Catovsky, 1980). As in patients with Hodgkin's disease, the increase in T_G cells was not accompanied by an increase in NK or ADCC activity of the T cells (Platsoucas *et al.*, 1980). Patients with myeloma have also been reported to have a significant increase in T_G cells (Oken & Kay, 1981).

In addition to alterations in proportions of normal Fc receptor bearing cells in patients with lymphoproliferative disorders, a number of investigations have focused on the expression of Fc receptors on monoclonal proliferating lymphoid cells themselves. Lymphocytes from a high proportion of patients with Sezary syndrome, a T-cell cutaneous lymphoma, bear

Table 5. Changes in circulating T lymphocyte RFc expression in disease states*

	T_M	T_G
Primary immunodeficiencies		
Miscellaneous immunodeficiencies	↓(1, 2)	↑(1, 2)
Hypogammaglobulinaemia with thymoma	→(1)	↑(1)
Ataxia telangiectasia	↓(3)	→(3)
Lymphoproliferative disorders		
Hodgkin's disease	↓(4, 5)↑(6)†	↑(4, 5)↓(6)†
Non-Hodgkins	↓(7)	↑(7)
B-Cell CLL	↓(8–10)	↑(8–10)
Infectious mononucleosis	↓(11)	↓(11)
Haemopoietic disorders		
Severe aplastic anaemia		↑(12)‡
Red cell aplasia		↑(13)§
Selected neutropenias		↑(14, 15)
Autoimmune disorders		
Active SLE	→(16, 17)	↓(16, 17)
Active RA	→(18)	→↑(18, 19)
Idiopathic Thromocytopenic Purpura		↓(20)
Inflammatory bowel disease	↓(21)	
Chronic liver disease	↓(22)	
Other disorders		
Sarcoidosis		↑(23, 24)
Multiple sclerosis		↑↓(25)¶
Atopic diseases		↓↑(26**, 27)

* Numbers in parentheses refer to references as follows: (1) Moretta L. *et al.*, 1977b; (2) Gupta & Good, 1981; (3) Trompeter *et al.*, 1978; (4) Romagnani *et al.*, 1978; (5) Moretta L. *et al.*, 1979; (6) Gupta 1980; (7) Beck *et al.*, 1980b; (8) Kay *et al.*, 1979; (9) McCaan *et al.*, 1980; (10) Lauria *et al.*, 1980; (11) Haynes *et al.*, 1979; (12) Bacigalupo *et al.*, 1980; (13) Linch *et al.*, 1981; (14) Callard *et al.*, 1981; (15) Boom-van-Noorloos *et al.*, 1980; (16) Fauci *et al.*, 1978; (17) Moretta A. *et al.*, 1979; (18) Hanglow *et al.*, unpublished; (19) Sharpin *et al.*, 1981; (20) Trent *et al.*, 1981; (21) Victorino & Hodgson, 1980; (22) Williams *et al.*, 1980; (23) Katz *et al.*, 1978; (24) Johnson *et al.*, 1981; (25) Huddlestone & Oldstone, 1979; (26) Canonica *et al.*, 1979; (27) Shuster *et al.*, 1980. Arrows indicate increase ↑, decrease ↓, or no change → in percentage of T_M or T_G.

† Spleen data.

‡ Bone marrow data—cells suppress CFU.

§ Cells suppress erythroid colony formation *in vitro*.

¶ Decreased in attack; increased in remission.

** Decrease in severely ill patients with respiratory allergy but increased to normal following desensitization.

RFcμ (Gupta, Safai & Good, 1978) and exhibit non-specific helper cell function *in vitro* (Broder, Edelson, Lutzner, Nelson, Macdermott, Durm, Goldman, Meade & Waldmann, 1976). Leukaemic blasts from patients with T-cell ALL express RFcμ, RFcγ or both (Moretta L., Mingara, Moretta & Lydyard, 1977a; Beck, Haghbin, Wollner, Mertelsmann, Garrett, Koziner, Clarkson, Miller, Good & Gupta, 1980a), but it is unclear whether they occur together on most (Moretta L. *et al.*, 1977a) or few (Beck *et al.*, 1980a) blasts. One T-CLL studied, carried RFcγ, Ia and was suppressive in an *in vitro* assay (Strong, Pandolfi, Slease, Budd & Woody, 1981). The majority of CLL tumours are of B-cell type and possess RFcμ (Pichler & Knapp, 1977; Burns, Cawley, Worman, Barker & Hayhoe, 1979), perhaps simultaneously with

RFcγ and RFcα (Lydyard, Powell, Fanger, Worman & Cawley, 1981). Cells from patients with hairy cell leukaemia also possess RFcμ, RFcγ and RFcα, whereas non-Hodgkin's lymphoma cells express RFcμ and RFcγ but little RFcα (Lydyard *et al.*, 1981). Patients with non-T, non-B ALL express RFcα (Reaman, Poplack, Broder & Pichler, 1980b) in addition to RFcμ and RFcγ (Reaman, Pichler, Broder & Poplack, 1979).

Haemopoietic disorders

The possibility that T cells regulate haematopoiesis has been suggested by the observation of increased levels of T_G in the circulation and bone marrow of a patient with red cell aplasia (Linch, Cawley, Macdonald, Masters, Roberts, Antonis, Waters, Silff & Lydyard, 1981) and in the bone marrow of patients with severe aplastic anaemia (Bacigalupo, Podesta, Mingari, Moretta, Van Lint & Marmont, 1980). Whereas bone marrow from the patient with red cell aplasia gave rise to few erythroid colonies *in vitro*, bone marrow from severe aplastic anaemia patients was deficient in myeloid colony forming units. Removal of T_G cells results in significant enhancement of colony formation in both patient groups (Linch *et al.*, 1981; Bacigalupo *et al.*, 1980). Interestingly, in another study, patients with high T_G levels rejected allogeneic bone marrow grafts whereas those with normal levels of T_G cells were reconstituted by bone marrow grafts (Gupta & Good, 1981). High levels of T_G cells have also been reported in some patients with neutropenia, suggesting that T_G cells may suppress granulopoiesis (Callard *et al.*, 1981; Boom-van-Noorloos, Pegels, Van Oers, Sitberbusch, Feltkamp-Vroom, Goudsmit, Zieglermaker, Borne & Melief, 1980).

In patients who have received allogeneic bone marrow grafts and are exhibiting graft *v.* host activity, a significant increase in T_G has been observed (Bacigalupo *et al.*, 1980) which may correspond with expression of T-cell RFcγ following activation by allogeneic human lymphocytes *in vitro* (Moretta A., Mingari, Colombatti & Moretta, 1981).

Infectious mononucleosis

In the acute phase of infectious mononucleosis the patient's blood carries irregularly shaped T cells many of which do not possess either RFcγ or RFcμ (Haynes, Schooley, Grouse, Payling-Wright, Dolin & Fauci, 1979). These cells express the cytotoxic/suppressor phenotype defined by OKT8 and appear to possess both cytotoxic and polyclonal suppressor cell function (Crawford, Brickell, Tidman, McConnell, Hoffbrand & Janossy, 1981; Tosato, Magrath, Koski, Dooley & Blaese, 1979).

Autoimmune disorders

Numerous studies have evaluated the proportions of Fc-receptor-bearing cells in the circulation of patients with autoimmune conditions since such disorders may involve a dysfunction of immune regulation. Significantly lower T_G:T_M ratios and a decrease in absolute T_G numbers have been reported in patients with systemic lupus erythematosus (Fauci, Steinberg, Haynes & Whalen, 1978; Moretta A, Mingari, Santoli, Perlmann & Moretta, 1979), and chronic idiopathic thrombocytopenic purpura (Trent, Adams, Erhardt & Basten, 1981). Whether this is a real or only an apparent decrease in the number of T_G cells resulting from inhibition of Fc binding or RFc modulation by circulating immune complexes, has yet to be resolved. Decreased T_M have been observed in the circulation of some patients with chronic inflammatory bowel disease (Victorino & Hodgson, 1980) and liver disease (Williams, Strickland & Montano, 1980). The data with regard to RFc expression in rheumatoid arthritis (RA) appears conflicting (Fröland, 1981). We have consistently found no changes in RFcμ and RFcγ expression by peripheral blood T cells in patients with early or established and active RA compared with age and sex matched controls (Hanglow, Hartley, Young & Lydyard, unpublished observations). In contrast, few T cells expressing RFcγ or RFcμ are found in the synovial fluid of patients with active disease. Similar discrepancies in the current literature involve changes in RFc-bearing T cells in patients with autoimmune thyroid disease (Gupta & Good, 1981). Although increased T_G cells have also been reported in the blood of patients with sarcoidosis (Katz, Haynes & Fauci, 1978; Gupta & Good, 1981), these cells may be activated monocytes/macrophages (Johnson, Brostoff, Hudspith, Boot & McNicol, 1981).

Multiple sclerosis

Patients with active disease have depressed levels of T_G during attacks which increase to above normal levels during remission (Huddlestone & Goldstone, 1979). Active blasts, which predominate in the cerebrospinal fluid even during inactive disease appear to possess both RFcγ and RFcμ (Merrill, Biberfeld, Kolmodin, Landin & Norrby, 1980).

Allergic disorders

That production of each of the Ig classes is under the regulation of T lymphocytes has led to the suggestion that in patients with allergic disorders mediated by IgE, T-cell regulation of IgE production is abnormal. In one study comparing children with and without bronchial asthma, there was no significant difference in the proportions of RFcγ and RFcμ-bearing T cells (Gupta, Fikrig & Good, 1980a). In other studies, patients with severe respiratory allergy (Canonica, Mingari, Melioli, Colombatti & Moretta, 1979) and severe atopic dermatitis (Shuster, Bongiovanni, Pierson, Barbaro, Wong & Levinson, 1980) had low numbers of circulating T cells. In patients with severe respiratory allergy, T_G increased to normal levels following specific hyposensitization associated with an improvement in clinical manifestations (Canonica *et al.*, 1979). Increased levels of RFcε bearing T cells have also been reported in patients with allergic asthma and high IgE serum levels (Gupta, 1981).

Pregnancy

Although not regarded as a disease state(!) pregnancy is associated with immunological abnormalities. Although no change in the percentages of T and B lymphocytes in pregnant compared with non-pregnant women has been observed, the percentage of T_M is decreased and T_G increased during pregnancy and the *post partum* period (Hirahara, Gorai, Tanaka, Matsuzaki, Sumiyoshi & Shiozima, 1980). One could speculate that such increases in T_G are due to maternal reactivity to paternal antigens in the foetus, and correlate with changes from T_M to T_G observed following exposure of T_M to allogeneic cells *in vitro* and in graft versus host disease *in vivo* (Bacigalupo *et al.*, 1981). Newborn infants also have a high ratio of T_G to T_M compared with adults (Gupta & Good, 1979). Paradoxically, in ageing individuals there is also an increase of T_G cells which correlates with decreased PHA responsiveness of their lymphocytes (Gupta & Good, 1979; Kishimoto, Tomino, Inomata, Kotegawa, Saito, Kuroki, Mitsuya & Hishamitsu, 1978).

In conclusion, no consistent pattern of changes in expression of RFc-bearing cells in disease states is evident. This may reflect differences in stages of disease and/or the sensitivity of the detection systems used by different investigators. Furthermore, confusion as to the identity of RFcγ-bearing E rosetting cells makes it difficult to define the nature of the cell populations which have altered as the result of the disease process.

Functional associations and possible role of Fc receptors in the immune response

The functional significance of lymphocyte Fc receptors in immunity has been studied primarily with regard to their role in ADCC effector functions and in immune regulation. There seems little doubt that RFcγ are mandatory for the ADCC activity of K cells. Although it has been suggested that RFcμ may also mediate cytotoxicity directly (Wahlin, Perlmann & Perlmann, 1976; Fuson & Lamon, 1977), in our experience both IgM and IgA can only act in concert (perhaps via their respective Fc receptors) to augment killing by IgG antibodies (Shen *et al.*, 1981; Shen & Fanger, 1981).

It is clear that antibodies are capable of suppressing specific immune responses. As a result of the formation of antigen–antibody complexes and their removal by RFc-bearing phagocytic cells, antigen is prevented from interacting with antigen-sensitive immune cells. Suppression mediated by $F(ab)'_2$ fragments at high concentrations may also involve antigenic masking (Hoffmann, 1980). On the other hand, numerous studies have suggested that lymphocytes carrying Fc receptors may be directly involved in immune regulation and that antibody itself may regulate the immune response through mechanisms involving Fc receptors. Evidence both from *in vivo* and *in vitro* studies in mice has shown that the Fc portion of the *IgG* antibody is required for optimal antibody suppression of an immune response occurring in the presence of antigen (Sinclair & Chan, 1971; Oberbarnscheidt & Kölsh, 1978). In contrast, specific enhancement of the T-dependent primary antibody response can be achieved with antigen specific *IgM* antibodies (Henry & Jerne, 1968; Forni, Coutinho, Koehler & Jerne, 1980; Powell, Hutchings, Cooke & Lydyard, 1982). Similarly, incubation of primed T cells *in vitro* with specific IgM or IgG enhances or suppresses, respectively, the ability of cell recipients to mount an immune response (Playfair, Marshall-Clarke & Hudson, 1974). Moreover, studies using anti-idiotypic antibody of different subclasses *in vivo* suggest that suppression or enhancement of the specific T-dependent antibody responses, may be achieved by the use of different IgG subclasses (Eichmann, 1974; Eichmann & Rajewsky, 1975). These findings support the concept (Playfair, 1974) that T-dependent regulation of the immune response could involve RFc for the appropriate Ig class on specific T cells.

A role for T_G in immune suppression in humans is

suggested by a number of observations including: (i) T_G cells activated by pokeweed mitogen and insoluble antigen-IgG antibody complexes release a factor which suppresses B-cell maturation *in vitro* (Moretta L. *et al.*, 1977c, 1979). (ii) Differentiation of both polyclonally-activated and specific B cells induced by T cells with RFcμ can be regulated by factors released from T_G (Moretta L. *et al.*, 1979; UytdeHaag, Heynen, Pot & Ballieux, 1979). (iii) Removal of T_G enhances *in vitro* T-cell responsiveness to *Veillonella albicans* in patients with severe peridontal disease (Ivanyi, Topic & Lydyard, 1981). (iv) T cells, but also monocytes and neutrophils release an IgG-binding factor, with the properties of RFcγ which may inhibit *in vitro* immune responses (Fridman *et al.*, 1981).

Fc-receptor-mediated suppression of immune response could involve interaction of T-cell RFcγ with IgG-antigen complexes which directly or through mediators induce interference with T–B cell collaboration (Fridman *et al.*, 1981). Alternatively, direct binding of IgG antigen complexes to RFcγ on B cells may dampen B-cell responsiveness (Kölsh, Oberbarnscheidt, Bruner & Heuer, 1980). In either scenario, the ratio of antigen : antibody in a complex or the concentration of complex could be expected to be important to both the quality and quantity of regulation (Moretta L. *et al.*, 1977c).

On the other hand, although T_G cells express suppressor activity the heterogeneity of these cells makes it unclear as to whether or not 'true' T cells themselves mediate suppression. Moreover, in the absence of antigen–antibody complexes, PGE_2 (Goodwin, Wük, Lewis, Bankhurst & Williams, 1979) and histamine (Gupta, Fernandes, Rocklin & Good, 1980b) induce the release of suppressor factors from T_G cells. Thus, although RFcγ *per se* may, under some conditions, be important to immune suppression they are apparently not essential for expression of this function.

That T_G may suppress haematopoiesis is suggested by several studies (Bacigalupo *et al.*, 1980; Linch *et al.*, 1981; see section on Disease States). In one study, circulating T_G cells expressing the suppressor/cytotoxic phenotype, OKT8, inhibited erythroid colonies *in vitro* but were unable to suppress differentiation of B cells *in vitro* (Newland, Linch, Lydyard & Turnbull, unpublished observations). Thus, separate T-cell sets may be involved in suppression of haemopoietic and B-cell differentiation.

Another possible suppressive function associated with RFcγ bearing cells, and thus RFc, may involve the release of factors useful in the effector phase of the immune response. T_G cells but not T_M produce macrophage migration inhibition factor when stimulated with Con A *in vitro* (Warrington, Olivier, Sauder & Rutherford, 1981). K cells directly activated through RFcγ by IgG antigen–antibody complexes also release a molecule which inhibits leucocyte migration (Neville & Lischner, 1981). In contrast, T_M but not T_G cells produce neutrophil migration inhibition factor (Kapadia, O'Reilly, Good & Gupta, 1978). However, an evaluation of the role(s) of these cells must take into consideration the requirement of accessory cells for the production of these factors.

The association of T_M cells with help for antibody responses (Moretta L. *et al.*, 1977c) indicated that RFcμ might be associated with this function. To date, however, the direct role of this receptor in help has not been established. On the other hand, recent data have shown an association between RFcα and IgA responses. Removal of T cells by fluorescent-labelled IgA results in specific reduction in IgA responses *in vitro* (Endoh *et al.*, 1981).

Thus far we have emphasized the positive relationships between RFc and immune regulation and in particular RFcγ with suppression. Although some associations do exist between certain Fc receptor bearing cells and function and/or disease state, there are numerous exceptions. In specific instances these relationships may appear compelling, whereas in a more general sense their meaning is obscured. In fact, considerable evidence can be mustered against the association of a specific regulatory function with lymphocytes expressing particular RFc. It seems clear from a consideration of the literature that Fc receptors are relatively ubiquitous. The expression of RFcγ, RFcε and RFcα is not even confined to the lymphoid series of cells. Even within the lymphoid group, it is apparent that Fc receptors for each of the classes of Ig can be expressed on functionally distinct subgroups of cells. RFcμ, for example, are associated with T, B and the non-T non-B group of lymphocytes. Furthermore, although it was initially thought that T_M cells were exclusively helper cells, it is now evident that among these cells is a population capable of suppression or induction of suppression of B-cell responses (Hayward, Layward, Lydyard, Moretta, Dagg & Lawton, 1978; Lydyard & Hayward, 1979). In addition, T cells within the T_M population carry both helper and suppressor phenotypes as determined by monoclonal antibodies (Reinherz *et al.*, 1980). It seems apparent, therefore, that RFc for any Ig class do not represent

markers for functionally distinct groups of cells or for cell subpopulations.

A corollary to this conclusion is that particular Fc receptors *per se* do not determine nor exclusively mediate the function of the cell population on which they reside. Obviously, binding of RFcμ to IgM-antigen complexes would not result in help if the cell to which this complex binds, is a K, NK or B cell. Similarly, the role of the other RFc would depend on the cell subpopulations on which they reside. Moreover, under some conditions, Fc receptors may not be necessary for the expression of the function of the cell subpopulation with which they are associated. Rather, these receptors may have, in many instances, only a secondary role, but one which may still be important, perhaps in facilitating or enhancing differentiation and/or the expression of some function initiated by another event. For example, binding of specific T cells with low affinity to antigen may be enhanced by specific IgM bound through RFcμ to the T cells. In addition, T suppressor cells, some of which express RFcγ, may, for example, be triggered by antigen–antibody complexes under conditions in which RFcγ may be important in stabilizing the interaction of the complex with the suppressor cell. Alternatively, binding of RFc may provide a second or supplementary signal, perhaps involving cytokines, for the direction of differentiation or its extent. Similar possibilities for the association of RFcμ with helper cell populations could be imagined. In this regard, specific antibodies of different isotypes or their subclasses may be important to immune regulation.

Finally, it is important to note that evaluation of the expression of a particular kind of Fc receptor on a cell population is dependent on the sensitivity of the assay system used, the state of activation of the cell and the presence of RFc modulators. Based on these variables and on the previously noted diverse association of these RFc with different lymphocyte subgroups, it does not seem an unreasonable extrapolation to imagine that all lymphocyte subpopulations are, under appropriate conditions, capable of expressing each of the different Fc receptors. T-helper cells may, for example, express at one time and to one extent or another not only RFcμ and RFcα but also RFcδ, RFcε, and even RFcγ. The expression of any or all of these receptors by a cell population would not determine the function of that group of cells but could perhaps facilitate that function. Fc receptors should perhaps be viewed as potential facilitators of the predetermined function of the cell population with which they are associated—molecules that can come and go at the discretion of the cell but which endow a cell population with multiple functions and an increased sensitivity to its environment.

Conclusions

Lymphocytes are capable of expressing RFc for all immunoglobulin classes, with a single cell being capable of simultaneously expressing some (perhaps all) of the isotype-specific RFc. RFc can be modulated on lymphocyte cell surfaces in both a positive and negative way by cell activation and by various ligands. Some RFc can be released and may play a functional role in lymphocyte responses. Although only RFcγ are directly involved in lymphocyte cytotoxicity, RFcα and RFcμ may facilitate killing via RFcγ. The ubiquity of RFc, together with the data obtained using monoclonal antibodies indicate that Fc receptors for different classes of Ig do not delineate distinct genetically programmed lymphocyte subpopulations, but rather may facilitate the expression of the function of different lymphocytes. The specific enhancement of RFc expression by specific antibody classes alone, may be a mechanism whereby cells are encouraged to differentiate toward the development of responses involving a particular Ig isotype. In sites of high IgA concentration, for example, cells might be encouraged to express IgA receptors which could in turn influence the regulation of IgA responses.Thus, Fc receptors may be viewed as endowing lymphocyte subpopulations with multiple functions and increased sensitivity to local environmental signals.

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