The Two-Pronged Phosphorylation of ACE2 Underlies Cardiovascular Health and Disease

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Angiotensin-converting enzyme 2 (ACE2) and its catalytic product Angiotensin (1-7) [Ang (1-7)] constitute the beneficial arm of the renin-angiotensin-aldosterone system. Post-translational modifications (PTMs) of ACE2 are indispensable in determining the ACE2 level, activity, and functions. With AMPK phosphorylation of ACE2 Ser-680 decreasing the proteosome-mediated degradation, we identified that ACE2 Ser-623 phosphorylation enhanced ACE2 degradation, which is opposite to that of Ser-680. Using in silico analysis and in vitro kinase assays, we demonstrated that Aurora kinase A (AURKA) is the kinase phosphorylating ACE2 Ser-623. By analyzing the ACE2 crystal structure and further analysis by AlphaFold3 software, it appears that phosphorylation of Ser-623 or Ser-680 hinders phosphorylation of the other residue, due to their spatial proximity. The two-pronged Ser-623 and Ser-680 phosphorylation led to opposite transcriptional regulation in vascular endothelial cells (ECs). Whereas ACE2 Ser-623D (phospho-mimetic mutation) and Ser-680A (dephospho-mimetic mutation) rendered the pro-inflammatory and proliferative phenotype of ECs, ACE2 Ser-623A and Ser-680D maintained EC homeostasis. Ser-623A and Ser-680D knock in (KI) mice exhibited reduced carotid restenosis, in comparison with Ser-623D and Ser-680A KI mice. In the accelerated atherosclerosis model in mice, Ser-623A and Ser-680D KI mice showed reduced atherosclerosis. Thus, this two-pronged phosphorylation of ACE2 Ser-623 by AURKA versus Ser-680 by AMPK would be new and important mechanism governing EC in health and disease