The Shioda laboratory is interested in how exposure of pregnant women to toxic chemicals or nutritional changes affects health of their children throughout their lifespan and beyond generations. The Developmental Origins of Health and Diseases (DOHaD) hypothesis claims that exposure of fetuses in the uterus to various types of stresses may permanently damage the epigenetic mechanisms regulating gene expression in stem cells, increasing the risk of common adult-onset diseases including obesity and cancer. If epigenetic damages are introduced into the genome of germ cells, inheritable disorders may emerge without involving mutations in the genome. One of the major hurdles in the present research community of this field is the lack of effective and reliable models for mechanistic studies of the DOHaD phenomena. Taking advantage of the latest progress in reproductive and stem cell biology as well as the cutting-edge deep sequencing technology, our laboratory has been trying to develop human and mouse cell culture models of germline stem cells and gametes such as primordial germ cells (PGCs) and sperms using iPS cells.

In vitro production of primordial germ cells and gametes from human and mouse pluripotent stem cells

It is impossible to expose pregnant women or their fetuses to potentially disease-causing stresses for research purposes. In an effort to establish credible and effective surrogate models, we have been trying to generate human and mouse PGC-Like Cells (PGC-LCs), which are cell culture models of PGCs differentiated from the pluripotent iPS cells. Deep sequencing analyses of mouse PGC-LCs and gonadal natural PGCs for mRNA expression, DNA methylation, DNA hydroxymethylation, and histone modifications have demonstrated significant epigenomic and transcriptomal similarities between them, supporting the usefulness of PGC-LCs as a model for epigenomic research on germline cells. By genome-wide comparisons of the germline-specific epigenomic marks between human and mouse PGC-LCs and mouse natural PGCs, we have been evaluating the advantages and limitation of the use of the human PGC-LCs as a surrogate model of human natural PGCs. To examine effects of toxic agents on monoallelic gene expression in germline cells, we have generated mouse iPS cells whose paternal and maternal chromosomes are derived from Mus spretus and Mus musculus, respectively, by interspecific in vitro fertilization. Taking advantage of the rich SNPs between these two distant species of Mus, which appear at approximately every 100 bp in their nucleotide base sequences, we are presently developing a deep sequencing pipeline for sensitive and quantitative determination of monoallelic gene expression in these iPS cells, their differentiated products such as PGC-LCs, and various tissues of animals generated by tetraploid complementation. Monoallelic gene expression will be further examined in the context of single cell analysis, which may...
reveal significant intercellular heterogeneity among normal cells and cellular responses to epimutagens.

**Environmental epigenomics**

Exposure of pregnant mice to the environmental toxic chemicals such as Bisphenol A or tributyltin causes transgenerationally transmittable disorders including breast hyperplasia or obesity. Collaborating with multiple extramural laboratories that perform animal exposure studies, our laboratory has been searching for possible epigenetic changes in germline cells as well as tissues showing the adult-onset phenotypes (e.g., mammary glands, adipocytes, and mesenchymal stem cells). The goal of these collaborative projects is to identify toxicant-induced “epigenetic lesions” that are responsible for the late-onset and/or transgenerational disease phenotypes in the genomes of the exposed fetuses and their progenies. For example, exposure of pregnant mice to tributyltin, a commonly used anti-fouling agent, causes transgenerationally transmittable obesity of the offspring. Tributyltin is a strong PPAR-γ agonist, and the transgenerational obesity is also caused by exposure of pregnant mice to rosiglitazone, a clinically used anti-diabetic drug and a PPAR agonist. The mesenchymal stem cells isolated from these obese animals tend to differentiate into the adipocytic lineage at the expense of osteogenic lineage. Our recent studies, which we are conducting in collaboration with Dr. Bruce Blumberg, have identified epigenetic aberrations caused by the in utero exposure to the PPAR agonists at regions relevant to regulation of mitochondrial functions.

**Selected Publications:**


