Title: The role of central carbon metabolism in DNA replication regulation in human dermal cells

Central carbon metabolism (CCM) plays a key role in all living cells. Depending on cellular demands, it increases or decreases production of energy and precursors for amino acids, nucleotides and many other cell factors. Any perturbations in the regulation of these processes may significantly influence the DNA replication, mainly by changes in the energy flux and the pool of the available nucleotides. However, recent data suggests that there might exist a direct link between both of these processes in prokaryotic cells. It has been shown, that the negative effects of mutations in replication genes in *B. subtilis* and *E. coli* cells, could be specifically suppressed by mutations in genes encoding enzymes catalyzing terminal reactions of glycolysis and acetate overflow mechanism. In the light of these data, and based on the known similarities between DNA replication process in prokaryotic and eukaryotic cells, we asked a question whether a similar relationship is present in eukaryotic cells? This hypothesis also seems to be supported by information indicating that eukaryotic metabolic enzymes are also present in the nucleus and they are involved in regulation of DNA replication (including fidelity of this process), transcription, DNA repair, apoptosis, cell senescent and many other processes. Because, most of these data came from the studies carried out on yeast, fruit flies, mouse and human cancer cells, we chose the human dermal fibroblast (HDFa) cell line, as a model to test this hypothesis. In the first step, we silenced the expression of genes coding for enzymes involved in all steps of glycolysis, pentose-phosphate pathway and tricarboxylic acid cycle with the use of specific siRNA. The partial silencing of specific genes had significant effects on the efficiency of the DNA synthesis and entrance to the S phase of the cell cycle. Then, we chose eight genes coding for replication proteins and silenced them in the same way. Silencing most of them changed the number of cells entering the S phase and significantly decreased DNA amount. Among these genes we selected four, which showed the strongest negative effects. Next, we performed experiments with double gene silencing of genes coding for replication proteins and CCM enzymes. Our data showed that negative effects of silencing of replication genes were suppressed by silencing the set of specific genes that encodes the enzymes involved in glycolysis, TCA cycle and pentose-phosphate pathways in unique way for each of them.