Biochemical and Biophysical Research Communications 422 (2012) 207–212

Contents lists available at SciVerse ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Analysis of the CD23-αv integrin interaction: A study with model peptides

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ARTICLE INFO

Article history:
Received 5 April 2012
Available online 27 April 2012

Keywords:
CD23
αv Integrins
Surface plasmon resonance

ABSTRACT

The human CD23 protein binds to αvβ3 and αvβ5 integrins. The integrins recognize a short tripeptide motif of arg-lys-cys (RKC) in CD23, and peptides containing this motif inhibit the binding of CD23 to B cells and monocytes; neither fibronectin, nor vitronectin, which contain arg-gly-asp motifs, inhibit binding of RKC-containing peptides to cells. RKC-containing peptides derived from CD23 show dose-dependent, biphasic binding profiles to both αvβ3 and αvβ5 that are cation-independent but sensitive to high chloride ion concentrations. Substitution of one basic residue in the RKC motif with alanine reduces but does not abolish integrin binding or the ability of peptides to stimulate pre-B cell growth or cytokine release by monocytes. Substitution of both basic residues abolishes both integrin binding and biological activity of CD23-derived peptides. These features indicate that binding of RKC-containing peptides to αv integrins has clearly distinct characteristics to those for binding of RGD-containing ligands.

1. Introduction

Integrins are heterodimeric cell surface transmembrane glycoproteins that mediate adhesion interactions between cells and matrix structures [1,2]. There are 18 possible α subunits and eight β subunits and these are known to form 24 αβ heterodimers. Integrins recognize short stretches of sequence in target proteins in a cation-dependent manner. The αvβ3 integrin binds an arg-gly-asp (RGD) motif in fibronectin (Fn) and vitronectin (Vn) [3] and both integrin subunits contribute to binding of the RGD motif [4,5]. The peptide arginine binds in a crevice in the β-propellor domain of the αv subunit and the terminal guanidinium group makes a bi-dentate salt link with asp^{218} at the bottom of the crevice [4,5]. The peptidic aspartate is secured in a deep pocket in the βA domain of the β3 subunit and the carboxylate oxygens are coordinated via amide groups of the β3 subunit peptide backbone and by ionic interactions with Mn^{2+} (or Mg^{2+}) in the metal ion-dependent adhesion site [4,5]. The glycine of the peptide motif sits in a small groove at the αv/β3 interface. The binding of integrins to matrix ligands in adhesion interactions is therefore cation-dependent and sensitive to alterations in target motif structure.

There is increasing evidence that integrins bind soluble ligands in an RGD-independent manner. The binding of the snake venom jararaghin to α2β1 integrins proceeds via recognition of basic structures in the toxin by the α2β1 I-domain [6], association of the HIV TAT protein with αvβ5 requires basic sequences in the viral protein [7] and binding of fibrinopeptides to αIIbβ3 integrin is dependent upon a pair of key lysine residues. Soluble forms of CD23 (sCD23) exhibit a range of cytokine-like activities [9,10], and the sCD23-αv integrin interaction also depends on basic residues. The extracellular domain of CD23 comprises eight β-strands and a pair of orthogonal α helices and resembles a C-type lectin domain [11]. Two of the cytokine-like activities of sCD23, regulation of cytokine release by monocytes and enhancement of growth of B lymphoid precursors, are mediated by binding to αvβ3 [12] and αvβ5 [13,14], respectively. αvβ5 Recognizes an arg-lys-cys (RKC) tripeptide motif on a solvent-exposed loop between the β0 and β1 strands of the sCD23 protein with micromolar affinity [13]; the RKC motif is spatially distinct from those parts of sCD23 that bind ligands such as CD21 or IgE [11].

Here we explored further the interaction of the αv integrins with sCD23 and sCD23-derived peptides. Binding of sCD23-derived peptides to αv integrins and their biological activities are tolerant of some substitution in the recognition motif. The interaction itself is cation-independent and salt-sensitive, features that are quite different to those that are characteristic of integrin binding to matrix ligands.

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http://dx.doi.org/10.1016/j.bbrc.2012.04.076

2. Materials and methods

2.1. Materials

RPMI-1640, OptiMEM and protein-free hybridoma media-II (PFHM-II) were from Life Technologies Ltd., Paisley, UK, foetal calf serum (FCS) was supplied by TCS Cellworks, Buckingham, UK, and L-glutamine and penicillin–streptomycin solution were from Sigma Chemicals, Poole, UK; Sigma also supplied *N*-hydroxysuccinimidobiotin and phycoerythrin-conjugated streptavidin. Purified human integrin αvβ3 and αvβ5 proteins were from Chemicon via Millipore (UK) Ltd., Watford, UK, while recombinant human soluble CD23 and the TNFα ELISA system were from R&D Systems Europe Ltd., Abingdon, UK. C1 sensor chips, specialist buffers and consumables for surface plasmon resonance studies were from GE Healthcare UK Ltd., Little Chalfont, UK, who also provided tritiated thymidine ([^{3}H]-TdR).

2.2. Synthetic peptides

Synthetic peptides were purchased from Mimotopes Ltd., Victoria, Australia, and were prepared as N-terminally-biotinylated peptides (with a common SGSG linker) and as unmodified peptides. The sequences of the peptides were:

#9, KWINFQRKC; **#9RQ**, KWINFQQKC; **#9RA**, KWINFQAKC; **#9KA**, KWINFQRAC; **#9RKAA**, KWINFQAAC; **#9CS**, KWINFQRKS.
#11, FQRKCYYFG; **#11RQ**, FQQKCYYFG; **#11RK**, FQKKCYYFG; **#11KA**, FQRACYYFG; **#11RKAA**, FQAACYYFG.
#12, RKCYYFGKG; **#12RA**, AKCYYFGKG; **#12KA**, RACYYFGKG; **#12RKAA**, ACYYFGKG.
Long peptide (LP), KWINFQRKCYYFGKG.

2.3. Cell culture, proliferation and cytokine release assays

SMS-SB cells, a human B cell precursor cell line responsive to sCD23 stimulation [13,14], and THP-1 and U937 monocytic cells were maintained in RPMI-1640 medium supplemented with 10% (v/v) FCS, 2 mM glutamine and 100 μg/mL penicillin and streptomycin at 37 °C in a 95% O_2/5% CO_2 humid incubator. For stimulation experiments, SMS-SB cells were washed extensively in PFHM-II, then 2.5×10^4 cells were cultured with sCD23-derived peptides (10 μg/mL) in a final volume of 100 μL PFHM-II. Cells were cultured at 37 °C for 48 h, with 0.1 μCi [^{3}H]-TdR being added for the final 6 h. Cultures were harvested onto glass fibre filter mats and incorporation of [^{3}H]-TdR detected by liquid scintillation spectrometry. For cytokine release assays, cells were harvested, washed thrice and suspended in OptiMEM supplemented with 2 mM glutamine and 1%(v/v) antibiotics at 5×10^6/mL. Cells were then stimulated with 5 μg/mL CD23-derived peptides and cultured for 24–72 h at 37 °C. Supernatants were harvested, centrifuged to pellet cells and insoluble debris and assessed for cytokine levels by ELISA.

2.4. Flow cytometry

Biotinylated sCD23 was generated by incubating recombinant sCD23 (0.1 mg/mL) with 1 mg/mL *N*-hydroxysuccinimidobiotin in carbonate buffer pH 9.5 on a rotator overnight at 4 °C. Unconjugated biotin was removed by dialysis against ice-cold phosphate-buffered saline (PBS), pH 7.2. Cells were harvested by centrifugation, washed twice with ice-cold PBS and 100 μL of cell suspension (5×10^6 cells/mL) incubated with biotinylated sCD23 or biotinylated CD23-derived peptides for 30–60 min at 4 °C. The cells were washed twice, incubated with streptavidin–phycoerythrin for 30–60 min at 4 °C, washed twice more and analysed using a Becton Dickinson *FACScan* instrument and *CellQuest* software (BD Bioscience, San Jose, CA, USA).

2.5. Surface plasmon resonance

Interactions between CD23-derived peptides and αvβ3 and αvβ5 integrins were performed at 25 °C using a BIAcore 2000 instrument. Integrins were immobilised at approximately 4000 response units on a C1 sensor chip using amine coupling chemistry. An underivatised reference cell was employed as a control surface. CD23-derived peptides in HBS-EP buffer (0.01 M HEPES–KOH pH 7.4, 0.15 M NaCl, 3 mM EDTA, 0.005% (v/v) surfactant P20) were injected over the test and control chip surfaces at a flow rate of 40 μL/min and allowed a 3 min association phase followed by a 6 min dissociation phase. The sensor surfaces were regenerated to baseline by injection of 0.2 M glycine–HCl, pH 2.5, where necessary. In all experiments, peptides bound exclusively to the test cell, there was no non-specific binding to the control reference cell and regeneration of a stable baseline was readily achieved. Data collected were standardised using control and blank injections prior to kinetic analysis, according to standard double referencing data subtraction methods [15]. All kinetic analyses were performed using BIAevaluation 3.1 software.

3. Results

The definition of the tripeptide motif in the CD23 protein recognized by αvβ5 integrin was achieved by probing a library of 83 overlapping sCD23-derived peptides in ELISA [13]. Fig. 1A demonstrates the pattern of binding of the same library of biotinylated peptides to αvβ5$^+$ (αvβ3$^-$) SMS-SB cells. The greatest level of binding to SMS-SB cells is achieved by peptides #9–12 in the library, and the sole feature that these peptides share is an RKC motif commencing at arg^{172} in the CD23 protein; these data are entirely consistent with previous results using solid-phase ELISA assays [13]. Binding of peptides to THP-1 cells (αvβ3$^+$ and αvβ5$^+$) is also clearly evident (Fig. 1B); a control peptide, #8, shows no binding to THP-1 cells. The binding of the RKC-containing peptide #11 to THP-1 cells is attenuated by sCD23, and peptide #11 significantly inhibits binding of sCD23 to cells (Fig. 1C). By contrast, neither Vn nor Fn prevents binding of peptide #11 to THP-1 cells (Fig. 1C) demonstrating that the RGD-binding site of the αvβ3 or αvβ5 integrins is not required for capture of RKC-containing peptides.

Previous data indicated that the binding of sCD23 to αvβ5 has an affinity of approximately 6 μM [13], a value similar to that for binding of sCD23 to its other protein ligands, CD21 and IgE [11]. The binding of the four RKC-containing nonapeptides from the library and the RKC-containing pentadecameric 'long peptide' (LP) to αvβ3 and αvβ5 was assessed in a surface plasmon resonance experiment (Fig. 2). LP shows a strong level of binding to both αvβ3 and αvβ5 while a control peptide (#58) shows no binding to either integrin. Peptides #9–12 bind to the integrins to differing extents, and all show biphasic association and dissociation kinetics for both integrins. Peptides #9 and #10 show very low affinity binding to αvβ3 at different concentrations of input peptide, while a greater extent of binding and clear dose-dependence is noted for binding of peptides #11 and #12 (Fig. 2A). By contrast, binding of nonapeptides #9–12 to αvβ5 is readily detectable, with clear dose–response curves being evident for all peptides (Fig. 2B).

A striking feature of the interaction between integrins and RGD-containing ligands is the cation-dependence of binding [3,16,17]. Fig. 3A demonstrates that performing binding reactions in the absence of either Mg^{2+} or Mn^{2+} does not compromise binding of

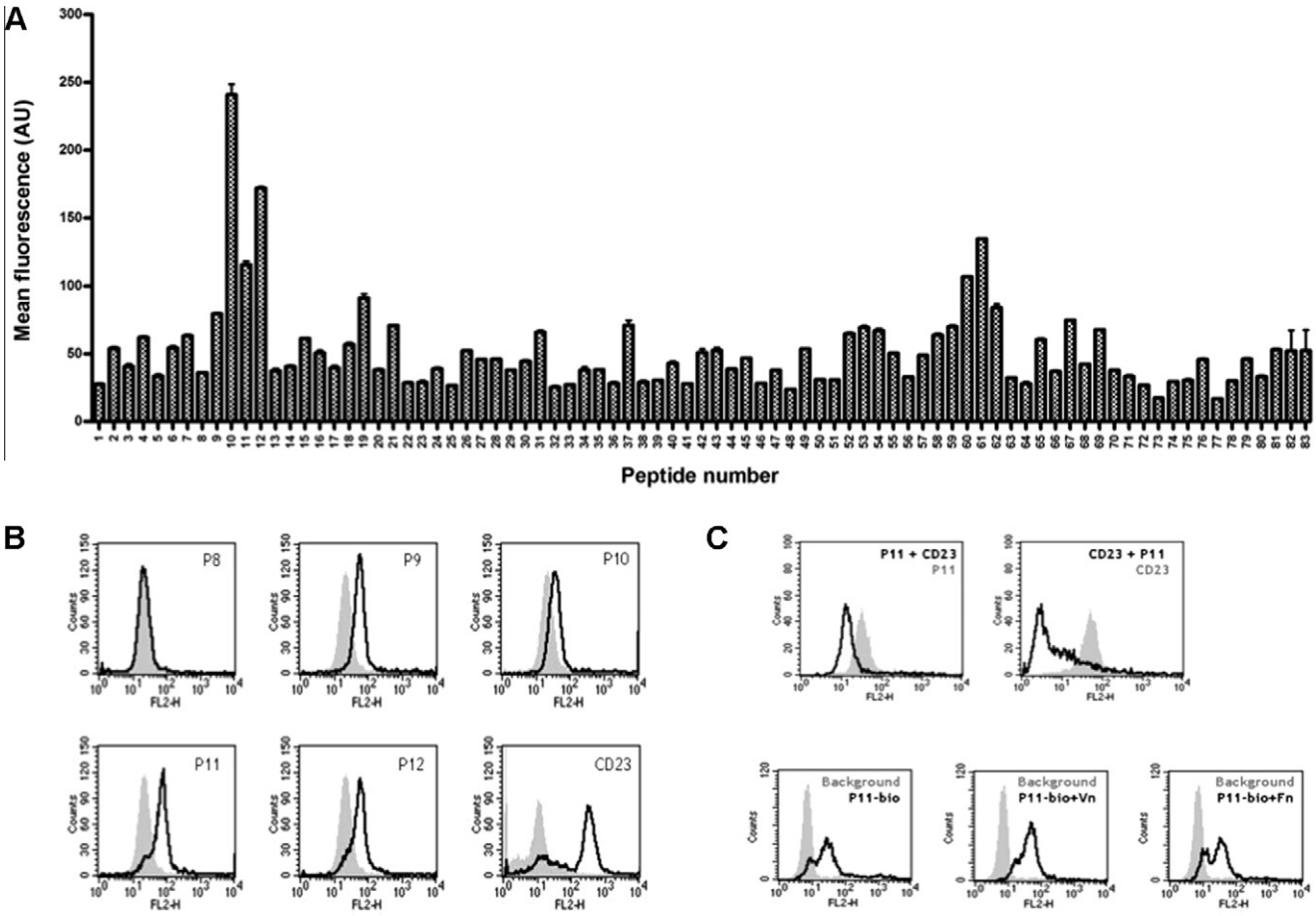

Fig. 1. Definition and properties of CD23-derived αv integrin-binding peptides. (Panel A) Biotinylated CD23-derived nonapeptides were incubated on ice with SMS-SB cells and binding visualised by flow cytometry using streptavidin-PE. The mean fluorescence intensity for binding of each peptide was normalised for background fluorescence and plotted against peptide number. The data are representative of at least three separate experiments. (Panel B) THP-1 cells were incubated on ice with the indicated biotinylated peptides or CD23. Binding of biotinylated peptides was detected using streptavidin-PE, and CD23 binding was visualised by PE-anti-CD23 antibody. The black line represents staining and the grey area the autofluorescence control; note that the peptide eight control overlaps with the autofluorescence negative control trace. (Panel C) THP-1 cells were incubated with peptide #11 (P11) or CD23 prior to binding of biotinylated CD23 or P11, respectively; the binding of CD23 or P11 alone is shown as grey shading and the binding in the presence of the competitor is shown as black line. THP-1 cells were incubated with Vn or Fn prior to binding of biotinylated P11; the background binding is shown as grey shading and the binding of P11 with or without RGD-containing ligands is shown as a black line.

peptide #11 or LP to either αvβ3 or αvβ5. These data suggest that, in contrast to binding of RGD-containing ligands to integrins, binding of RKC containing ligands is cation-independent. Addition of a further chloride ion, as $MgCl_2$, severely disrupts binding of both peptide #11 and LP to either αvβ3 or αvβ5 (Fig. 3A). These data indicate that the interaction of RKC-containing basic ligands with the αv integrins is sensitive to high salt levels, and are consistent with findings of others that the interaction of the HIV TAT protein with αvβ5 is salt-sensitive [7].

Integrins display strict requirements for recognition of target motifs in matrix proteins, with very minor substitutions abrogating integrin binding [3–5]. Fig. 3B-i illustrates that substitution of arg^{172} with either alanine or glutamine reduces the ability of the substituted peptide to bind to THP-1 cells; the same is true for substitution of lys^{173} with alanine or a peptide bearing a double substitution where both arg^{172} and lys^{173} are replaced by alanine (Fig. 3B-i). A peptide #9 variant bearing a cysteine to serine substitution also shows impaired binding to cells. The peptide #9 double substitution variant (9RKAA) does not inhibit binding of sCD23 to cells (Fig. 3B-ii). SPR analysis (Fig. 3C) confirms that substitution of the basic residues attenuates binding of the peptides to purified αvβ5 integrin. However, it is clear from the SPR studies that substitution causes a reduction in binding rather than a total loss of binding. Thus, a substitution of either arg^{172} or lys^{173} in peptides #9 (Fig. 3C-i) and #11 (Fig. 3C-ii) reduces the total amount of binding by one-half to two-thirds, but some binding clearly remains. Doubly-substituted peptides (i.e., #9RKAA and #11RKAA) are devoid of binding activity (Fig. 3C).

Soluble CD23 [12] and monoclonal antibodies directed to CD23-binding integrins [18] promote cytokine release from monocytic cells, and both peptides #9 and #12 drive strong release of TNFα from monocytes (Fig. 4A). This is strikingly reduced when either arg^{172} or lys^{173} are replaced by alanine, and doubly-substituted peptide variants are devoid of activity in the monocyte model (Fig. 4A). In B cell precursors, wild-type peptides #9 and #12 promote strong growth of SMS-SB cells compared to untreated cells and cells treated with the control peptide #58 (Fig. 4B). Substitution of either arg^{172} or lys^{173} with alanine in peptide #9 results in a diminution of growth-promoting activity relative to wild type peptides but, consistent with the SPR data, this activity is not completely lost. However, peptide variants in which both arg^{172} and lys^{173} are replaced by alanine have minimal growth-promoting capacity. Substitution of one basic reside, resulting a change of overall peptide charge at neutral pH from 3+ to 2+ diminishes but does not ablate either binding to purified integrin (Fig. 3C) or biological activity (Fig. 4), but substitution of both basic residues,

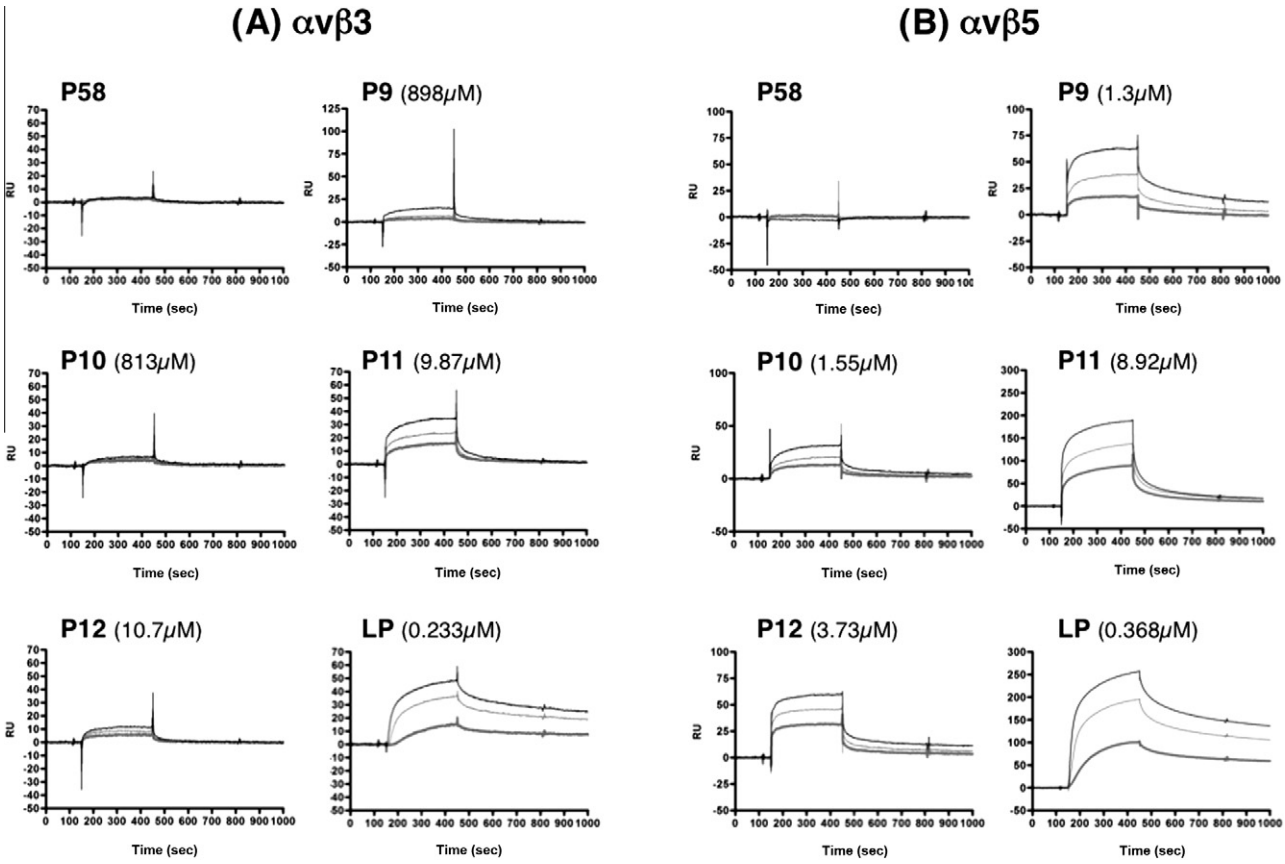

Fig. 2. Binding of CD23-derived peptides to αvβ3 and αvβ5 integrins. Purified αvβ3 (Panel A) or αvβ5 integrin (Panel B) was immobilized on the C1 sensor chip surface. The indicated CD23-derived peptides at different concentrations were injected over the test and control surfaces. For peptides #9–12 and #58, the light grey line is 5 μM, the dark grey line is 10 μM and the black line is 20 μM. For LP, the light grey line is 0.25 μM, the dark grey line is 0.5 μM and the black line is 1 μM. Data collected were standardised using control and blank injections prior to kinetic analysis, according to standard double referencing data subtraction methods, using BIAevaluation 3.1 software. K_D values for each peptide are shown in parentheses.

with a reduction in net peptide charge to 1+, severely compromises both integrin binding and biological activity towards B cell precursors and monocytic cells.

4. Discussion

The data of this report indicate that αvβ3 and αvβ5 integrins bind peptides with basic target elements that are distinct from the classical RGD motif with biphasic kinetics in a cation-independent manner. The capacity of peptides to bind purified integrins and to drive biological responses in human B cell precursors and monocytic cells is dependent on both the overall charge of the peptide and, to a lesser extent, the presence of arg^{172}.

SPR studies of integrins have focused on interactions involving recognition of the RGD motif in target proteins. The importance of specific cations is well understood, with the requirement for manganous ion in binding of αvβ3 to fibrinogen being an exemplar of this effect [16]. The interaction between αvβ3 and procathepsin X is biphasic and is sensitive to both mutation of a key RGD binding site in procathepsin and the presence of RGD-containing competitor peptides; binding also requires Mn^{2+} [19]. The K_D for the binding of procathepsin X to αvβ3 is 144nM, compared to a K_D of 64 nM for the binding of Vn in the same experimental system [19]. An analysis of αvβ3 integrin in clasped or unclasped states, mimicking low and high affinity configurations, revealed that αvβ3 captures Vn only in the extended or unclasped form [17]; the affinity was 25 nM, comparable to that observed by others [16,19]. Endostatin, a fragment of collagen XVIII, associates with the αvβ3 integrin with a K_D of 1.7 μM, despite lacking an RGD sequence [20]. The interaction shows biphasic kinetics and is disrupted by RGD-containing competitor peptides or mutation of two arginine residues in endostatin. Molecular modelling supports the competitor data in suggesting that endostatin binds to the RGD-binding site of the αvβ3 integrin [20]. An analysis of the association of αvβ3 with cardiotoxins that also lack any RGD binding motif demonstrates biphasic kinetics; in this system a K_D of approximately 0.3 μM was observed for cardiotoxin A5, whereas cardiotoxin A6 had an affinity of 15 μM for αvβ3 [21]. The A5 cardiotoxin has a pair of lysines at positions 28 and 29 that are replaced by valine and alanine, respectively, in the lower affinity A6 toxin [21]. These data underscore the important contribution that basic residues make to non-RGD-dependent interactions between αv integrins and target proteins.

Human sCD23 has a range of cytokine activities [10], mediated via αv [12] and β2 [22] integrins in monocytic cells, αvβ5 in B cell precursors [13] and CD21 in mature B cells [23]. Murine CD23 lacks a cluster of acidic residues required for interaction with CD21 [11], partly explaining the lack of cytokine-like activities associated with murine CD23. In the case of sCD23-dependent cytokine activity delivered via αv integrins, the human CD23 protein has the sequence FQRKCYY at the relevant exposed loop between the β0 and β1 strands of the lectin head domain, whereas murine CD23 has the sequence FQQKCYY. Peptides #9 or #11 bearing a substitution of arg^{172} to gln^{172} show dramatically reduced binding to purified αvβ5 integrin (Fig. 3C) and, indeed, peptide #9RQ fails to stimulate

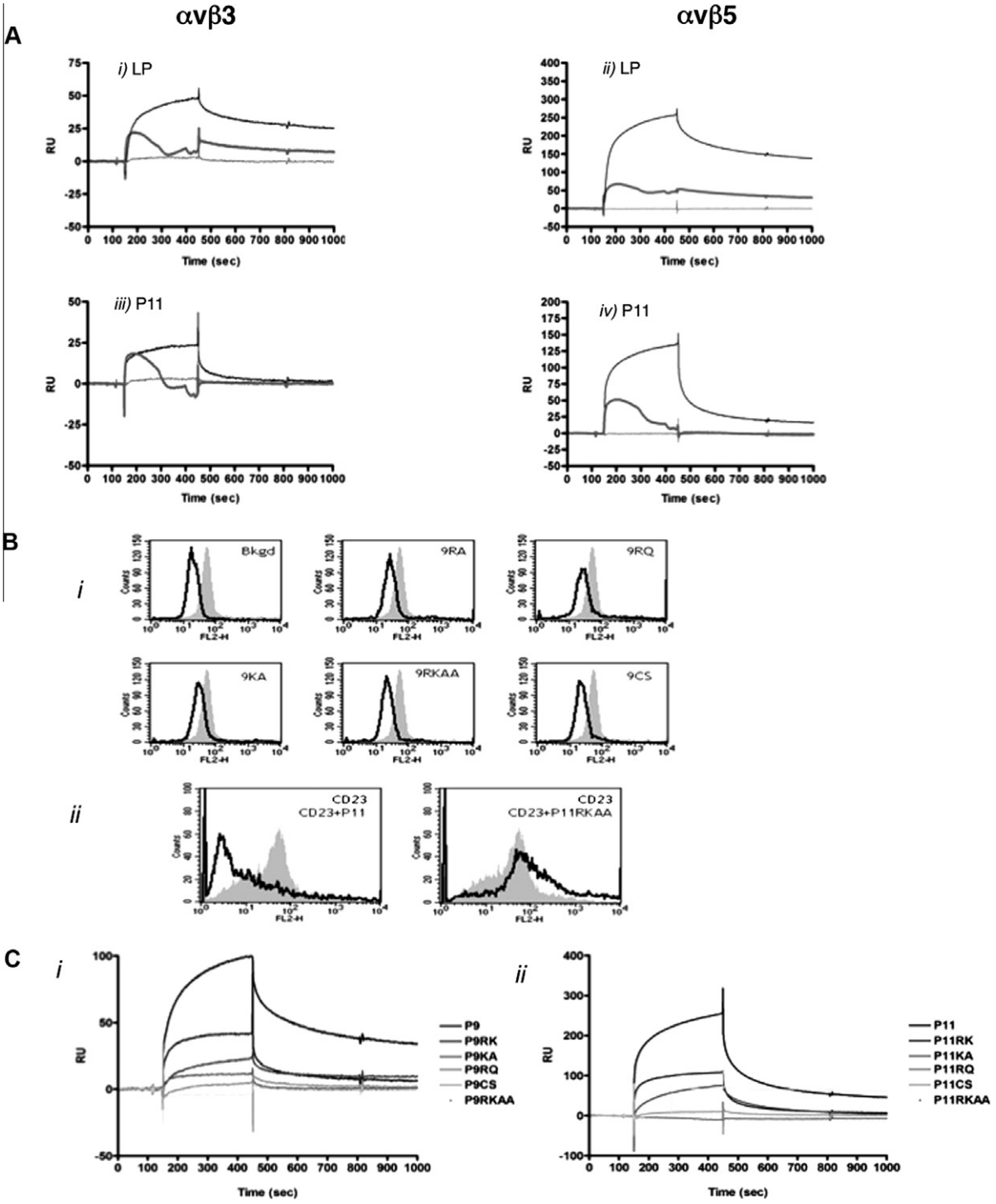

Fig. 3. Effect of substitutions on CD23-derived peptide activity. (Panel A) Shows the binding of CD23-derived LP to the purified αvβ3 (i) and αvβ5 (ii) integrins, and binding of peptide #11 to the purified αvβ3 (iii) and αvβ5 (iv) integrins. In all graphs, the black line shows the binding sensorgram for the indicated peptide in the absence of divalent cations. The thin grey line shows the binding of CD23-derived negative control peptide #58, and the thick grey line shows the binding of the specific peptide in the presence of divalent cations and chloride ions (0.01 M HEPES–KOH pH 7.4, 0.15 M NaCl, 0.1 M $MgCl_2$, 3 mM EDTA, 0.005% (v/v) surfactant P20). Data collected were standardized and analysed as described in the legend to Fig. 2. (Panel B-i) THP-1 cells were incubated with biotinylated peptide #9 or the indicated individual or double substitution mutants and binding detected by streptavidin-PE. The background binding and binding of biotinylated P9 mutants is shown as a black line compared to binding of wild-type peptide #9 in the grey area. (Panel B-ii) Cells were incubated with CD23 in the presence of peptide #11 or the equivalent RKAA double mutant, prior to detection of CD23 binding by PE-anti-CD23 antibody. The binding of CD23 alone is shown in grey shading and binding of CD23 in the presence of competitor peptide is shown as a black line. (Panel C) Purified αvβ5 integrin was immobilized on the C1 sensor chip surface and peptide #9 (i) or peptide #11 (ii) and indicated substitution mutants of these peptides injected at a concentration of 10 μM. An underivatised reference cell was employed as a control surface. The colour coding used for identification of each injected peptide is shown on the panel itself. Data collected were standardized and analysed as described in the legend to Fig. 2.

growth of human or murine B cell precursors (*data not shown*). While 9KA and 9RA substituted peptides show a reduced charge relative to wild-type peptide #9, and have a reduced ability to promote growth of B cell precursors and cytokine release, the

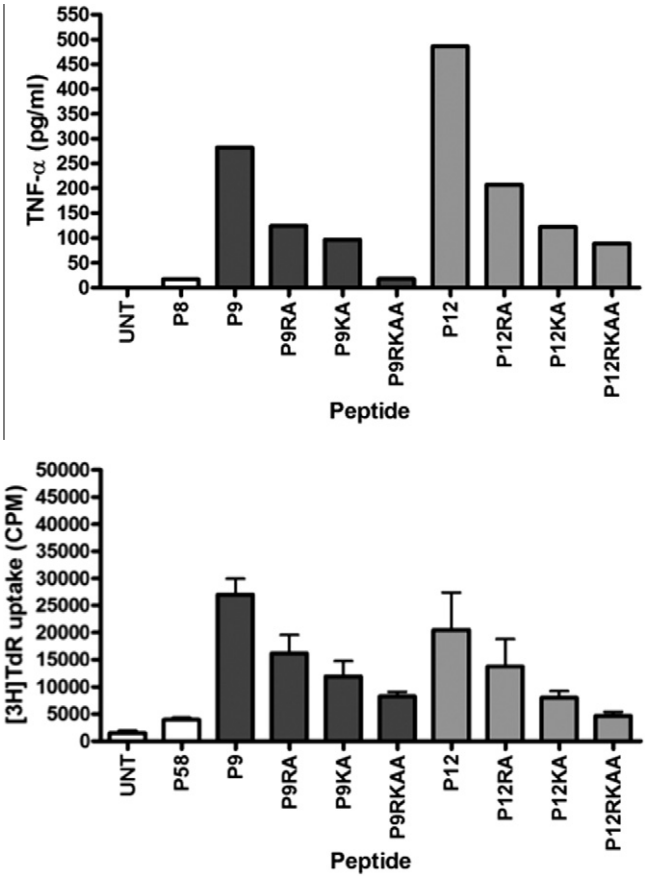

Fig. 4. Effect of substitutions on CD23-derived peptide activity. (Panel A) U937 cells were cultured with 5 μg/mL of wild-type and the indicated substituted variants of peptide #9 (dark grey bars) or peptide #12 (light grey bars) at 37 °C for 72 h and TNFα release measured by ELISA. The experiment illustrated is one representative of at least three. (Panel B) SMS-SB cells (2500 cells/100 μL PFHM-II) were cultured at 37 °C for 72 h in the presence of 10 μg/mL of the indicated peptides. Cells were pulsed with 0.1 μCi/well ([^{3}H]-TdR) for the final 6 h of the culture and incorporation determined by liquid scintillation spectrometry. The graph shows data for untreated and peptide #58-stimulated cells as controls (white bars), for peptide #9 and mutants (black bars) and from peptide #12 and mutants (grey bars). The data are from one experiment representative of three.

9RQ peptide is further compromised in terms of binding activity. This suggests both overall charge of the interaction surface and an element of sequence are important in binding to αv integrins. The data are also consistent with arg^{172} being important for those CD23 cytokine activities that are delivered via interaction with αv integrins.

Binding of αv integrins to CD23-derived peptides bearing the RKC recognition motif is both chloride ion-sensitive and cation-independent, in contrast to the well-established cation dependence of integrin binding to RGD-containing ligands [4,5]. Our own data show that RGD-containing peptides neither impede binding of RKC-containing peptides to cells nor inhibit their biological activities [13] and, moreover, the RKC motif cannot be accommodated in the RGD binding site due to the size of the lysine side chain. Available data suggest that a second distinct binding site on αv integrins exists that binds ligands including HIV Tat [7], cardiotoxins [21], fibrinopeptides [8] and sCD23 in a manner that is both cation-independent and tolerant of some sequence changes. Our far-Western data suggest this binding site resides mainly on the β3 or β5 subunits [13], but an unequivocal determination of location and structure of this second binding site remains to be achieved.

Acknowledgments

A.L.E. was a postgraduate scholar in the Wellcome Trust funded four-year PhD programme *Molecular Functions in Disease*. B.W.O. is supported by Cancer Research UK. The work was additionally supported by a grant from the *Arthritis Research Campaign*.

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