Beta amyloid (beta-40), a short peptide associated with the onset of Alzheimer disease, can exist in the alpha-helix, beta-sheet or global conformation depending on its environment. The role of self-assembling lipid nanodomains on the conformation and interactions of this peptide was examined using both fluorescence and computer simulations. A fluorescent sterol was used to investigate the rotational dynamics of the sterol and the proximity of the peptide to the membrane via fluorescence anisotropy and fluorescence resonance energy transfer measurements, respectively. In addition, both all-atom and coarse-grained molecular dynamics simulations on several peptide/lipid/water complexes were initiated to study the stability of various forms of beta-40 with a nanoscale lipid domain. Our results suggest a critical role of the nanostructure of lipid bilayer surface, particularly the distribution of cholesterol, on beta amyloid interactions with lipid membranes.