BINDING OF THE ERA NUCLEAR RECEPTOR TO DNA IS COUPLED TO PROTON UPTAKE

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Nuclear receptors act as ligand-modulated transcription factors and orchestrate a plethora of cellular functions central to health and disease. Although studied for more than half a century, many mysteries surrounding the mechanism of action of nuclear receptors remain unresolved. Herein, using isothermal titration calorimetry (ITC) in conjunction with macromolecular modeling (MM), we provide evidence that the binding of ERa nuclear receptor to its DNA response element is coupled to proton uptake by two ionizable residues, H196 and E203, located at the protein-DNA interface. Alanine substitution of these ionizable residues decouples protonation and hampers the binding of ERa to DNA by nearly an order of magnitude. Remarkably, H196 and E203 are predominantly conserved across ~50 members of the nuclear receptor family, implying that proton-coupled equilibrium may serve as a key regulatory switch for modulating protein-DNA interactions central to nuclear receptor function and regulation. Taken together, our findings unearth an unexpected but a critical step in the molecular action of nuclear receptors and suggest that they may act as sensors of intracellular pH.