was applied in the last five minutes of ischemia and first ten minutes during reperfusion. After anaesthesia the myoelectric activity of the gastrointestinal tract was monitored during ischemia (50 minutes) and reperfusion (120 minutes). Samples of the duodenum, ileum and colon were collected at the end of reperfusion phase. After an overnight fixation whole-mount preparations were prepared for immunhistochemical (HuC/HuD, nNOS and eNOS) staining. Biopsies from the small intestine were collected for biochemical studies. Tissue superoxide levels, xanthine oxidoreductase activity were determined to monitor the oxidative stress, and tissue nitrite/nitrate and nitrotyrosine levels were determined to study the levels of nitrosative stress.

At the beginning of ischemia the myoelectric activity sharply increased, then decreased gradually until the end of the reperfusion period. After methane inhalation a post-ischemic peak appeared in myoelectric activity at the beginning of the reperfusion period which then declined sharply and reached near the control level by the end of the reperfusion period.

After IR the total number of myenteric neurons did not change, but the density of nNOS and eNOS-positive myenteric neurons increased. Increase of the nNOS-immunreactive neurons in the duodenum were significant. After methane inhalation the density of the nitrergic myenteric neurons was similar to the neuronal density found in sham-operated rats. During IR the levels of tissue nitrite/nitrate, nitrotyrosine, and xanthine oxidoreductase activity increased significantly, while the methane inhalation prevented the intestinal tissues from the increase of oxidative and nitrosative stress markers.

Based on these results we hypothesize that due to the increased density of nitrergic myenteric neurons in IR the descending inhibition of intestinal peristalsis was enhanced. At the same time methane inhalation in the early stages of reperfusion prevented from the increase in the number of nitrergic myenteric neurons and the intestinal motility disorders.

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Development of a novel, somatic gene transfer system in the mouse

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Cancer is the leading cause of death in the developed world. Tumorigenesis requires the acquisition of mutations in proto-oncogenes and tumor supressor genes. Such genetic changes can be caused by mutagenic agents, chromosomal translocations or the disruption of the balance in epigenetic networks. A class of mutations, called „driver" mutations, affect a relatively limited number of genes that are functionally related to the key attributes of cancer cells. Contrary to driver mutations, „mutator" mutations act as enhancers of the tumorigenic process. According to the mutator hypothesis, mutator mutations decrease genome stability and, hence, accelerate the accumulation of random mutations, including those in proto-oncogenes and tumor suppressor genes. Our aim is to create a novel, somatic genetransfer system for the identification of candidate genes involve in the enhancement of tumorigenesis through the over-expression of native/mutant coding sequences or gene silencing with artificial miRNAs.

Type 1 tyrosinemia is a liver-based *metabolic disorder* caused by a deficiency of the enzyme fumarylacetoacetate hydrolase (Fah). The mouse model of this disease (Fah knock-out strain [Fah -/-]) offers the possibility to develop the new transgenic system. The primary treatment for type 1 tyrosinemia is nitisinone (NTBC). This drug prevents the formation of fumarylacetoacetic acid, which has the potential to be converted to succinyl acetone, a toxin that damages hepatocytes. Consequently, liver degeneration occurs due to the withdrawal of NTBC. However, the high regenerative capacity of this organ can be utilized to establish a new, healthy liver: wild type hepatocytes (Fah +/+) can migrate to the diseased organ and repopulate that within a few months after cell transplantation into the spleen. Thus, a Fah +/+ transgenic liver can be obtained from a genetically engineered hepatocyte pool in a Fah -/- recipient mouse.

Liver repopulation can be monitorised with a fluoresence marker gene that also serves the expression of artificial miRNAs, in addition to its indicator role. Furthermore, this somatic gene transfer system is adaptable for library screens due to the large amount of hepatocytes potentially involved in repopulation, resulting in the possibility to express multiple transgenes. Considering the somatic nature of the system, the classical method for generating transgenic mice can be avoided, and the number of experimental animals reduced. These adventages make this new practice faster and more cost effective. We hope that our technique for producing transgenic liver will become a valuable tool for cancer genetics.

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