【Symposium 2】

S2-1 Three dimensional and multi-cellular culture model for analyzing vascular diseases

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In early stage of atherosclerosis, infiltration of blood leukocytes especially monocytes across vascular endothelial cells (ECs) in intima is thought to be key events to disease progression. We have analyzed two major junctional proteins, PECAM-1 and VE-cadherin in ECs during trans-endothelial migration (TEM) of monocytes in 3 dimensional multi-cellular culture model. A GFP-tagged PECAM-1 was expressed in IL-1beta-stimulated human umbilical vein endothelial cells. Some fluctuations of PECAM-1-GFP fluorescence at junctional region were observed in ECs without monocytes, indicating the constitutive PECAM-1 trafficking in endothelial membranes. Live-cell imaging and quantitative image analysis showed a gradual and continuous accumulation of PECAM-1 at the TEM spot for ～20 min after TEM, which was seen even after monocytes left the spot. Significant reduction of PECAM-1 was observed at neighboring cytoplasm near the TEM spot, suggesting that this region provides a source for PECAM-1 accumulation. The accumulation was not seen at junctional spot without TEM, indicating that TEM itself induces the accumulation. Flow cytometric analysis demonstrated an increased surface expression of PECAM-1 and a decreased surface expression of VE-cadherin on ECs co-incubated with monocytes. These data suggest a possible positive-feedback regulation of TEM in which a single TEM event induces conformational changes of endothelial junctions, i.e. PECAM-1 accumulation and VE-cadherin reduction, both of which can pave the way to make easy for following monocytes to infiltrate by enhanced homophilic binding between monocyte-endothelial PECAM-1, and impaired barrier integrity, respectively.

S2-2 Animal experiments related to development of artery biomodels

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Cerebral aneurysm is one of the most severe disease for the cause of death if it is rupture. The operation (treatment) needs medical devices such as coil and stent. The designs of these medical devices strongly lead the results of the treatment. And the activities of training, pre-operation simulation and education using the devices will increase the success rate of operation. The biomodels will show and increase the quantitative quality of these devices and activities with repeatability. We have developed a biomodel using PVA-H for long time. The PVA-H model has a proper friction coefficient with metal and choose a wide range of visco-elasticity when compared to silicone model. Animal experiments are used for evaluation of the quality of biomodels. In this paper, using viscoelastic measurements, tensile tests, and circulation test, the comparisons of the results were performed to show the advantage and disadvantage of the model experiments.

The results show that the model has a good consistent with the geometrical reconstruction. However, the final goal of the operation is to cover endothelial cells (endothelialization) and so the current model still needs developments. In conclusion, animal experiments are required to evaluate the biomodel and to complement each other.

S2-3 REDEEM – Re-education Program for Biomedical Engineering

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REDEEM is a re-education program for industrial engineers to introduce and to get acquaintance of the basic knowledge and way of thinking of medicine, organized at Tohoku University for more than 15 years. A regular course of the REDEEM consists of 51 unit lectures and 20 units of animal experiments for one year. A candidate who completes the full course including lectures as well as experiments is awarded a certificate and full credit of the lectures of the doctorate course of the Graduate School of Biomedical Engineering, Tohoku University.

Formal education for the biomedical engineering has not been well promoted in Japan. Our Graduate School is only one dedicated graduate school for biomedical engineering in Japan for more than 9 years, although the development of biomedical engineering is crucial for Japan's rapidly progressing aging society and increase of needs for supporting medical cares by engineering. It was thought that animal experiment is mandatory to the re-education for engineers, because most of them lack experiences to manipulate real animals during their engineering education. The experiments include three days of molecular and cellular biological experiments, such as extraction of DNA, PCR, and transfection of fluorescent protein genes to cultured cells. For the last two days, a modified Langendorff experiment is demonstrated to understand the cardiac physiology, and systemic dissection of a rabbit is conducted by the engineers. This is a unique course provided to the non-medical specialists which is useful to widen their views and at the same time to reduce mental and psychological barrier to deal with real living animal when they are engaged in the biomedical development and to collaborate with medical partners in the joint development studies of medical devices and system.

S2-4 Medical device development coordinated with animal experiment

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Most of the medical devices used in Japan are imported from overseas countries due to the reason of weak industrialization mechanism of medical devices in Japan. One of the problems is that clinical needs are not transferred smoothly to the manufacturing scene. As a result, medical professionals mostly feel difficulties to use the Japanese made device and employ the excellent devices produced in USA and other oversea countries.

To achieve a strong commercialization of medical devices, there is the necessity to provide matching opportunities and an environment for close collaboration between medical doctors and engineers. However, it is still very difficult to fuse them due to disciplinary boundaries and different working priorities between the medical and engineering fields in Japan. This leads to the question in which way these barriers could be exceeded to enable collaboration between medical and the engineering field. Therefore, we need to create a platform where medical professionals enable to get in touch with the engineers to find out the subject of development of devices useful in the clinical institutions. Then the medical professionals start the development closely with the engineers based on the mutual understanding of clinical purpose and technological feasibility.

When the classification of device is more than two, animal experiment is definitely required to verify the performance and safety in the preclinical phase. However the expertise of animal experiment is not sufficient to contribute to the device development. The future improvement of infrastructure and personnel education in the area of animal experiment is strongly desirable.

Animal experiment for development of Biodegradable medical devices ～ Challenges while fumlbig Until now and from now ～

S2-5

○ Tsutomu Sano (Consortium member: Yukihiko Shibata, Unpei Matsui, Kazunobu Hashigawa, Makoto Inoue, Akira Miyamoto)

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