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Certain *Saccharomyces cerevisiae* strains produce killer toxins which kill sensitive cells. This phenomenon is important for strains to survive in natural and industrial populations. Toxins are able to kill the nonkiller and different type killer yeast belonging to the same or other genera while the producing cells remain immune to the action of its own or relative toxins. Depending on the differences of toxins' molecular features, killer effects and encoding genetic determinants there are three types of killer systems: K1, K2, and K28. Among those, the mechanism of action of K2 killer is the least understood. In order to describe the mechanism of K2 action it is necessary to analyse not only the intraspecial activity but also its effect on other microorganisms. It is known that some yeast killer strains have antibacterial activity but the performed microbiological tests are not sensitive enough to determine it. Instrumental studies carried out with susceptible yeasts and bacteria are more sensitive.

The objective of our work was the evaluation of K2 killer toxins' impact on different microorganisms applying microbiological methods and performing bioluminescence and electrochemical analysis to characterise the energetical state of cells. It was shown that during the action K2 toxin decreases the level of ATP and the gradients of small molecules. Our study demonstrated that measurements of bioluminescence and electrochemical analysis are very useful methods for determination of the sensitivity of cells to toxin and the analysis of killing mechanisms.

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Melanocytes — A novel tool to study mitochondrial dysfunction in Duchenne muscular dystrophy

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Dystrophin is a subsarcolemmal protein critical for the integrity of muscle fibers by linking the actin cytoskeleton to the extracellular matrix via the dystroglycan complex (DGC). DGC also occurs at dermal–epidermal junction in skin. Here we report for the first time that epidermal melanocytes express dystrophin. The full-length muscle isoform of dystrophin (mDp427) was clearly detectable in skin sections as assessed by RNA analysis. Dystrophin was selectively expressed at the basal layer of melanocytes where it co-localized with basement membrane (BM) components. Dystrophin was absent in the epidermis of Duchenne muscular dystrophy (DMD patients), while dystroglycans and BM components were normally expressed. We have characterized mitochondrial function in primary cultures of melanocytes from one normal donor and two DMD patients. Mitochondria readily accumulated tetramethylrhodamine methyl ester, indicating that they are energized irrespective of the presence of dystrophin. On the other hand, and at variance from mitochondria of control donors, mitochondria of DMD patients readily depolarized upon the addition of oligomycin, suggesting either that they are maintaining the membrane potential at the expense of glycolytic ATP, or that they are affected by a latent dysfunction unmasked by inhibition of the ATP synthase. We are currently investigating the basis for this anomalous response to oligomycin, which in Ullrich congenital muscular dystrophy is caused by sensitization of the permeability transition pore. Since melanocyte cultures can be easily obtained by conventional skin biopsies, they represent a promising cellular model for studying and monitoring dystrophinopathies and their response to experimental treatments.

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21P14

Mitochondrial bioenergetics and drug-induced toxicity in a panel of mouse embryonic fibroblasts with mitochondrial DNA single nucleotide polymorphisms

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Mitochondrial DNA (mtDNA) variations including single nucleotide polymorphisms (SNPs) have been proposed to be involved in idiosyncratic drug reactions. However, current *in vitro* and *in vivo* models lack the genetic diversity seen in the human population. Our hypothesis is that different cell strains with distinct mtDNA SNPs may have different mitochondrial bioenergetic profiles and may therefore vary in their response to drug-induced toxicity. Therefore, we used an *in vitro* system composed of four strains of mouse embryonic fibroblasts (MEFs) with mtDNA polymorphisms. We sequenced mtDNA from embryonic fibroblasts isolated from four mouse strains, C57BL/6J, MOLF/EiJ, CZECHII/EiJ and PERA/EiJ, with the latter two being sequenced for the first time. The bioenergetic profile of the four strains of MEFs was investigated at both passage 3 and 10. Our results showed that there were clear differences among the four strains of MEFs at both passages, with CZECHII/EiJ having a lower mitochondrial robustness when compared to C57BL/6J, followed by MOLF/EiJ and PERA/EiJ. Seven drugs known to impair mitochondrial function were tested for their effect on the ATP content of the four strains of MEFs in both glucose- and galactose-containing media. Our results showed that there were strain-dependent differences in the response to some of the drugs. We propose that this model is a useful starting point to study compounds that may cause mitochondrial off-target toxicity in early stages of drug development, thus decreasing the number of experimental animals used.

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21P15

Mitochondrial parameters in spinal bulbar muscular atrophy muscle tissue

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