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Reply

Drs. Manor and Atkinson argue, based on their recent study [1], that the specificity of SPF for α -tocopherol is relatively low, and that this may not be a 'true' ligand for this protein. Unquestionably, SPF and related proteins are relatively promiscuous in their lipid binding specificities, and identifying the 'true' ligand for SPF has been a problem since first studied in Konrad Bloch's laboratory in the late 1970's. The conclusion that SPF binds α -tocopherol was reached independently by two groups [1,3] that characterized this protein before it was recognized that the protein under study, tocopherol-associated protein (TAP), was identical with SPF. Although Drs. Manor and Atkinson may be correct that SPF does not play a central role in tocopherol biology, the purpose of my review was to point out this convergence of disparate research areas (tocopherol biology and cholesterol synthesis) on a single newly identified protein. Indeed, in our studies on SPF we have been unable to demonstrate a role for α -tocopherol in the stimulation of squalene monooxygenase activity by SPF [4]. Nonetheless, the study by Yamauchi et al., [3] revealed the surprising ability of a α -tocopherol to promote the movement of an SPF-GFP fusion protein from the cytosol into the nucleus of COS-7 cells, and to stimulate transcription of a reporter gene by GAL4-SPF fusion protein. Two caveats must be noted in evaluating this study: the concentration of α -tocopherol required in these experiments (5 to 50 μ M) was high relative to the K_d for α -tocopherol (0.5 to 0.6 μ M) reported by Panagabko et al. [1] and Zimmer et al. [2] for

SPF, and no other putative ligands for SPF (e.g., squalene, phosphatidylinositol) were tested for their ability to promote these biological effects. Nonetheless, these findings suggest that we may not understand all the roles, and ligands, of SPF. The work by Panagabko et al. [1] significantly advances our understanding of ligand binding specificity in this enigmatic family of proteins, and will provide a firm foundation for further experiments to elucidate the role, or roles, of SPF in the cell.

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doi:10.1016/S0955-2863(03)00073-1

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