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A novel bispecific recombinant biological agent modulating inflammation's early cellular events

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Multivalent and multifunctional bioactive molecules offer the promise of more effective therapeutics. In this work, we present selegrin, a new bispecific molecule that prevents the interaction of leukocytes circulating in the blood vessels with the endothelial barrier cells and could modulate the over flux of activated PMN to inflamed tissues. Prior to the development of selegrin, we have demonstrated using a rat model of skeletal muscle injury, that a recombinant form of the beta 2 integrin alpha chain CD11b, A or I domain prevents muscle inflammatory injury by transiently preventing leukocyte transmigration through the vascular endothelial cell barrier. Selegrin molecular design consisted in combining the CD11b A domain with the L selectin CD62, lectin-like domain in a single 52KDa fusion protein. Recombinant selegrin was produced in CHO cells under two structural forms, a linear and an IgG-like structure. Both form exhibited specific biological activity in real time of flow in physiological and inflammatory states using the *ex vivo* real-time imaging of leukocyte adhesion to the vascular endothelium of Sprague Dawley rats carotid arteries and HUVEC cell layers. Indeed, under inflammatory conditions, selegrin showed a significant inhibition of leukocytes tethering, rolling and adhesion to vascular endothelial cells. In addition, the transcription of IL6, ICAM1, VCAM1 and MCP1 gene and the expression of the corresponding proteins by respectively RT-PCR and immune fluorescence using specific Mabs, were significantly down regulated in endothelial cells treated with TNFα and in presence of selegrin. This delineates the underlying causes of the biological activity displayed by selegrin. This work demonstrated that selegrin exerts inhibitory effects on human leukocytes interaction with vascular endothelium cells under flow in physiological and inflammatory conditions. The data provide strong mechanistic information behind the anti-inflammatory properties of selegrin and are translatable in preclinical trial.

Biography

M Dahmani Fathallah is the chair Professor of Medical Biotechnology and International Expert in Biotechnology and Bioproducts Development. He is a certified Innovation Strategist and International Consultant in Medical Biotechnology & Technology Transfer strategies. He received his degrees and training in Molecular Biology, Molecular Genetics and Immunology from the University of Paul Sabatier, Toulouse, France, Oxford University, UK and Harvard University, Boston, MA, USA. He is currently the Dean of the College of Graduate Studies and the Chairman of the PhD Biotechnology program at the Arabian Gulf University Manama-Bahrain. He founded ArabOmiX a Medical Biotech & Technology Transfer consulting office for the MENA Pharma industry. He is a former senior investigator at the Institute Pasteur of Tunis (Head of the Medical Biotechnology Group) and the CSO of JeddahBiocity Inc and CEO/Founder of RethabBiotech Co. He holds five International patents for the development of five biopharmaceutical (Biosimilar & Innovative) products, two of which were licensed to two of the world top 10 biopharmaceutical companies. He authored 70 international scientific papers, three books and several general papers on Bio-economy, Transfer of BioTechnology and Education policies. He pioneered (1986) the development of DNA typing for Forensic purpose and set up 5 service laboratories specialized in DNA-based human profiling. He trained and supervised 25 PhDs, 56 Masters and 15 Medical Biotech engineers. He delivered over 100 lectures and conferences throughout the world. He is the founder and president of the Harvard Alumni of Tunisia and the co-founder of the Arab Policy Institute. He is the recipient of several prestigious international prizes and awards.

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