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Designing and characterizing small molecule inhibitor(s) for mitochondrial transcription factor A (TFAM) for therapeutic benefit of Cancer

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Cancer cells have altered mitochondrial metabolism. Although high levels of glycolysis in tumor cells have been observed in several cancer types, many studies revealed that mitochondria are actually functional in most tumor cells. Oncogene activation increases mitochondrial metabolism. Mitochondrial function is essential for cancer cell proliferation. Mitochondrial transcription factor A (TFAM) plays a critical role in transcription, replication and organization of mitochondrial DNA (mtDNA). TFAM offers some protection to mtDNA against oxidative stress. Mitochondrial functions depend on mtDNA and its proteins. TFAM is necessary for the mtDNA transcription and replication. Loss of TFAM leads to depletion of mtDNA, and its proteins which are essential for respiratory chain function. Absence of TFAM decreased tumorigenecity in mouse model of lung cancer. Overexpression of TFAM increased the growth of cancer cell lines, while its down-regulation inhibited cancer growth. Selective delivery of inhibitor(s) to the mitochondria of tumor cells is the newly developing strategy for the cancer treatment, and targeting TFAM inhibitors to mitochondria will help us to understand the role of mitochondria in cancer treatment. By inhibiting TFAM's DNA binding, we would be able to deplete mtDNA & its proteins and ultimately lose mitochondria, which will inhibit the growth of cancer cells. We have identified 7 inhibitors with binding free energies of -8kcal/mol to both HMG boxes of TFAM. When these 7 ligands are docked to TFAM, they overlap with DNA. Thus, presence of these inhibitors may prevent TFAM from binding to DNA. The designed molecules will then be tested experimentally for suitability.

Biography

Emine Guven Maiorov has completed her B.S. from Bogazici University, Molecular Biology & Genetics. She obtained her M.S. degree from Koc University, Chemical & Biological Engineering department and she continues to her Ph.D in the same department

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