Identification of B38-CAP as an ACE2-like enzyme to suppress hypertension and cardiac dysfunction in mice.

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Angiotensin-converting enzyme 2 (ACE2) is a negative regulator of the renin-angiotensin system, critically involved in blood pressure regulation, heart function, lung injury, or fibrotic kidney disease. Recombinant human ACE2 protein (rhACE2), currently clinically evaluated to treat acute lung failure, is a glycosylated protein, requiring time- and cost-consuming protein production in mammalian cells. Here we show that the B38-CAP, a carboxypeptidase derived from *Paenibacillus sp.* B38, is a novel ACE2-like enzyme to decrease angiotensin II levels in mice. Comparative analysis of protein 3D structures revealed that B38-CAP homologue shares structural similarity to mammalian ACE2 without any apparent sequence identity, containing the consensus HEXXH amino acid sequence of the M32 peptidase family. In vitro, recombinant B38-CAP protein catalyzed the conversion of angiotensin II to angiotensin 1-7, as well as other known ACE2 target peptides, with the same potency and kinetics as human ACE2. Treatment with B38-CAP reduced plasma angiotensin II levels and suppressed angiotensin II-induced hypertension, cardiac hypertrophy and fibrosis in mice. Moreover, continuous infusion of B38-CAP inhibited pressure overload-induced pathological hypertrophy, myocardial fibrosis, and cardiac dysfunction in mice, without any overt toxicity of liver and kidney. Our data identify the bacterial B38-CAP as an ACE2-like carboxypeptidase, which exhibits ACE2-like functions in vitro and in vivo. These results indicate that evolution has shaped a bacterial carboxypeptidase to a human ACE2-like enzyme. Bacterial engineering could be utilized to design improved protein drugs for hypertension and heart failure.