Evidence for, and function of, sub-resolution ordered membrane domains

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Lipid microdomains are postulated to regulate many membrane-associated processes but have remained highly controversial. Here we provide the first direct evidence that the plasma membrane of intact, live cells is comprised of a sub-resolution mixture of approximately 76% ordered and 24% disordered lipid domains, which correspond to liquid-ordered and liquid-disordered model membranes. These measurements were based on the un-mixing of fluorescence lifetime decays (phasor analysis) obtained from environmentally sensitive membrane dyes that report the degree of lipid packing. Using the transmembrane protein Linker for Activation of T cells (LAT) as an example, we demonstrated that association with ordered domains retarded LAT diffusion and decreased clustering in meso-scaled protein domains as analysed by super-resolution microscopy. Our data therefore propose a membrane model in which the majority of the plasma membrane is covered by cholesterol-dependent, ordered lipid domains that contribute to the non-random distribution and diffusion of membrane constituents.