in A431 increases by two orders of magnitude from  $10^{-2}$  of native cells to 1 of M  $\beta$ CD treated cells. Noteworthy, the  $V(\overline{R_\tau}^2)$  value can be increased to higher than 10 in M  $\beta$ CD treated HeLa and MCF-12A cells, revealing that a deterministic dimerization interaction will dominate after membrane cholesterol is depleted. These observation results exhibit the vital role of membrane cholesterol in mediating the interaction between liganded receptors in the three cell lines under study.

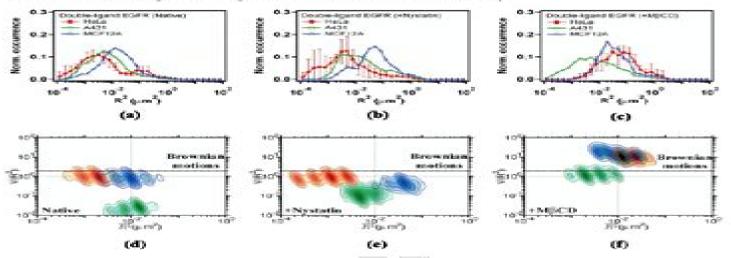


Fig. 6 a, b, c Histograms of MSDs and (d, e, f) V(R<sub>τ</sub><sup>2</sup>)-R<sub>τ</sub><sup>2</sup> plots of correlated Qdot585-EGF-EGFRs diffusing in the plasma membrane of (a, d) native cells, (b, e) nystatin-pretreated cells, and (c, f) M βCD-pretreated cells. Trajectory segments with a degree of correlation exceeding 0.8 were analyzed. Trajectories were sampled with a frame period of τ=25 ms. Data are shown in red for HeLa cells, green for A431 cells, and blue for MCF12A cells

#### Discussion

A receptor protein can induce order in the surrounding lipids through the receptor-lipid interaction Gómez-Llobregat et al (2013). The degree of induced lipid order is determined by the effects of receptor-lipid interaction and the amount of cholesterol in the plasma membrane. Recent molecular dynamics (MD) simulations of human receptor tyrosine kinases in various lipid bilayers revealed that the predominant drivers of the receptor-induced lipid ordering domains may originate from electrostatic interactions between the anionic lipids and clustering basic residues in the juxtamembrane starting region of receptors "Hedger et al (2015). Lipid domains had been predicted to exist in multicomponent membranes and experimentally observed on artificial membranes. For example, thermal fluctuations on a multicomponent membrane can produce inhomogeneities of lipid phases because the order parameters of lipid systems depend not only on the lipid composition but also on the compositional difference of two lipid leaves Shlomovitz et al (2014). Coupling between inner and outer leaves of an asymmetric lipid bilayer could also produce inhomogeneities of lipid phases with a nonzero curvature Shlomovitz and Schick

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