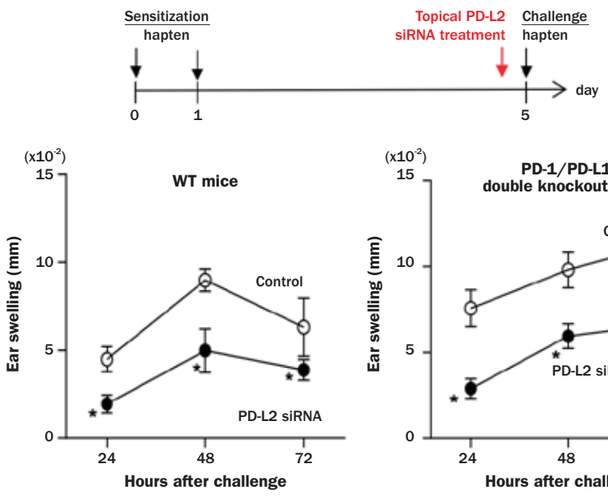
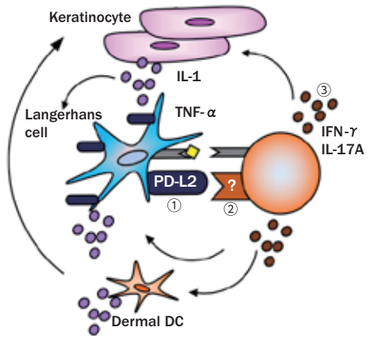
Nucleic acid ointment, the new contact-dermatitis cream

Allergic skin diseases, including contact dermatitis, affect millions worldwide. PD-L2 is a PD-1 immune-checkpoint ligand with unclear regulatory function. To understand the role of PD-L2, a team of TMDU researchers led by Emi Furusawa used small-interfering RNA (siRNA) to silence PD-L2 in a mouse model of contact hypersensitivity (CHS). PD-L2 expression was induced in epidermal Langerhans cells using a hapten antigen. Topical application of PD-L2 siRNA ointment inhibited the elicitation of CHS by suppressing early pro-inflammatory signals. Neutralization of PD-L2 protein using an anti-PD-L2 mAb produced similar results, showing that these results are PD-L2 specific. Topical PD-L2 siRNA also inhibited the development of CHS in mice lacking both PD-1 and PD-L1, indicating that this effect is PD-1 and PD-L1 independent. Although PD-L2 was thought to be an inhibitory molecule, these results show that PD-L2 may function as an activator in the elicitation phase of the CHS. It is expected that these results will lead to the development of PD-L2-targeted siRNA nucleic acid drugs for topical skin application.

J. Invest. Dermatol., **doi: 10.1016/j.jid.2019.02.037**

Topical PD-L2 siRNA treatment inhibits elicitation of contact hypersensitivity in PD-1-independent manner





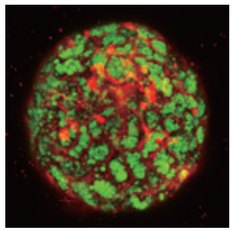
①Induction of PD-L2 in Langerhans cells (LCs)
②PD-L2 in LCs interacts with local memory T cells.
③Activated T cells secrete cytokines, resulting in the amplification of local inflammatory responses.

Inflamed 3D-miniature human livers open the way to drug discovery

Nonalcoholic steatohepatitis (NASH) is a common liver disease that may progress to cirrhosis or liver cancer. An effective treatment against the disease has not existed; highly therapeutic drugs have not been developed because of the lack of a culture system that recapitulates the pathology of steatohepatitis, especially inflammation and fibrosis. TMDU researcher Rie Ouchi and Professor Takanori Takebe's group, in collaboration with researchers from Cincinnati Children's Hospital Medical Center, have established the liver organoid model from human-induced pluripotent stem cells (iPSCs). The model includes immune cells that induce inflammation in liver, called the Kupffer cell, and stromal cells that are involved in fibrosis, called Stellate cells. The human liver organoid, including hepatocytes, Kupffer cells, and Stellate cells, accumulated fatty acids, including triglycerides with exposure of free fatty acid (FFA). The longer culture with FFA caused inflammation and fibrosis. The organoids from iPSCs derived from patients with congenital steatohepatitis, called Wolman disease, developed significant steatohepatitis phenotype after exposure to FFA. Importantly, the treatment of obeticholic acid and FGF19, which showed the effectiveness in clinical trials of NASH, alleviated the symptoms. This novel organoid technology may lead to the discovery of new effective drugs for steatohepatitis, including NASH, and moreover, become a platform for personalized treatment of the disease.

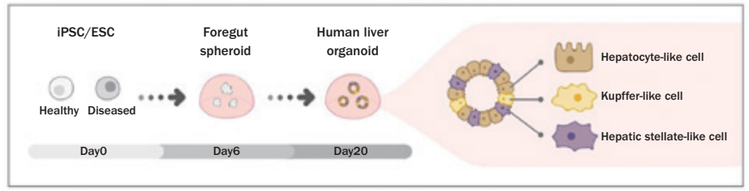
Cell Metabolism, **doi: 10.1016/j.cmet.2019.05.007**

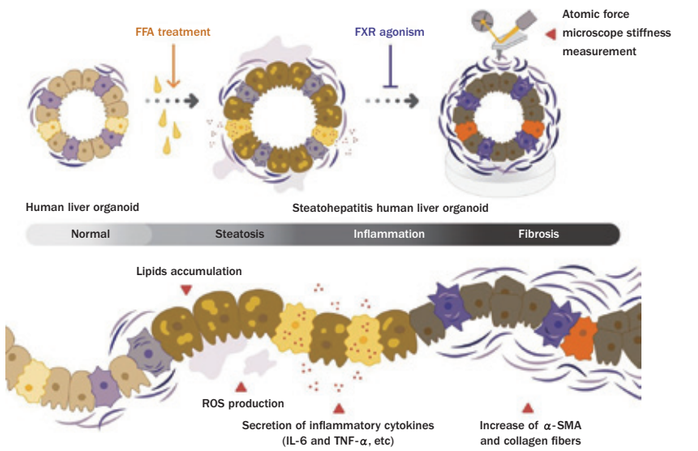
Confocal imaging of fatty liver organoid in a dish



Green indicates lipid accumulation; Red visualizes cellular membrane in a single organoid.

Generation of human fatty livers using custom-engineered induced pluripotent stem cells





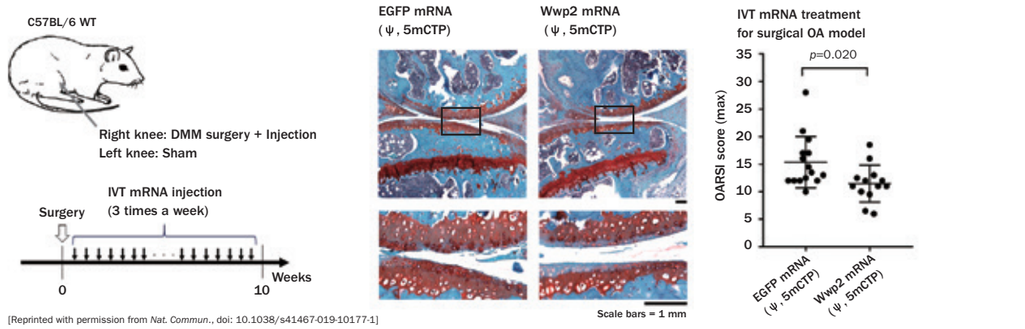
[Reprinted with permission from *Cell Metabolism*, doi: 10.1016/j.cmet.2019.05.007]

Wwp2 protects against cartilage damage in osteoarthritis

Osteoarthritis (OA) is a debilitating joint disease commonly seen in the elderly. The onset of OA involves the destruction of the articular cartilage, which is the tissue that forms the joint. Recently, it was discovered that the protein Wwp2 (WW domain-containing protein 2) is expressed abundantly in articular cartilage. Wwp2 is an ubiquitin E3 ligase, which functions to bind ubiquitin to a substrate. However, the role of Wwp2 in the articular cartilage remains unclear. To determine the function of Wwp2, an international team of researchers led by Hiroshi Asahara generated and examined Wwp2 gene-modified mice. Mice lacking Wwp2 and mice with an inactive Wwp2 showed increased symptoms of OA. Furthermore, when artificially synthesized mRNA (*in vitro* transcribed (IVT) mRNA) with the ability to produce Wwp2 in cells was introduced into the articular cartilage of mice, OA symptoms were reduced. The results from this study reveal that Wwp2 plays a role in protecting the articular cartilage from OA. Additionally, this may pave the way to new therapy options for treating OA.

Nat. Commun., **doi: 10.1038/s41467-019-10177-1**

IVT Wwp2 mRNA ameliorates articular cartilage destruction Injected mixture = IVT mRNA (ψ, 5mCTP) + invivofectamine + atelocollagen



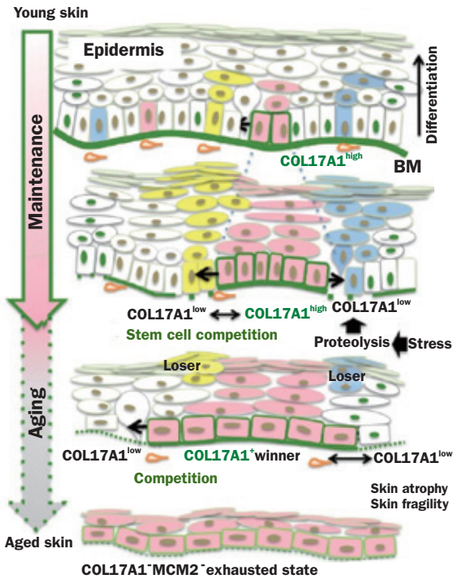
[Reprinted with permission from *Nat. Commun.*, doi: 10.1038/s41467-019-10177-1]

Skin vitality maintained through cellular "survival of the fittest"

Skin is thought to age when skin cells lose their ability to repair damage from environmental stress, but the connections between repair and aging are poorly understood. Researchers at TMDU, led by Emi Nishimura, investigated the dynamics of skin aging in mice and developed a model for how youthful skin persists over time. They found that epithelial stem cells respond to stress by breaking down collagen XVII (COL17A1), a protein that attaches cells to the membrane under the skin. As COL17A1-deficient cells easily detach from the membrane, adjacent COL17A1-rich cells outcompete them by multiplying and physically pushing them to the skin's surface for elimination. The selective competition processes keep skin "young" by continually replacing damaged cells. The researchers argue that skin ages when stem cells can no longer maintain high levels of COL17A and the pool of replacement cells is lost, and found that increasing cellular COL17A with topical chemicals ameliorates skin deterioration due to age. The discovery may lead to new restorative treatments for skin aging and age-associated diseases.

Nature,
doi: 10.1038/s41586-019-1085-7

Schematic of the epidermal aging program through COL17A1-mediated cell competition



COL17A1^{high} clones (winners) dominate in the basal interfollicular epidermis (IFE), whereas COL17A1^{low} clones (losers) are delaminated from the basal IFE during aging

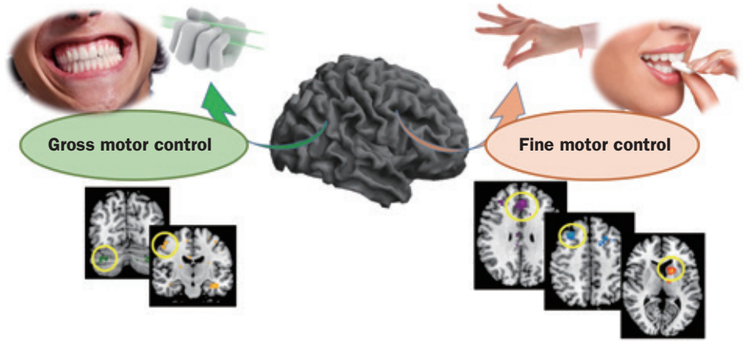
[Modified from *Nature*, doi: 10.1038/s41586-019-1085-7]

The brain and biting: brain activity correlates with incisal and molar bite force

Although biting is known to have a preventive effect against dementia, the relationship between biting and brain function remains largely unknown. The distinct functions of teeth (incisors for cutting and molars for grinding) are analogous to handgrip types (precision and power grips). Unlike handgrips, the brain correlates of fine and gross motor control during mastication have not been investigated. A research team led by Keiji Moriyama studied the motor-control systems engaged during incisal and molar biting. During molar biting, activity in motor function-related brain areas increased with increasing bite force, similar to the power grip. During incisal biting, activity in fine motor function-related areas decreased with increasing bite force levels, similar to precision grip. This indicates that the action of biting engages a single command system in the brain, but also engages two different movement control mechanisms. These findings elucidate the brain correlates of biting, and may help to elucidate the potential therapeutic effects of biting. Furthermore, our results may also help to clarify how occlusal hypofunction and dental treatments for it affect cortical motor-control systems.

Sci. Rep., **doi: 10.1038/s41598-019-44846-4**

Two different movement-control mechanisms in the brain are at work when biting an object

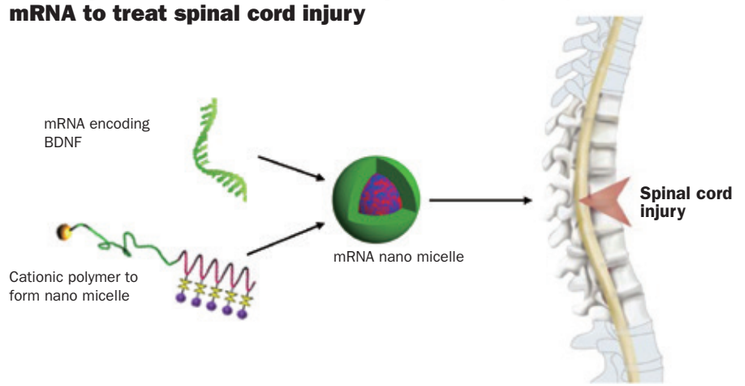


Delivery of BDNF mRNA enhances motor function following spinal cord injury in mice

"Secondary injury" in the days following spinal cord injury can impair motor recovery; therefore, finding ways to keep neural tissue alive during this critical period is key. Brain-derived neurotrophic factor (BDNF) is a secreted protein that promotes neuron survival. However, BDNF cannot cross the blood–brain barrier and its delivery requires frequent injections. While delivery of BDNF DNA can overcome these limitations, BDNF messenger RNA (mRNA) may be better yet; mRNA can transfect more cells and may produce more protein than DNA. To examine this, researchers at TMDU, led by Keiji Itaka, created a mouse model of spinal cord injury and administered BDNF mRNA to the injury site. mRNA-treated mice had doubled BDNF levels in spinal cord tissue (vs. no treatment) and an earlier motor recovery than non-treated and DNA-treated mice. This demonstrates the efficacy of BDNF mRNA treatment, which has implications for nerve function repair and regenerative therapy that does not require cell transplantation. mRNA drug treatments for central nervous system diseases and trauma are expected in the near future.

Mol. Ther. Nucleic Acids,
10.1016/j.omtn.2019.06.016

Delivery of brain-derived neurotropic factor (BDNF) mRNA to treat spinal cord injury

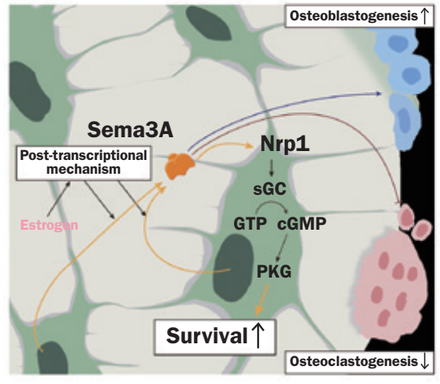


Activation of Sema3A signaling may protect against age-related osteoporosis

Osteoporosis is a disease characterized by reduced bone density and deterioration of the bone matrix, leading to fractures that can be physically disabling. Women are at a greater risk of developing osteoporosis as they age and reach menopause, when estrogen levels diminish significantly. While estrogen loss is known to cause the death of osteocytes needed to maintain bone homeostasis, the underlying mechanism is unclear. Tomoki Nakashima, leading a research team centered at TMDU, found that estrogen enhances the expression of an osteoprotective protein, semaphorin 3A (Sema3A), by suppressing microRNAs that target the 3' untranslated region of the Sema3A gene. They found that the Sema3A protein is secreted by osteocytes and promotes osteocyte survival through an autoregulatory loop. This loop was shown to operate through Sema3A acting on the sGC (soluble guanylate cyclase) signaling pathway. Importantly, the researchers were able to protect estrogen-deficient mice from bone loss by intravenously administering a small-molecule activator of sGC signaling. The findings suggest that targeting the Sema3A–sGC axis may be a viable therapeutic strategy to protect against bone loss due to aging.

Cell Metab.,
doi: 10.1016/j.cmet.2018.12.021

Autoregulatory loop of osteocytes via Sema3A



Estrogen induces expression of the osteoprotective protein semaphorin 3A (Sema3A), which acts on osteocytes to promote their survival and maintain bone homeostasis. An activator of soluble guanylate cyclase-cGMP signaling mimicked Sema3A action and ameliorated bone loss after ovariectomy.