

SPATIO-TEMPORAL IMAGE CORRELATION SPECTROSCOPY AND SINGLE MOLECULE LOCALIZATION REVEAL ELUSIVE MEMBRANE ORGANIZATION OF ACE2, THE RECEPTOR OF SARS-COV-2

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Angiotensin-converting enzyme 2 (ACE2) is a ubiquitous membrane protein that exerts antihypertensive effects by catalyzing the hydrolysis of the vasoconstrictor peptide Angiotensin II into the vasodilator angiotensin (1-7). Actually, ACE2 counterbalances the activity of the related enzyme ACE, which converts the peptide hormone angiotensin I in angiotensin II. Together, ACE2 and ACE are central components of the Renin-Angiotensin system (RAS), which control the blood pressure in the body. ACE2 has several other less-known biochemical functions, and its expression is tightly regulated at transcriptional and post-translational level [1]. Recently, it has been discovered that ACE2 serves as the initial cellular target of at least six coronaviruses (CoVs) [2], including the recent SARS-CoV2, responsible of COVID-19 [3]. SARS-CoV2 engages with ACE2 through its spike (S) protein, which consists of two subunits: S1, which mediates binding to the host receptor through its Receptor Binding Domain (RBD); S2, which induces membrane fusion of the viral envelope delivery of the viral genome. The RBD-ACE2 interaction eventually determines viral host range, and in tandem with the host proteases is responsible for virus tropism in the body.

On account of the remarkable role of ACE2 as multifunctional membrane protein and cross-cutting species “hotspot” harnessed for CoV entry, we set out to investigate its “interactome” on cell membrane by means of single molecule localization methods (SMLM) and spatiotemporal image correlation spectroscopy (STICS). Interestingly, we found out that ACE2 clusterizes predominantly out of lipid raft regions, at odds with previously reported data [4]. Additionally, our data suggest a complex dynamic interplay with the cytoskeleton, that might be mediated by some interactions of ACE2 with integrins [5]. We hypothesized that these features could be relevant also for viral attachment and entry.

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