

P041 The “linker” region (aa 38-47) of the disintegrin elegantin is a novel inhibitory domain of integrin $\alpha_5\beta_1$ -dependent cell adhesion on fibronectin
Rushika Sumathipala¹, Cunshuan Xu^{1*}, Julian Seago^{1#}, A. Paul Mould², Martin J. Humphries², Sue Elizabeth Craig², Yatin Patel¹, Errol S. Wijelath³, Michael Sobel³ And Salman Rahman¹

1The Laboratory of Thrombosis and Vascular Remodelling, Division of Cardiovascular Medicine, King's College London School of Medicine, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, UK.

2Wellcome Trust Centre for Cell-Matrix Research, Department of Biological Sciences, University of Manchester, M13 9PT, UK.

3Division of Vascular Surgery, University of Washington School of Medicine and VA Puget Sound Health Care System, Seattle WA. USA.

Disintegrins are a family of potent inhibitors of cell-cell and cell-matrix adhesion. In this study we have identified a region of the disintegrin elegantin, termed the “linker domain” (aa 38-47), with inhibitory activity towards $\alpha_5\beta_1$ -mediated cell adhesion on fibronectin (Fn). Using a chimeric structure-function approach in which sequences of the functionally distinct disintegrin kistrin were introduced into the elegantin template at targeted sites, a loss of inhibitory function towards $\alpha_5\beta_1$ -mediated adhesion on Fn was observed when the elegantin linker domain was substituted. Subsequent analysis comparing the inhibitory efficacies of the panel of elegantin-kistrin chimeras towards CHO α_5 cell adhesion on recombinant Fn III₆₋₁₀ fragments showed that the loss of inhibitory activity associated with the disruption of the elegantin linker domain was dependent upon the presence of a functional Fn III₉ synergy site within the Fn III₆₋₁₀ substrate. This suggested that the elegantin linker domain inhibits primarily the activity of the Fn synergy domain in promoting $\alpha_5\beta_1$ integrin-mediated cell adhesion. Construction of a cyclic peptide corresponding to the entire region of the elegantin linker domain showed that this domain has intrinsic $\alpha_5\beta_1$ inhibitory activity comparable with the activity of the RGDS peptide. These data demonstrate a novel biological function for a disintegrin domain that antagonizes integrin-mediated cell adhesion.