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Review

Complement Receptor 1: Disease associations and therapeutic implications

Rohan Khera, Nibhriti Das*

Department of Biochemistry, All India Institute of Medical Sciences, New Delhi 110029, India

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ABSTRACT

Exaggerated complement activation is a key event in the pathogenesis of a range of autoimmune and inflammatory diseases. Complement Receptor 1 (CR1) has emerged as a molecule of immense interest in gaining insight to the susceptibility, pathophysiology, diagnosis, prognosis and therapy of such diseases. This review brings forth a composite view of the current understanding on the structure, functions, genetics, disease associations and therapeutic implications of CR1.

1. Introduction

Complement Receptor 1 (CR1), the receptor for C3b/C4b complement peptides (Iida et al., 1982) is present on different cells, plasma and urine. CR1 has drawn huge attention of the scientists because of its gene polymorphisms, structural variances, diversity of functions and disease associations. Potential of CR1 as a diagnostic and prognostic marker is being increasingly realized. Extensive research on CR1 has brought insight to the pathophysiology of a galaxy of diseases including the autoimmune and inflammatory disorders.

Studies on animal models have suggested CR1 as a therapeutic against inflammatory chain reactions and tissue damage in several diseases. This review attempts at giving a composite and current view of different aspects of CR1 with special emphasis on the diseases associations and therapeutic implications of this protein.

2. Complement Receptor 1: forms and localization

CR1 is a multifunctional polymorphic glycoprotein which is variably expressed on the plasma membrane of erythrocytes, eosinophils, monocytes, macrophages, B-lymphocytes, a subpopulation of CD4+ T cells, dendritic cells, Langerhan cells in the skin and glomerular podocytes (Weiss et al., 1989; Rodgaard et al., 1991; Fang et al., 1998).

Non-membrane bound soluble form of CR1 (sCR1) found in plasma is released from leukocytes especially polymorphonuclear leukocytes into the circulation by cleavage of the surface form of CR1 (Danielsson et al., 1994). Urinary CR1 (uCR1) is found in urine in association with the membrane vesicles (Pascual et al., 1994) derived from the glomerular podocytes.

3. Structure of Complement Receptor 1 (CR1)

The Complement Receptor 1 (Fig. 1) is composed of 30 short consensus repeats (~60 amino acids each). The first 28 are organized into four long homologous repeats (LHRs) each with seven consecutive SCRs (Wong et al., 1989). The functional domains of the CR1 protein are also specifically distributed among the different LHRs. LHR-A principally binds with C4b. LHR-B and LHR-C both bind with C3b/C4b (Klickstein et al., 1988) and PfEMP1 (Rowe et al., 2000) and have the cofactor activity (Ross et al., 1982) for factor I The LHR-D has binding sites for Mannan-binding lectin (MBL) (Ghiran et al., 2000) and C1q (Klickstein et al., 1997). The SCR 25 in LHR-D has the binding sites of Swain–Langley (Sl) and McCoy (McC) Knops blood group antigens (Moulds et al., 2001). The structure of sCR1 is simi-

Abbreviations: CR1, Complement Receptor 1; SLE, systemic lupus erythematosus; SARS, severe acute respiratory syndrome; sCR1, soluble Complement Receptor 1; uCR1, urinary Complement Receptor 1; SCR, short consensus repeats; LHR, long homologous repeats; PfEMP1, *Plasmodium falciparum* erythrocyte membrane protein 1; ECR1, erythrocyte Complement Receptor 1; kDa, kilo Dalton; RFLP, restriction fragment length polymorphism; SNP, single nucleotide polymorphism; LCR1, leukocyte Complement Receptor 1; Sl, Swain–Langley; McC, McCoy; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; ESAT, early secreted antigen target; rCR1, recombinant Complement Receptor 1; TNFα, tumor necrosis factor α; TNFβ, tumor necrosis factor β; IL, interleukin; IFNγ, interferon γ; NCR1, neutrophil Complement Receptor 1.

* Corresponding author. Tel.: +91 11 26593407; fax: +91 11 26588641.
E-mail address: nibhriti@hotmail.com (N. Das).

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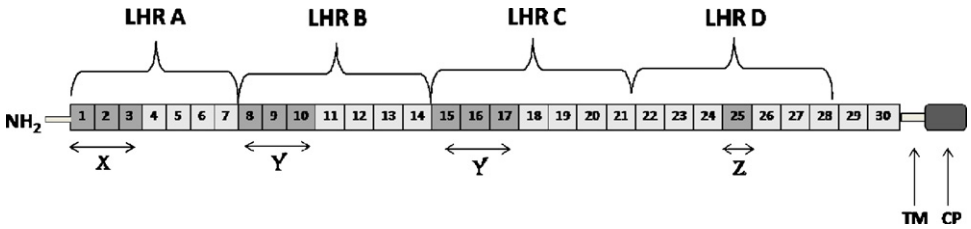

Fig. 1. Schematic representation of the F allele (CR1-A) of CR1: from the NH_2 terminus–Site X binds C4b, Sites Y show binding to C3b, C4b PfEMP1, Site Z (SCR 25) is the site for Swain–Langley (Sl) and McCoy (McC) Knops blood group polymorphism. LHR-D also has sites specific for MBL (Mannan-binding lectin) and C1q. TM: transmembrane region; CP: cytoplasmic Tail.

lar to that of surface CR1 except that it lacks a cytoplasmic tail and is generated by proteolytic cleavage in the C-terminal region of the transmembrane domain of the surface CR1 molecule (Hamer et al., 1998).

4. Biological functions of the cell surface Complement Receptor 1

4.1. Regulation of the complement cascade

The Complement Receptor 1 has multiple actions that define its role as a complement regulatory protein (Fig. 2A). The CR1 molecule acts as a receptor for C3b and C4b thereby destabilizing and enhancing the decay of Classical Pathway C3 (C4b2a) and C5 (C4b2a3b) covertases and Alternate Pathway C3 (C3bCBb) and C5 (C3bBb3b) covertases (Iida and Nussenzweig, 1981). Another prominent function is its activity as the cofactor for Factor I mediated inactivation of C3b (Ross et al., 1982) and C4b (Medof and Nussenzweig, 1984) acting as another step in the regulation of the alternate pathway. The role of CR1 as a MBL receptor (Ghiran et al., 2000) may be involved in regulating the MBL pathway of complement activation.

4.2. Clearance of immune complexes

The Erythrocyte CR1 (ECR1) is able to bind to C3b/C4b opsonized immune complexes (Yoshida et al., 1986) and localize them on the erythrocytic membrane (Fig. 2A). The immune complexes thus trapped are transferred to the macrophages in the liver and spleen (Cosio et al., 1990; Craig et al., 2002) The Kupffer cells and other large phagocytes of the liver and spleen engulf and metabolize the immune complexes (van Es and Daha, 1984; Skogh et al., 1985).

4.3. Receptor for phagocytosis

Various immune complexes and particles coated with polymeric C3b can be recognized by the CR1 molecules on the polymorphonuclear (PMN) cells and monocytes particulary those in the clathrin coated pits (Fearon et al., 1981; Abrahamson and Fearon, 1983). The Fc-gamma receptors and CR1 operate in synergism to promote uptake of particles opsonized by immunoglobulins and complement proteins. The particles are internalized and destroyed in the lysosomes. (Fig. 2B) (Ehlenberger and Nussenzweig, 1977; Schorlemmer et al., 1984). The C3b receptor molecules are present as cytoplasmic secretory vesicles (demonstrated in neutrophils) which are translocated to the plasma membrane on cell activation (Sengelov et al., 1994).

4.4. Regulation of the B-cell and T-cell responses

4.4.1. B-cells

The Complement Receptor 1(CR1) present on B-cells appears to control the proliferation of B-cells (Fingeroth et al., 1989). When CR1 is occupied by its ligand, the stimulatory drive of suboptimal anti-IgM$(Fab)_2$ fails to bring about B-cell proliferation (Fig. 2C) (Jozsi et al., 2002; Erdei et al., 2003). The physiological importance of such an interaction may relate to the inhibition of B-cell activation by weak antigenic stimuli evoked by an auto-antigen.

4.4.2. T-cells

Although the presence of CR1 on CD4+ and CD8+ T lymphocytes has been proved (Rodgaard et al., 1991), the functional significance of the same is not clear. Increased expression of CR1 on poly clonally activated T cells had been demonstrated. This suggested a possible role of CR1 in T-cell mediated immune regulation (Rodgaard et al., 1995).

5. Biological functions of soluble CR1

The sCR1 appears to have highly efficacious complement regulatory and anti-inflammatory activities (Hamer et al., 1998). The physiological plasma levels of sCR1, however, are too low to have any significant functional role (Pascual et al., 1993). Soluble CR1 had been isolated from the bronchoalveolar lavage of the patients with inflammatory lung disorders (Hamacher et al., 1998) and from the plasma of the patients suffering from hepatic and renal failure and lymphomas and leukemias (Pascual et al., 1993). Increased levels of sCR1 in plasma had also been reported in SLE and glomerulonephritis (Das et al., 2002). It is hypothesized that sCR1 is a locally active molecule. sCR1 is envisaged as a molecule of choice for various novel CR1-based therapeutic strategies.

6. Molecular genetics of Complement Receptor 1

The Complement Receptor 1 gene is located on the Chromosome 1 at the locus 1q32 (Weis et al., 1987). It has been mapped to the region of regulators of complement activation (RCA) gene cluster (Rodriguez de Cordoba and Rubinstein, 1986). Various gene polymorphisms have been studied for CR1. The gene variance may range from grossly molecular weight altering insertion–deletion polymorphisms to the minimally protein altering intronic or exonic single nucleotide polymorphisms that affect the density of CR1 molecules on the cell surface. In addition to the above two, there is another set of polymorphisms, which are generated by single nucleotide polymorphisms and alter the CR1 protein to generate a separate group of blood group antigen variants, the Knops blood group antigens.

6.1. Intronic polymorphism

6.1.1. HindIII RFLP: the intronic density polymorphism

Various polymorphisms have been studied for their ability to alter the density of erythrocyte CR1 on the cell membranes. There might be a 10-fold difference between the ECR1 in different individuals owing to their specific genotypic composition (Wilson

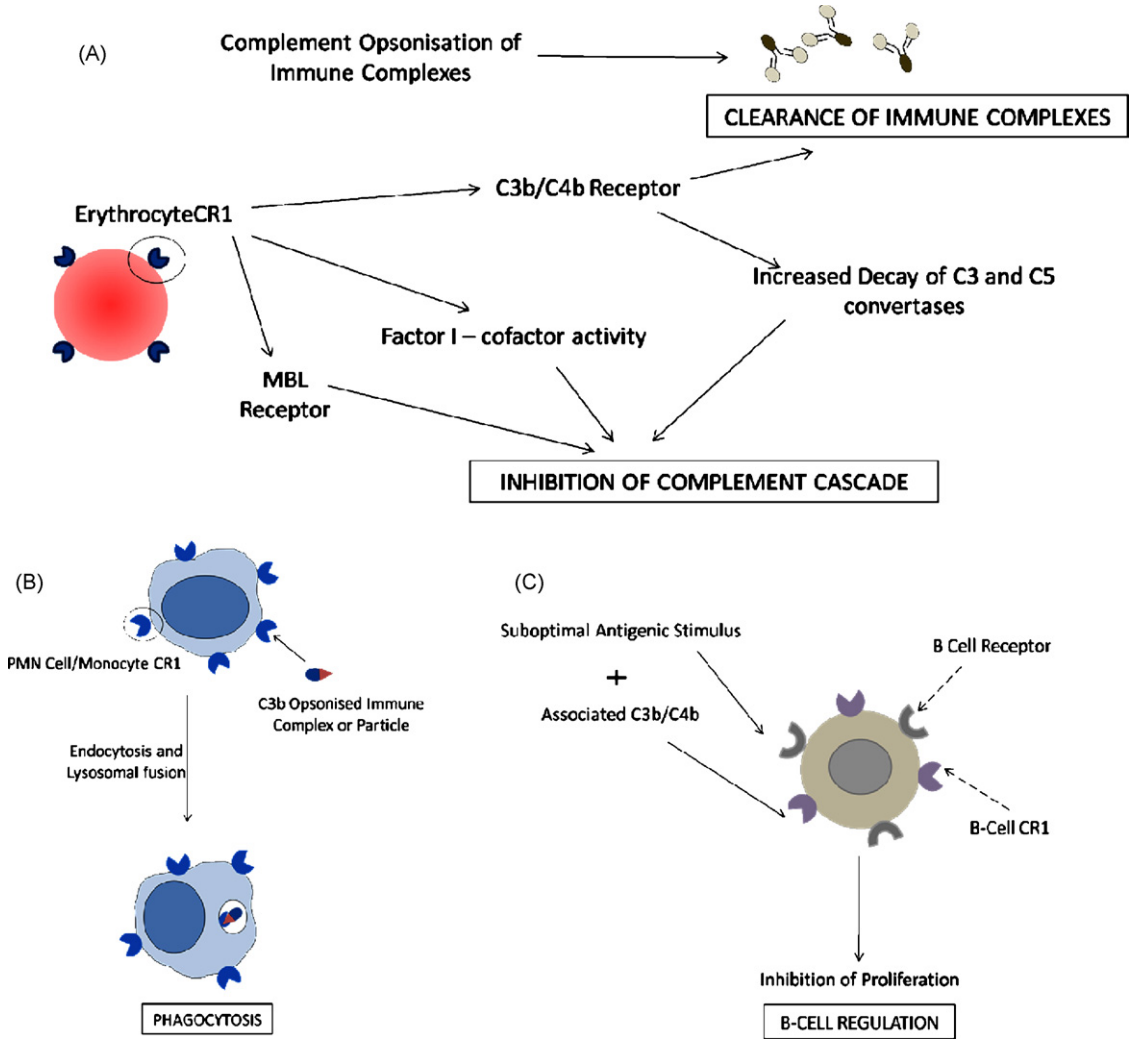

Fig. 2. Regulation of the complement cascade and immune complex clearance by CR1(A) erythrocyte CR1 involved in complement pathway regulation and immune complex clearance (B) polymorphonuclear (PMN) Cell CR1 and monocyte CR1 involved in phagocytosis (C) B-cell CR1 involved in B-cell regulation.

et al., 1982). The levels of CR1 on the leucocytes do not show variability like ECR1 (Wilson et al., 1986). The HindIII restriction fragment length polymorphism (HindIII RFLP) corresponds to a single nucleotide polymorphism in the intron 27(with a single base substitution, $T^{520}C$) of the CR1 gene (Wilson et al., 1987). The HindIII 7.4 kb genomic fragment, associated with high expression allele (H allele), and the 6.9 kb HindIII genomic fragment, associated with low expression allele (L allele). Presence of several exonic single nucleotide polymorphisms (SNPs) (Xiang et al., 1999, Table 1), in linkage disequilibrium with the HindIII RFLP polymorphism is suggested as a probable mechanism for alteration of ECR1 by the intronic HindIII RFLP. The H allele is now considered to contain G^{3093}, A^{3650}, and C^{5507} (encoding Gln^{981}, His^{1167}, and Pro^{1786}); and the L allele is considered to contain T^{3093}, G^{3650}, and G^{5507} (encoding His^{981}, Arg^{1167}, and Arg^{1786}). These variances in the amino acid composition are suggested to influence the stability of CR1 protein. The ECR1 levels show a trimodal distribution, high expression phenotype (~ 1000 molecules per cell) in association with the homozygous H, intermediate expression with heterozygous HL and low expression (~100 molecules per cell) with homozygous L genotype in Caucasians (Xiang et al., 1999) and Indians (Katyal et al., 2003) but not in Africans (Rowe et al., 2002).

Table 1
Polymorphisms in the coding sequence of CR1 (Xiang et al., 1999).

Nucleotide	Exon	Amino acid[a]	SCR
A207G	2	Silent in Glu19	1
T981C	6	Silent in Pro277	5
A1356G	9	Silent in Gly402	7
A1360G	9	T404A	7
T2078C	13	I1643T	10/11
T2367C	14	Silent in Tyr739	12
G3093T	19	Q981H	16
A3650G	22	H1167R	19
A4870G	29	I1574V	25
C5507G	33	P1786R	28
C5654T	34	T1835I	29

[a] Amino acid numbering has been altered from the original (Xiang et al., 1999) to standardize to the previous depiction.

6.2. Coding-region polymorphisms

6.2.1. Structural polymorphism: the molecular weight variants

The CR1 protein has four known allotypic variants varying in size from M_r 160 kDa to 250 kDa (Dykman et al., 1983, 1984, 1985). These are not post-translational modifications as their unglycosylated primary transcript possesses the same variation (Lublin et al., 1986). The genomic difference between each allotype ranges from 1.3 to 1.5 kb, equivalent to a single LHR (Wong et al., 1986, Holers

et al., 1987). The insertion-deletion mechanisms due to unequal crossing over of chromosomes have been considered responsible for such a variation (Holers et al., 1987). The CR1-C (160 kDa), CR1-A (190 kDa), CR1-B (220 kDa) and CR1-D (250 kDa) are the four variants as analyzed on SDS–PAGE under non-reducing conditions (Van Dyne et al., 1987). The LHR repeats give an additional C3b binding site to the larger variants (CR1-B and CR1-D) while the small CR1-C has only one such site, the functional implication, however, is not clear. The most frequent alleles are the CR1-A (F allotype) and the CR1-B (S allotype) followed by the CR1-C. CR1-D allele is very rare (Dykman et al., 1985; Moulds et al., 1996). The gene frequencies of CR1-A and CR1-B are 0.87 and 0.11 in Caucasians, 0.82 and 0.11 in African Americans, 0.89 and 0.11 in Mexicans (Moulds et al., 1996) and 0.916 and 0.084 in Asian Indians (Katyal et al., 2003). AA and AB are the most prevalent genotypes in all the populations studied.

6.2.2. Q981H: the exonic density polymorphism

The Q981H polymorphism (Birmingham et al., 2003) is characterized by an exonic SNP leading to the replacement of a single guanine with thymine (G3093T). The polymorphism is in the binding sites of ECR1 ligands (Xiang et al., 1999) and has drawn special attention in relation to the severity of *Plasmodium falciparum* malaria (Thomas et al., 2005).

6.2.3. Knops blood group polymorphism: blood group antigens localized on ECR1

The various antigens studied under this grouping include the allelic pairs Kn^a/Kn^b (Knops), McC^a/McC^b (McCoy), Sl^a/Vil (Swain–Langley/Villien) and Yk^a (York) (Moulds, 1981; Daniels et al., 1995). These antigens were identified by the occurrence of high avidity non-complement fixing and non-hemolysing antibodies in the circulation. Subsequently, it was identified that the corresponding antigens were present on the CR1 molecule (Moulds et al., 1991; Rao et al., 1991) and the genes coding them were located in the LHR-D region of the CR1 gene (Moulds et al., 2001; Tamasauskas et al., 2001). Recently Sl^a has been sub-classified into various conformational variants (Moulds, 2002). The various Knops blood group genotypes are generated by Single Nucleotide polymorphism in exon 29 (SCR–25) (Moulds et al., 2004). The identification of Knops blood group antigens as CR1 phenotypes was indicated by the discovery that the serologically null phenotype, the 'Helgeson phenotype' of the Knops blood group showed reduced CR1 levels (Moulds et al., 1992). The association of Knops blood groups with malaria and various inflammatory disorders is a topic of interest for many present day researches.

7. Association of Complement Receptor 1 with disease conditions

Extensive research on CR1 has brought new insight to the diagnosis, prognosis, pathophysiology and therapy of diseases from different domains. Studies however, have remained more focused to the autoimmune disorders.

8. Complement Receptor 1 and autoimmune disorders

Autoimmune disorders have been correlated to multiple factors. There has been considerable study into the pathogenic mechanisms involved in the autoimmune tissue injury. One of the mechanisms relates CR1 with the etiopathogenesis of the autoimmune disorders. It is suggested that C4b bound to self-antigens when presented to the CR1 molecule on bone marrow stromal cells leads to the down-regulation of autoreactive B-cells hence maintaining B-cell tolerance (Prodeus et al., 1998). At the effecter end, CR1 serves to protect host tissue by clearing the immune complexes which on deposition in the vasculature, glomeruli and synovium can lead to tissue damage by complement activation and Fc-mediated phlogistogenesis. In addition, the complement regulatory functions of CR1 may have an important role in amelioration of autoimmune host-tissue destruction.

8.1. Systemic lupus erythematosus

Complement Receptor 1 has been studied extensively in relation to Systemic lupus erythematosus (SLE). It has been shown that in SLE there is a marked decline in the levels of CR1 on erythrocytes (Ross et al., 1985; Corvetta et al., 1991; Birmingham et al., 2006), leukocytes (Wilson et al., 1986; Fyfe et al., 1987) and glomerular podocytes (Arora et al., 2000; Raju et al., 2001). Several mechanisms have been suggested to explain the decline of the cell surface CR1 in diseases.

8.1.1. Genetic factors

Inheritance of L allele of the HindIII density polymorphism was envisaged as a cause for the low levels of CR1 in patients. Intensive investigations however, refuted this assumption (Walport et al., 1985; Mitchell et al., 1989, Kumar et al., 1995). Nevertheless, some studies have shown positive correlation of the L allele with SLE (Wilson et al., 1987). The reduction in ECR1 levels in transfused RBCs in active SLE patients further showed non-genotype-specific reduction (Walport et al., 1987). Thus, most of the studies carried out in many ethnic groups found no association of CR1 L or C allele with the disease (Moulds et al., 1996).

A study from India demonstrated a highly significant association of CR1 HH genotype and the H allele with immune complex-mediated glomerulonephritis. Greater loss of erythrocyte CR1 was observed in patients carrying HH genotype. L allele thus, appeared protective. It was speculated that there are compensating mechanisms for those who inherit the low expression genotype as against those who inherited HH genotype (Katyal et al., 2003).

8.1.2. Acquired loss: proteolytic cleavage

While inheritance of low CR1 levels did not stand true for low levels of CR1 for most of the SLE patients, it is now believed that the low ECR1 levels in SLE are acquired (Walport et al., 1985; Holme et al., 1986). CR1 was shown to be highly susceptible to tryptic cleavage (Ripoche and Sim, 1986) and the 'CR1 stump peptide', possibly from proteolytic cleavage, was demonstrated on the podocytes in severe SLE associated glomerulopathies (Barbosa et al., 1992; Teixeira et al., 1996). Some indirect findings suggest that a decrease in ECR1 levels is seen in various inflammatory and malignant disorders, which also have higher levels of serum proteases like elastase (Currie et al., 1990). Cells like the mesangial cells and possibly some circulatory cells may be responsible for pericellular proteolysis in cells which have Terminal complex of complement (C5b-9) deposited onto the cell membranes (Adler et al., 1987; Lovett et al., 1987). They may possibly cleave surface CR1 molecules supersaturated with complement activating immune complexes of the disease. Hence, this mechanism of acquired loss is more widely accepted.

8.1.3. Transcriptional and post-translational control: modulation of leukocyte CR1 (LCR1): role of cytokines

Although an enhanced proteolytic cleavage stood as the most plausible mechanism for low levels of CR1 in SLE, possibility of reduced synthesis of CR1 as a putative mechanism was not entirely ignored. Evidences to validate the same were, absence of CR1 stump on glomerular podocytes expressing very low levels of GCR1 (Moll et al., 2001) and, a positive correlation between the levels of uCR1

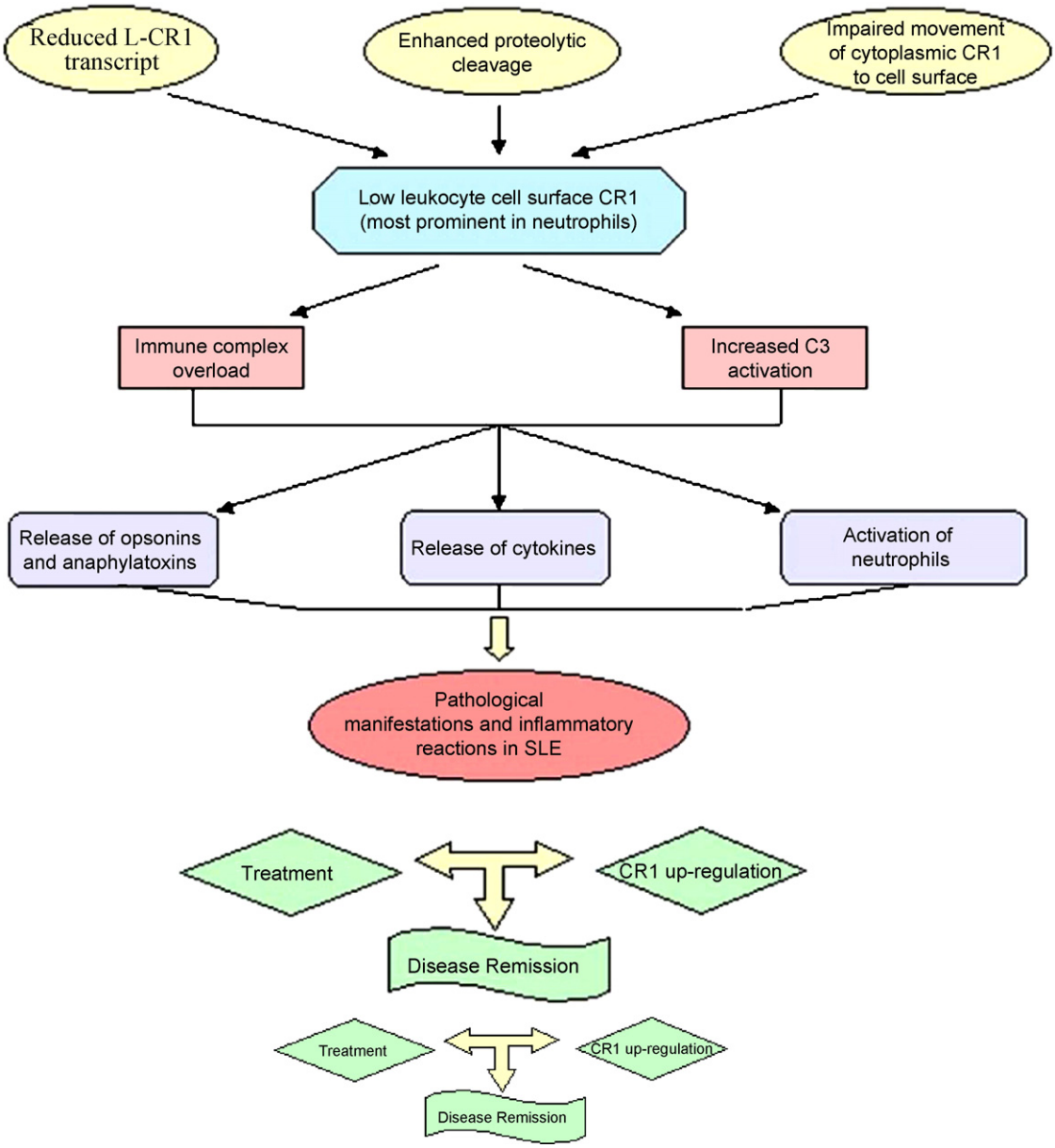

Fig. 3. Down regulation of LCR1 and its possible role in the pathophysiology of SLE. Also shown is the unexplained link between CR1 up-regulation and state of disease remission (adapted from the Ph.D. Thesis, Vaishali Arora, 2007).

and GCR1 in SLE patients with marked decline in the levels of GCR1 (Sivasankar et al., 2004). With the presumption that the mechanism of CR1 expression and its modulation on the nuclear cells might be different from that envisaged for the erythrocytes, Arora et al. conducted a series of experiments on leucocytes and neutrophils from the healthy individuals and patients with SLE. It was evidenced that reduced gene transcription, enhanced proteolytic cleavage and defective targeting of vesicular CR1 to the cell membrane, collectively contribute to the marked decline of leukocyte CR1 in SLE (Arora et al., 2004, 2007) (Fig. 3).

9. Other autoimmune disorders

Although less studied in comparison to SLE, similar patterns of CR1 involvement have been indicated in many other autoimmune disorders. Like SLE, in *Rheumatoid Arthritis*, CR1 expression on erythrocytes is reduced (Kumar et al., 1994) and is shown to be an acquired character (Kumar et al., 1994). However, there are reports to suggest higher levels of CR1 expression in RA (Jones et al., 1994). Low CR1 expression along with that of other molecules in the 'Regulators of complement activation (RCA)—alpha block' is a major susceptibility mechanism in primary *Sjögren Syndrome* (Lester et al., 2008). Acquired loss of ECR1 has also been reported in insulin-dependent diabetes mellitus (IDDM) (Ruuska et al., 1992). Differential pattern of CR1 expression on erythrocytes and glomerular podocytes had been reported for immune complex mediated, non-immune complex-mediated and minimal change nephritic syndromes (Raju et al., 2001).

10. Complement Receptor 1 and pathogenesis of falciparum malaria

Dreaded complications of *P. falciparum* malaria, such as massive hemolysis, anemia, cerebral malaria, renal failure, hypoglycemia,

acidosis, macroscopic hemoglobinuria and many others, have been explained on the basis of two broad etiopathogenetic mechanisms. The first mechanism suggests microvasular obstruction brought about by rosetting of erythrocytes in the microvasculature of various vital organs. The second mechanism suggested is immune complex mediated (Kaul et al., 1991), Immune complexes, by multiple downstream pathways and complement activation-induced metabolic dysfunction, cause tissue injury and multi-organ failure (June et al., 1979; Nagayasu et al., 2001). None of these suggested mechanisms could explain all the above complications. The CR1 molecule, especially, ECR1 by its capacity to contribute to both rosette formation and immune complex clearance has been widely studied with an aim to decipher the marker for severity as well as a target for immune-prophylaxis and therapeutic strategies.

The intra-erythrocytic phase of the malarial parasite presents the *P. falciparum* erythrocyte membrane protein1 (PfEMP1) on the erythrocytic membrane which by interaction with multiple receptors, prominently Erythrocyte CR1 leads to erythrocyte rosetting (clumping) (Rowe et al., 1997). This mechanism to a great extent, explains the role of CR1 in the malarial complications arising out of microvascular obstructive pathology, mainly the cerebral malaria. The other aspect of CR1 involvement includes the clearance of immune complexes (Cosio et al., 1990), which is a role that has been well studied in various autoimmune disorders.

Of particular interest has been the association of CR1 density polymorphisms with severe malaria. The HindIII RFLP has been shown to have variable relationship to severity. HH genotype, by increasing the ECR1 numbers, increases the CR1 mediated rosetting and associated sequelae. The LL genotype although associated with reduced rosetting, adversely affects the capacity of the erythrocytes to clear the immune complexes, associated with malarial infection, owing to the reduced ECR1 levels. Both the arguments have been supported by severity correlation in different groups of populations. The Caucasian study group of Cockburn et al. (2004) shows severity correlation to the HH genotype while, a study on the Thai population (Nagayasu et al., 2001) has shown that low rosetting, high immune complex state of LL genotype is correlated with malarial severity. As expected, a metabolic pattern of severity dominates in the Southeast Asian countries (Nagayasu et al., 2001). The African population has not shown correlation of CR1 density or malarial severity with any Hind III RFLP genotype (Rowe et al., 2002).

The selective pressure of malaria can be seen to affect the selection of many other CR1 polymorphisms. The exonic Q981H polymorphism, located in the PfEMP1 binding domain of CR1 (Thomas et al., 2005) may emerge as an effective marker of malarial severity. Preliminary (unpublished work) work of Madhukar et al. and Das et al. (Madhukar et al., Das et al., Presented at the Keystone Symposium, Albach, Austria, 2008)) have shown that malaria severity correlates with Q981H and HindIII RFLP. The Knops blood group antigens, specifically the McCoy and Swain–Langley group have a role to play in the malarial pathogenesis. The Sl (a−) antigenic variants have been shown to rosette less efficiently than the Sl (a+) (Rowe et al., 2000). It has been shown that chances of Cerebral Malaria are reduced in the Sl (a^-)/McC (a/b) genotypes as compared to the Sl (a^+)/McC (a/a) and hence there is possibility that SI (a−) and McC (b+) provide a selective advantage for their selection in malarial endemic regions of Africa, as shown for Mali in Table 2 (Moulds et al., 2000). Another study in Gambia has failed to find an association between malarial severity and Knops blood group antigens (Zimmerman et al., 2003).

Table 2
Phenotype frequencies of Knops blood group polymorphism in various ethnic groups (Moulds et al., 2000).

	Kn(a+)	McC(a+)	McC(b+)	Sl(a−)
European-Americans	0.98	0.98	0.01	0.01
African-Americans	0.99	0.90	0.44	0.39
Malians (Malaria endemic)	1.00	0.89	0.49	0.70

11. Complement Receptor 1 and HIV

The relation of CR1 to HIV infection is multidimensional. The effect of CR1 is observed in the establishment of infection, episodic exacerbations of disease condition and sustenance of infection during anti-retroviral therapy. CR1 levels have been associated to HIV disease progression as well.

11.1. Monocytic and thymocytic infection

Complement opsonized lymphotropic strains of HIV have been shown to infect monocytic cells even in suboptimal viral concentrations while similar unopsonized HIV are not infective at such concentrations. This activity has been attributed to CR1 and CR3 (Complement Receptor 3) but not to the CD4 receptors on monocytes. Monocytes treated with monoclonal anti-CR1and anti-CR3 but not those treated with anti-CR4 remained uninfected by HIV (Thieblemont et al., 1993). A similar mechanism of infection of thymocytes has also been proposed (Delibrias et al., 1994).

11.2. Increased viral replication

The replication of HIV in CD4+ lymphocytes has been shown to be enhanced by the activation of CR1 molecules by aggregated C3b (Mouhoub et al., 1996), suggesting a mechanism for the increased HIV viremia and decompensation into AIDS-related complex and AIDS, by the C3b bearing immune complexes or particles of co-occurring infections.

11.3. Sustenance of infection and further spread

The HIV infection when treated with anti-retroviral therapy leads to complement dependent binding of HIV particles along with HIV-immune complexes on to erythrocyte CR1 (Montefiori et al., 1994; Horakova et al., 2004), causing to persistence of infection even when the virus may be undetectable in blood. Newer studies have revealed that binding of opsonized HIV to ECR1 is transient in nature and Factor I-mediated processing of C3b (present with HIV) to iC3b and C3d, helps in transfers of HIV particle to CR2 expressing B-cells which are then subjected to B-cell mediated transfer to T-cell (Fig. 4) (Banki et al., 2006).

12. Miscellaneous disease associations

The importance of CR1 has lead to investigation of its role in many other diseases. The uptake of *Mycobacterium tuberculosis* into the monocytes/macrophages is partly mediated by monocyte CR1 which is blocked to a certain extent by monoclonal antibodies to it. A decline in adherence of *M. tuberculosis* by 40 ± 5% (Schlesinger et al., 1990) was observed. Preliminary investigations have indicated upregulation of CR1 by *M. tuberculosis* soluble antigen ESAT 6 (Preliminary findings accepted for presentation at XXII ICW, 2008, data not shown here). In patients with *carcinoma of* the *gallbladder*, the levels of ECR1 were found inversely proportional to the degree of cancer invasion and distant metastasis and hence to disease severity. Here too the decline in the levels of ECR1 was found to be an acquired phenomenon (Jiao et al., 2004). In Leishmanial infections the CR1 receptor has been shown to be involved in the

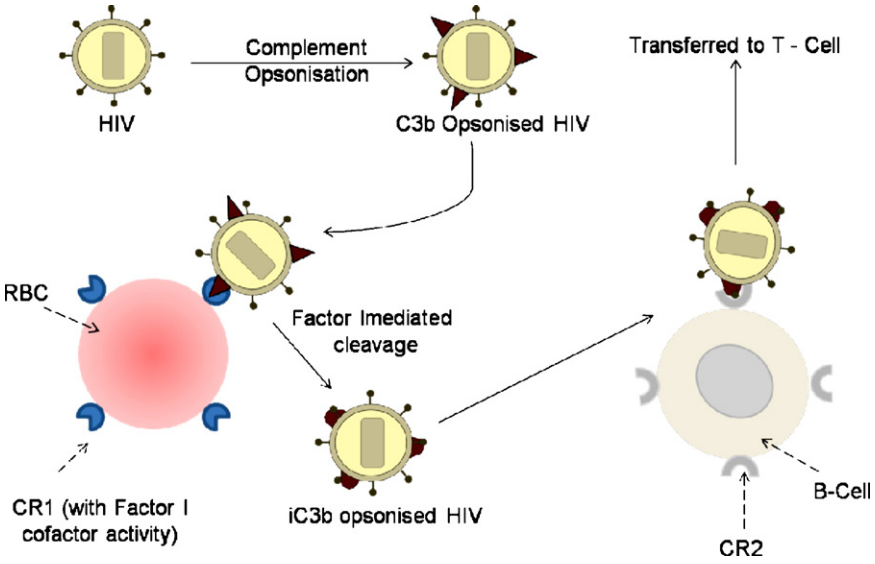

Fig. 4. Sustenance of HIV Infection and further spread–During anti-retroviral therapy virus survives in association with ECR1 and also spreads to B cells via CR2 (Complement Receptor 2) after Factor I mediated breakage of HIV associated C3b to iC3b.

binding of Leishamania major metacyclic promastigotes to human macrophages (Da Silva et al., 1989; Rosenthal et al., 1996). The levels of E-CR1 decline during phases of initiation and progression of severe acute respiratory syndrome (SARS) (Wang et al., 2005). The expression of CR1 on the neutrophils of patients with *severe atopic dermatitis* was higher than those with the mild form of the disease (Yoshida et al., 2002).

13. Prognostic significance of CR1

The above account on the disease associations of CR1 formed the basis of exploring the importance of CR1 as a disease marker. Again, more information is available in relation to SLE. Sivasankar et al. (2004) suggested urinary CR1 as a marker to diagnose glomerular involvement in SLE. Verma et al. (2005) in a case–control study found that the levels of leukocyte CR1 transcript were much lower in patients with lupus nephritis compared to non-nephritis patients, suggesting the role of CR1 as a disease severity marker for SLE. Arora et al. (2004) and Das et al. (2006) through their case-controlled studies and follow up studies found significant correlation between the levels of neutrophil CR1 (NCR1) transcript, CR1 protein and disease activity. They showed a negative correlation of the levels of CR1 transcript with disease activity and its prognostic course.

In HIV, the mean values of ECR1 when estimated for AIDS and AIDS related syndromes, gave a significant trend. Jouvin et al. (1987) found that ECR1 levels in asymptomatic seropositive individuals (822 ± 270) and patients with persistent generalized lymphadenopathy (PGL) (775 ± 320) did not differ significantly from the normal subjects while levels of CR1 decreased in the patients with AIDS related complications (543 ± 233, $p < 0.001$) and further in patients who suffered from AIDS (442 ± 271, $p < 0.0001$). The levels of CR1 showed a negative correlation with the severity of disease (Cohen et al., 1989). The loss of CR1 in AIDS was considered as an acquired rather than an inherited phenomenon.

14. CR1 gene polymorphisms as disease susceptibility markers

As discussed earlier, CR1 gene is a strong candidate for predicting susceptibility to severe malaria. CR1 has also been nominated as a candidate gene to assess the susceptibility to *sarcoidosis* on the basis of a case-controlled study but not through linkage analysis (Iannuzzi et al., 2002). Females with low expression genotype of ECR1 were shown to have higher tendency to develop *pre-eclampsia*, i.e. gestation-induced hypertension (Guo and Qian, 1989; Feinberg et al., 2005). An association of the HH genotype of CR1 Hind III polymorphism with immune complex glomerulonephritis had been suggested (Katyal et al., 2004). By and large, the studies remained confined to HindIII density and structural polymorphisms of CR1. With growing evidence for the existence of many different SNPs on CR1 gene (Xiang et al., 1999), an extensive analysis of CR1 gene needs to be carried out.

15. Novel therapeutic strategies: enhanced relevance of CR1 research

In addition to providing an insight into the molecular pathogenesis of many disorders, the CR1 molecule itself, owing to its multifunctional nature, is a promising therapeutic agent. The soluble form of CR1 though functionally active is normally present in very low concentrations in the plasma. A recombinant form of sCR1 has been designed to assess the therapeutic potential of CR1. This recombinant CR1, the rCR1 has the C3b and C4b binding sites and the activity as a cofactor for Factor I. Its therapeutic efficacy had been assessed for various autoimmune and inflammatory disorders (Weisman et al., 1990a). The animal model experiments have validated the resolution of inflammatory changes accompanying inflammatory lung injury (Rabinovici et al., 1992), Myocardial infarction (Weisman et al., 1990b), autoimmune thyroiditis (Metcalfe et al., 1996) and glomerulonephritis (Couser et al., 1995) with the use of recombinant soluble CR1. Use of sCR1 for managing incompatible blood transfusion by inhibition of complement activation and subsequent immune hemolysis had been suggested (Yazdanbakhsh and Scaradavou, 2004). Since sCR1 can potentially prevent E-resetting and clear immune complexes in patients, it is envisaged as a therapeutic for severe falciparum malaria (Cockburn et al., 2004). Soluble CR1 has long been expected to ameliorate the suffering from various disease conditions, but most of the studies which promise such a revolution in health care strategies, have been based on animal models of these diseases (Weisman et al., 1990b; Rabinovici et al., 1992; Couser et al., 1995), which may have limited

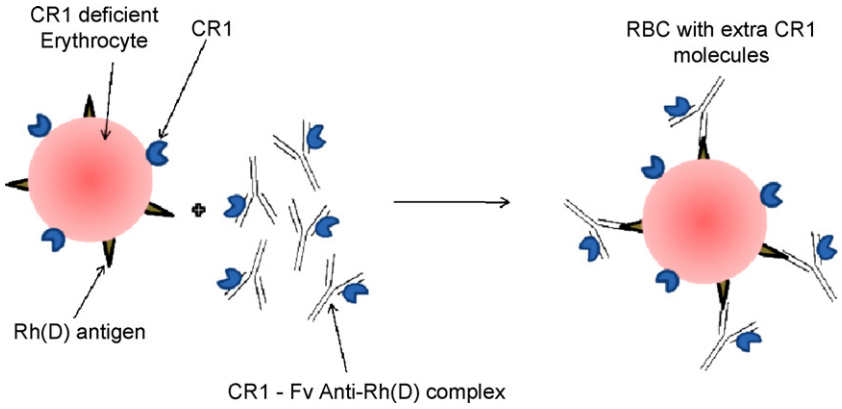

Fig. 5. CR1–Fv anti-Rh(D) complex-mediated increase in ECR1 levels in individuals with ECR1 deficiency.

value in light of important species differences in the mechanisms of immune complex clearance.

CR1-Fv anti-Rh(D) complex is designed to target and add extra CR1 molecules on CR1 deficient erythrocytes in various disorders (Oudin et al., 2000) (Fig. 5). Another strategy involves the use of an Antigen-based heteropolymer (AHP) which is a dsDNA molecule bound to mononclonal antibody against CR1. This molecule would specifically bind to the anti-dsDNA and target it to the E-CR1 through anti-E-CR1 to facilitate the removal of anti-ds DNA from circulation at a faster rate (Ferguson et al., 1995).

Another recent molecule, Sialyl Lewis(x) hybridized soluble Complement Receptor 1, *sCR1-sLe(x)* (Picard et al., 2000)is developed, In this, the sCR1 fragment acts as the complement inhibitor and the sLe(x) acts to inhibits the selectin-mediated interaction of lymphocytes and neutrophils with endothelium. *sCR1-sLe(x)* has been proposed to be useful in ischemia-reperfusion injury, thermal injury and immune complex mediated injury (Asghar and Pasch, 2000). Its efficacy in preventing lung ischemia-reperfusion injury as well as stroke reperfusion injury has been studied extensively (Stammberger et al., 2000; Ducruet et al., 2007). Pre-clinical evaluation for *sCR1-sLe(x)* conducted in non-human primate models of reperfused stroke, had to be terminated prematurely, as not only was it unable to perform the proposed function of reducing the infarct volume but also caused a few unfavorable reactions (Ducruet et al., 2007) thus, emphasizing the need for further research for this molecule.

For the purpose of specifically inhibiting the auto-reactive cells characteristic of autoimmune disorders, a DNA mimotope–CR1 complex has been designed which specifically inhibits the auto-reactive B-cells. The DNA mimotope has been included for specific binding ability to the anti-dsDNA antibody secreting B-cell while CR1 acts as a B-cell inhibitor (Fig. 6) (Voynova et al., 2008).

As a method to fight growing antibiotic resistance in bacteria, CR1-based immunotherapeutic strategies have been experimented. For the treatment of resistant *Staphylococcus aureus* infections, a bispecific monoclonal antibody complex (Heteropolymer, HP) specific to ECR1 and type 5 capsular polysaccharide of the T5 isolate of *S. aureus*, has been designed. This promotes binding of *S. aureus* to erythrocytes (via ECR1) with subsequent transfer to monocytes or macrophages for internalization and bacterial killing (Gyimesi et al., 2004).

CR1 has also been studied as an important molecule to circumvent hyper-acute tissue rejection, as occurring in allogenic transplants. Cells transfected with recombinant CR1 (Hammel et al., 1999; Manzi et al., 2006) or phosphatidyl inositol-bound mini CR1 (Mikata et al., 1998) showed enhanced survival when subjected to conditions simulating hyper acute rejection and such results have aroused great interest in scientists world over.

Most of the above strategies are still in a nascent stage and have a long way to go before they are ready for use, more so, because none of the strategies outlined above have been tested beyond the animal models of the respective diseases. However, these find-

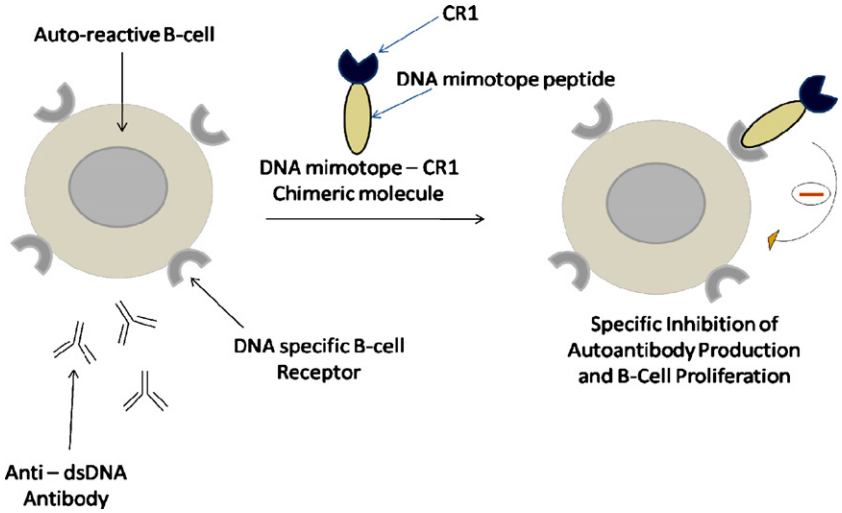

Fig. 6. Specific inhibition of autoreactive B-Cells (here dsDNA) by chimeric CR1-DNA mimotope.

ings do promise revolutionary therapeutic strategies centered on CR1.

16. Effect of cytokines and other factors on CR1 expression

With increasing realization that there is a close relationship between the disease pathology and the level of CR1 expression, it is desired that the factors that contribute to the maintenance of the normal CR1 levels and its modulation in the disease states be unraveled. Effect of several cytokines in this context is being investigated. Depending on the type of the cell, variable effects have been observed (Limb et al., 1991).

It is observed that TNFα, TNF β and IL4 increased CR1 levels on monocytes. The chemotactic peptides were shown to upregulate CR1 in different cells tested (Doi et al., 1995). In a recent investigation it was found that IFNγ increased the levels of CR1 transcript in the neutrophils of healthy individuals and patients with SLE (Arora et al., 2007). IL-4 and IL-10 suppressed the effects of IFNγ on CR1 expression (Das et al., 2008, data not shown, presented at FOCIS 2008, under publication). While elucidating the factors responsible for the decline of CR1 transcript in SLE, it was found that serum opsonized immune complexes reduced the levels of CR1 transcript in the neutrophils from the healthy individuals as well those from the patients (Arora et al., 2007). TNFα however, had no effect on NCR1 expression. Immune complexes, if not opsonized, had no direct effect on CR1 expression, but it suppressed the IFNγ-induced CR1 expression. With these findings, immune complexes have emerged as the major factor responsible for decline of NCR1 in SLE (Arora et al., 2007). Studies on different cell lines have shown retinoic acid to up-regulate CR1gene expression (Mucida et al., 2007).

An interesting relationship between CR1 HindIII polymorphism and the modulation of NCR1 levels by IFNγ and immune complexes has been observed (Anand, 2008, M.Sc. Thesis, Data under publication). It was observed that the HL genotype was more responsive to either the up-regulation or down-regulation of NCR1 levels by IFNγ or immune complexes, respectively. This gives some clue to why in Asian Indians L allele appeared protective against SLE.

17. Conclusion

To conclude, Complement Receptor 1 is an ideal target for translational research. There is ample evidence to suggest multifaceted association of Complement Receptor 1 with a vast array of diseases. CR1 is a functionally versatile protein with structural variance. Complement Receptor 1 genetics and its relationship with disease processes open up a fascinating area of research. CR1 is an extremely important molecule in disease processes where immune complex deposition and excessive complement system activation result in tissue damage. Its biological role allows it to be a future candidate as a marker for determining disease susceptibility, diagnosis and prognosis. Various trials on animal models with CR1 as a therapeutic had established this molecule as a chain breaker of complement-mediated inflammatory reactions and subsequent organ damage. The various aspects of CR1 as assembled in this review may intensify further investigations on CR1 in achieving better insight into a large number of diseases and to open up novel therapeutic strategies.

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