High-resolution plasma membrane-selective imaging by second harmonic generation

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The plasma membrane is the site of intercellular communication and subsequent intracellular signal transduction. The specific visualization of the plasma membrane in living cells, however, is difficult using fluorescence-based techniques owing to the high background signals from intracellular organelles. In this study, we show that second harmonic generation (SHG) is a high-resolution plasma membrane-selective imaging technique that enables multifaceted investigations of the plasma membrane. In contrast to fluorescence imaging, SHG specifically visualizes the plasma membrane at locations that are not attached to artificial substrates and allows high-resolution imaging because of its subresolution nature. These properties were exploited to measure the distances from the plasma membrane to subcortical actin and tubulin fibers, revealing the precise cytoskeletal organization beneath the plasma membrane. Thus, SHG imaging enables the specific visualization of phenomena in the plasma membrane with unprecedented precision and versatility and should facilitate cell biology research focused on the plasma membrane.