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ACE2 as a potential therapeutic agent for kidney disease

Angiotensin-converting enzyme 2 (ACE2) is a carboxypeptidase that potently degrades angiotensin II (Ang II) to form Ang-(1-7). Previous studies showed that injection of the enzymatic ectodomain of recombinant ACE2 (rACE2) markedly increasases circulatory levels of ACE2 activity, and effectively lowered blood pressure in Ang II-induced hypertension. However, due to the short plasma half-life of rACE2, its therapeutic potential for chronic use is limited. To circumvent this problem, we generated a chimeric fusion of rACE2 and the immunoglobulin fragment crystallizable (Fc) segment to increase its plasma stability. This rACE2-Fc fusion protein retained full peptidase activity and exhibited greatly extended plasma half-life in mice, from less than two hours of the original rACE2, to over a week. A single injection of 2 mg/kg rACE2-Fc elevated the overall Ang II-conversion activities in blood by up to 100 fold and lasted for over a week. Consequently, only rACE2-Fc, but not rACE2 injection, achieved sustained blood pressure control in response to a bolus infusion of Ang II. In the RenTgMK transgenic mice driven by the expression of synthetic renin cDNA, weekly injections of rACE2-Fc effectively lowered plasma Ang II and blood pressure. In addition the rACE2-Fc ameliorated albuminuria, and reduced kidney and lung fibrosis. These results show that this chimeric fusion strategy for rACE2-Fc can be suitable for future development of new RAS-based inhibition therapies.

Biography

Dr. Daniel Batlle received his MD from the University of Barcelona, Spain. He completed medical residency and later fellowship training at the University of Illinois in Chicago, Illinois. After this he joined the Division of Nephrology at the University of Illinois as a Faculty member and later moved to Northwestern University Medical School also in Chicago. Dr. Batlle was Chief of the Division of Nephrology and Hypertension from 1992 to 2009 and is currently the endowed Earle, DelGreco Levin Professor of Nephrology and Hypertension at this Institution. His main focus in research is the renin angiotensin system as it relates to hypertension and diabetic kidney disease. His research includes the design of novel forms of recombinant ACE2 that are currently being tested experimentally

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