Severe COVID-19 induces autoantibodies against angiotensin II that correlate with blood pressure dysregulation and disease severity

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Abstract

Patients infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can experience life-threatening respiratory distress, blood pressure dysregulation, and thrombosis. This is thought to be associated with an impaired activity of angiotensin-converting enzyme 2 (ACE2), which is the main entry receptor of SARS-CoV-2 and which also tightly regulates blood pressure by converting the vasoconstrictive peptide angiotensin II (AngII) to a vasopressor peptide. Here, we show that a significant proportion of hospitalized patients with COVID-19 developed autoantibodies against AngII, whose presence correlates with lower blood oxygenation, blood pressure dysregulation, and overall higher disease severity. Anti-AngII antibodies can develop upon specific immune reaction to the SARS-CoV-2 proteins Spike or receptor-binding domain (RBD), to which they can cross-bind, suggesting some epitope mimicry between AngII and Spike/RBD. These results provide important insights on how an immune reaction against SARS-CoV-2 can impair blood pressure regulation.

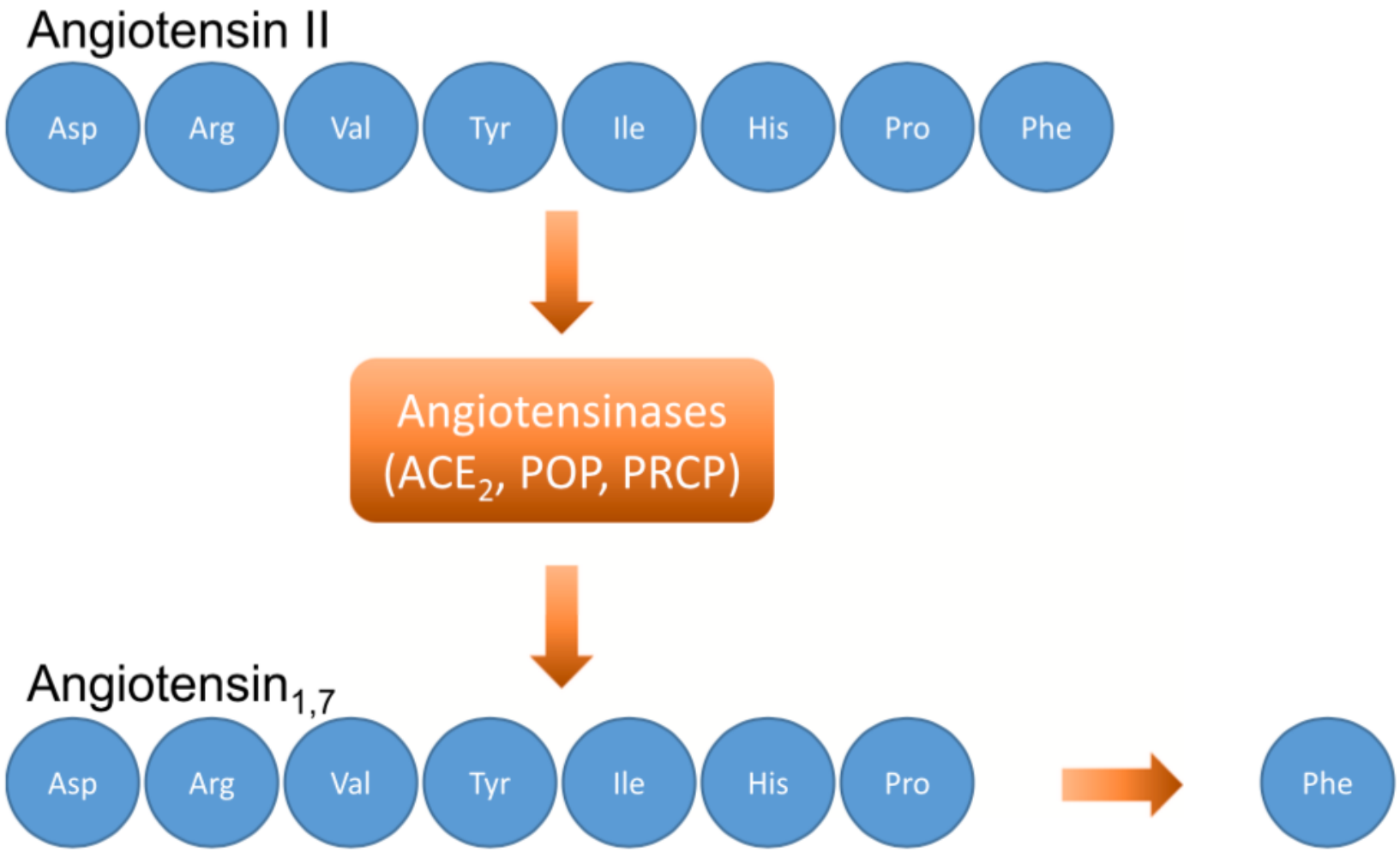

Fig. 4. Angiotensin$_{1,7}$ formation. Angiotensin$_{1,7}$ is formed by the action of the angiotensin-converting enzyme 2 (and other angiotensinases, including POP and PRCP) by the cleavage of an amino acid from Angiotensin II. **Legend:** ACE2=angiotensin-converting enzyme 2 receptor; POP=prolyl oligopeptidase; PRCP=prolyl carboxypeptidases.

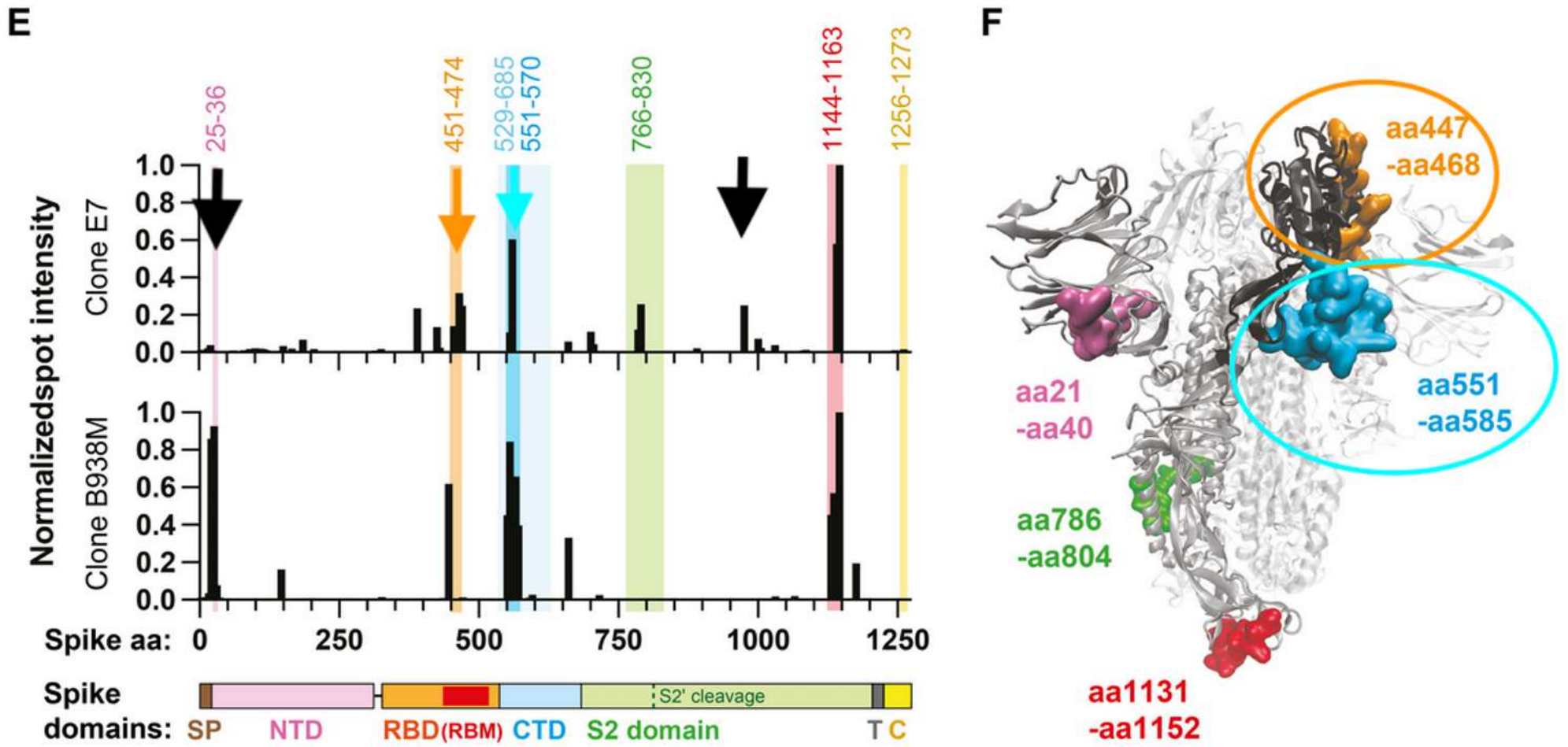

Fig. 6. Cross-binding of anti-AngII antibodies to the SARS-CoV-2 Spike and RBD antigens.

(**E**) Binding of monoclonal anti-AngII (clone E7 or B938M) to Spike linear epitopes using a peptide array. Highlighted colored regions represent the most immunogenic and recurrent B cell epitopes of Spike found in patients with COVID [Shrock *et al.* (*14*) and Li *et al.* (*15*)], and the associated numbers indicate the amino acid positions that delineate these regions. The *x* axis represents the full length of Spike (SP, signal peptide; NTD, N-terminal domain; RBD, receptor-binding domain; RBM, receptor-binding motif; CTD, C-terminal domain; NTD, RBD, and CTD together constitute the S1 domain of Spike; T, transmembrane domain; C, cytoplasmic tail). (**F**) Visualization of the main domains targeted by the monoclonal anti-AngII antibodies on the three-dimensional structure of Spike [Protein Data Bank: 6VXX; (*24*)]. Domains are highlighted in colors on one monomer of the trimeric Spike structure (RBD is in black; aa#, amino acid position of Spike).