Membrane activity investigation of indole containing DAG-lactones

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Diacylglycerole (DAG)-lactones function as biomimetic second messengers in cell signaling processes. N-methyl substituted diacylglycerol-indololactones (DAG-indololactones) are newly-synthesized effectors of protein kinase C (PKC) isoforms and exhibit substantial selectivity between RasGRP3 and PKC alpha. We describe analysis of membrane interactions and biological activities of several DAG-indololactones. Translocation and binding activity assays underline significant variations between the PKC translocation characteristics affected by the ligands as compared to their binding activities. In parallel, the fluorescent properties of the ligands were employed for analysis of their membrane association profiles. Specifically, we find that a slight change in the linkage to the indole ring resulted in significant differences in membrane binding and association of the DAG-indololactones with lipid bilayers. Our analysis shows that seemingly small structural modifications of the hydrophobic regions of these biomimetic PKC effectors contribute to pronounced modulation of membrane interactions of the ligands and dramatic changes in their biological properties.

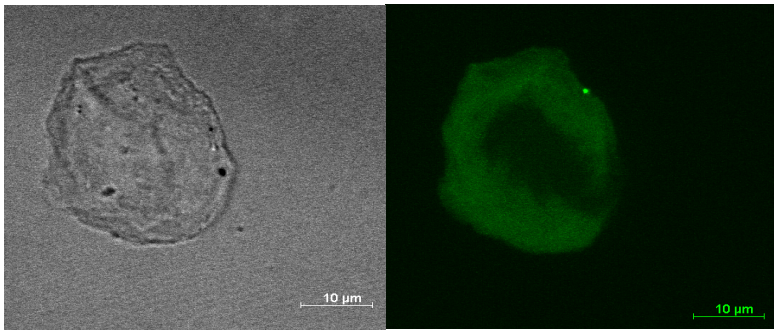

Figure 1: Giants unilamellar vesicle (GUV) [DMPC: DMPG (9:1] after addition of indole-containing DAG-lactones

References

1. N. Gal, S. Kolusheva, N. Kedei, A. Telek, N. E. Lewin, L. Lim, P. Mannan, S. H. Garfield, V. E. Marquez, P. M. Blumberg, R. Jelinek, "N-methyl-substituted fluorescent DAG-indololactone isomers exhibit dramatic differences in membrane interactions and biological activities", in press.