Structure-Function Analysis of the Glioma Targeting NFL-TBS.40-63 Peptide Corresponding to the Tubulin-Binding Site on the Light Neurofilament Subunit

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We previously reported that a 24 amino acid peptide (NFL-TBS.40-63) corresponding to the tubulin-binding site located on the light neurofilament subunit, selectively enters in glioblastoma cells where it disrupts their microtubule network and inhibits their proliferation. Here, we analyzed the structure-function relationships using an alanine-scanning strategy, in order to identify residues essential for these biological activities. We showed that the majority of modified peptides present a decreased or total loss to penetrate in these cells, or to alter microtubules. Correspondingly, circular dichroism measurements showed that this peptide forms either β-sheet or α-helix structures according to the solvent and that alanine substitution modified or destabilized the structure, in relation with changes in the biological activities. Moreover, substitution of serine residues by phosphoserine or aspartic acid concomitantly decreased the cell penetrating activity and the structure stability. These results indicate the importance of structure for the activities, including selectivity to glioblastoma cells of this peptide, and its regulation by phosphorylation.

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