THE ROLE OF THIOREDOXIN SYSTEM ENZYMES AND THEIR TRANSCRIPTIONAL REGULATION IN OXIDATIVE STRESS RESISTANCE OF HUMAN CANCER CELLS

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In all mammalian cells, thiol peptides are the main defence against oxidative stress. Resistance to reactive oxidants is especially important for cancer cells – it is also important from the clinical point of view since numerous anti-cancer drugs act by exerting oxidative damage. While glutathione is responsible for the bulk of basal antioxidant defense, thioredoxin and enzymes of its metabolism, due to their versatility and complex regulation at transcriptional and post-translational levels, may be important in the emergence of induced resistance. In our study, we characterized resistance against exogenous oxidative stress and endogenous production of reactive oxidants using a number of biochemical screening methods for a panel of 12 human cancer cell lines of various tissue origin. Subsequently, we have studied the basal and oxidative stress-stimulated expression of genes encoding components of the thioredoxin system (thioredoxin, thioredoxin reductase, thioredoxin peroxidases/peroxiredoxins and peroxiredoxin reductases/sestrins) by real-time PCR measurement of mRNA levels and enzymatic activity assays. The contribution of transcriptional induction of individual thioredoxin system enzymes to the emergence of oxidative stress resistance was subsequently verified and related to the basal level of expression of these genes. Results show clearly that thioredoxin system genes are co-ordinately regulated at the transcriptional level – we have performed an *in silico* analysis of their promoters to identify the transcription factors most likely responsible for this phenomenon. While thioredoxin and thioredoxin reductase are most strongly upregulated by oxidative stress in the investigated cell lines, induction of peroxiredoxin and sestrin expression is a better predictive determinant of oxidative stress resistance in cancer cells, proving a crucial role for these enzymes in the regulation of cellular redox homeostasis.