Zika virus (ZIKV) is a common single-stranded RNA virus in the Flaviviridae family that was first isolated 60 years ago. However, ZIKV infections have been unexpectedly linked to severe clinical consequences including Guillain-Barré syndrome (GBS) in adults and microcephaly in fetuses and newborn infants during recent outbreaks of ZIKV in the Americas. ZIKV is primarily transmitted to humans through mosquito bites or sexual contact. The excretion and persistence of contagious ZIKV in various body fluids have been well documented in ZIKV patients; however, the risk of direct contact exposure and whether ZIKV could transmit through close contact remains unclear.

Here, we first assessed the infectivity of ZIKV in guinea pigs (Hartley strain), which has been widely used for mimicking transmission of many viruses. Interestingly, all guinea pigs upon subcutaneous (s.c.) challenge with an Asian lineage ZIKV strain developed seroconversion and robust viral secretions in sera, saliva, and tears, indicating guinea pig are susceptible to ZIKV. Then, we tested the transmissibility of ZIKV by performing a direct contact experiment in the guinea pig model. As expected, all animal inoculation by s.c inoculation developed viremia and viral secretion in saliva and tears were detected in all index animals; remarkably, all guinea pigs (100%) that were co-aged with the s.c. inoculated animals readily developed similar viremia to that of their cagemates. Meanwhile, the viral shedding kinetics in saliva and tears of the contact animals were also comparable to that of the index animals. In particular, ZIKV inoculation via intranasal (i.n.) route was fully capable of establishing acute infection in guinea pigs, and viral antigens are readily detected in multiple tissues including brain and parotid glands, which was closely associated with robust viral replication in the parotid glands. Finally, we expanded our results to non-human primates, and cynomolgus macaques efficiently acquired ZIKV infection via i.n. and intragastric (i.g.) inoculation routes. Overall, our results showed that ZIKV was able to transmit from infected guinea pigs to the naïve co-caged animals by close contact, highlighting the potential risk of direct contact with or oronasal exposure to ZIKV contaminants from symptomatic or asymptomatic patients.
During aging process, functional decline in distinct tissues may have different outcomes on the systemic regulation. Accumulating evidence suggested that muscles are central tissues to coordinate organism-wide processes including aging and metabolic homeostasis. To test the hypothesis, we created tissue-specific knockout (KO) mice of Cisd2 gene, which encodes a mitochondrial outer membrane protein mediating mitochondrial integrity and aging in mammals, to drive specific cell degeneration in different tissues, including neurons, skeletal muscle and adipose tissues. Our result revealed that the Cisd2 muscle-specific KO (mKO) mice phenotypically copied the systematic Cisd2 KO mice; both mouse models exhibit a systemic aging phenotypes. Intriguingly, a genetically rescue mouse model partially restored the organism-wide aging phenotypes of Cisd2 KO mice, especially the adipose atrophy. These results showed that muscle degeneration has a profound effect on non-muscle tissues. On the other hand, we also identified that Fgf21 and Gdf15, which are myokines regulating a muscle-adipose crosstalk, were up-regulated in the degenerating skeletal muscles of the Cisd2 KO and mKO mice. In summary, our mouse study revealed that skeletal muscles play an important role to coordinate organism-wide processes and that muscle degeneration seems to have a profound effect on the homeostasis of adipose tissues.
Epidemiological evidence suggests that high intake of soy is associated with reduced breast cancer risk. We recently reported that pubertal exposure to dietary soy isoflavones (IFs) resulted in enhanced mammary gland lobular differentiation alongside subtle effects on estrogen receptor (ER) activity in the breast of cynomolgus monkey model (*Macaca fascicularis; Mf*) during early adulthood. It is unknown, however, if the mechanism involved mammary stem cells and whether such phenotype will have lasting effect on cancer prevention. Here, we performed breast biopsy on female nulliparous Mf to isolate mammary cells and developed them into mammosphere culture to enrich mammary stem cell population. The 3-dimensional (3D) primary cell culture model was utilized to evaluate the effect of soy IF genistein on mammary cell differentiation and responsiveness to estrogen challenge. Cell differentiation was evaluated using a 3D assay with matrigel approach; organoid budding was quantified, and expression of markers for differentiation (*GATA3, STAT5, CSN2*) was evaluated by qPCR. Further, differentiated cells were challenged with estradiol, and expression of markers for cell proliferation (*MKI67*) and ER activity (*TFF1*) was evaluated by qPCR. The study showed that genistein enhanced cell differentiation whereby organoid formation was higher compared to that in placebo-treated cells. The result was consistent with lower expression of *GATA3* (*P*<0.05), higher expression of *STAT5* (*P*<0.01) alongside a marginally higher *CSN2* expression. Following estradiol challenge, expression of TFF1 in genistein-treated cells was lower (*P*<0.05) in a dose-dependent manner. Expression of proliferation marker *MKI67* was marginally lower with genistein. These results indicate that genistein, which is the main bioactive compound of soy may promote differentiation of mammary stem cells, and dampen estrogen responsiveness with subtle effect on reducing estrogen-induced cell proliferation, which are phenotypes consistent with lower breast cancer risk.
Role of Protein disulfide isomerase A3 in the ischemic spinal cord

Dae Young Yoo¹, Woosuk Kim¹, Dae Won Kim², In Koo Hwang¹

¹Department of Anatomy and Cell Biology, College of Veterinary Medicine, and Research Institute for Veterinary Science, Seoul National University, Seoul, South Korea
²Department of Biochemistry and Molecular Biology, Research Institute of Oral Sciences, College of Dentistry, Gangneung-Wonju National University, Gangneung, Korea

In the present study, we searched for possible candidates that can prevent ischemic damage in the spinal cords of New Zealand white rabbits. For this study, we used two-dimensional gel electrophoresis followed by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, in sham- and ischemia-operated animals. As the level of protein disulfide-isomerase A3 (PDIA3) significantly decreased 3 h after ischemia/reperfusion, we further investigated its possible role against ischemic damage using an in vitro spinal cord cell line and in vivo spinal cord ischemic model. The administration of Tat-PDIA3 significantly reduced the hydrogen peroxide-induced formation of reactive oxygen species and cell death, based on terminal deoxynucleotidyl transferase-mediated biotinylated dUTP nick end labeling and a colorimetric WST-1 assay. Further, Tat-PDIA3 significantly ameliorated the ischemia-induced deficits in motor function, based on Tarlov’s criteria, 24–72 h after ischemia/reperfusion, as well as the degeneration of motor neurons in the ventral horn 72 h after ischemia/reperfusion. Tat-PDIA3 administration also reduced the ischemia-induced activation of microglia and lipid peroxidation in the motor neurons 72 h after ischemia/reperfusion. PDIA3 also potentially ameliorated the ischemia-induced increase in oxidative markers in serum and decreased the activity of Cu,Zn-superoxide dismutase, Mn-superoxide dismutase, and glutathione peroxidase in spinal cord homogenates, 24 h and 72 h after ischemia/reperfusion. These results suggest that Tat-PDIA3 could be used to protect spinal cord neurons from ischemic damage, due to its modulatory action on the oxidative/anti-oxidative balance. Tat-PDIA3 could be applicable to protects neurons from the ischemic damage induced by thoracoabdominal aorta obstruction.
Laboratory mice are widely used in biomedical research as models for human diseases that also provide insight into the toxicity of various xenobiotics. Fasting of mice prior to dosing is common practice in toxicological studies to ensure uniformity in drug absorption. The APAP mouse model has been extensively used for studies on pathogenesis and intervention of drug-induced liver injury (DILI) based on the cytochrome P450 (CYP450) mediated formation of N-acetyl-p-benzoquinoneimine (NAPQI). Two mouse models, out-bred CD-1 and in-bred C57BL/6J mice were used to investigate the differences in their response to acetaminophen (APAP) overdose and the effect of fasting prior to dosing to cover both acute liver injury and regeneration. The results on control mice showed that fasting alone significantly reduces the body weight up to 12%. A reduction of the glutathione (GSH) content was observed at 1 hour post dosing (hpD) in CD-1 mice and at 3 hpD in C57BL/6J mice before the levels increased gradually until the end of the study period. In fasted CD-1 mice, GSH levels returned to control levels with delay; this was variable in C57BL/6J mice until the levels were similar to control animals at 36 hpD. In both strains of fasted mice, while ATP levels remained lower, serum alanine aminotransferase (ALT) activity showed a progressive increase after APAP dosing. In fed mice, cell death via apoptosis was initially seen and most abundant at 3 and 5 hpD in CD-1 mice. In C57BL/6J mice, there was prolonged evidence of centrilobular hepatocyte necrosis, which declined but was still present at 36 hpD. In fasted mice of both strains, there was evidence of substantial ongoing hepatocyte death and neutrophil recruitment until the end of the study, together with delayed hepatocyte proliferation. Fed mice, and in particular CD-1 mice, showed higher hepatic and splenic IL-6, IL-10, NF-kB and cyclin-D1 mRNA levels than fasted mice, correlating with effective liver regeneration. The quantitative assessment of hepatocyte proliferation, based on the in situ expression of proliferating cell nuclear antigen (PCNA), confirmed the earlier onset and faster liver recovery in fed animals, with an earlier onset also in CD-1 than C57BL/6J mice. In conclusion, we provide definite evidence that fasting prior to APAP overdose does not only modulate the resulting liver injury, but delay the subsequent liver regeneration. We also confirm that the C57BL/6J mice are more susceptible to APAP-induced liver injury when fed prior to dosing, but both strains react in a similar way when dosed after a period of fasting.

**Keywords:** Acetaminophen (APAP), fasting, liver injury, liver regeneration