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Molecular correlates of the action of bis(etyl)polyamines in breast cancer cell growth inhibition and apoptosis

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Polyamines are known to be involved in cell growth regulation in breast cancer. To evaluate the efficacy of bis(etyl)polyamine analogs for breast cancer therapy and to understand their mechanism of action we measured the effects of a series of polyamine analogs on cell growth, activities of enzymes involved in polyamine metabolism, intracellular polyamine levels, and the uptake of putrescine and spermidine using MCF-7 breast cancer cells. The IC<sub>50</sub> values for cell growth inhibition of three of the compounds, N<sup>1</sup>,N<sup>12</sup>-bis(etyl)spermine, N<sup>1</sup>,N<sup>11</sup>-bis(etyl)norspermine, and N<sup>1</sup>,N<sup>14</sup>-bis(etyl)homospermine were in the range of 1-2μM. Another group of three compounds showed antiproliferative activity at about 5μM level. These compounds are also capable of suppressing colony formation in soft agar assay and inducing of MCF-7 cells. The highly effective growth inhibitory agents altered the activity of polyamine biosynthetic and catabolic enzymes and down-regulated the transport of natural polyamines, although each compound produced a unique pattern of alterations in these parameters. HPLC analysis showed that cellular uptake of bis(etyl)polyamines was highest for bis(etyl)spermine. We also analyzed polyamine analog conformations and their binding to DNA minor or major grooves by modelling and molecular dynamics simulations. Results of these analyses indicate that tetramine analogs fit well in minor groove of DNA whereas, larger compounds extend out of the minor groove. Although major groove binding was also possible for the short tetramine

analogs, this interaction led to a predominantly bent conformation. Our studies show growth inhibitory activities of several potentially important analogs on breast cancer cells and indicate that multiple sites are involved in the mechanism of action of these analogs. While the activity of an analog may depend on the sum of these different effects, molecular modeling studies indicate a correlation between antiproliferative activity and stable interactions of analogs with major or minor grooves of DNA.