LbL Assemblies Using Van der Waals or Affinity Interaction and Their Application

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The design and control of substrate surfaces with nanometer- or micrometer-sized polymer films are of considerable interest for both fundamental and applied studies in the biomedical field because of the required surface properties. The layer-by-layer (LbL) technique was discovered in 1991 by Decher and co-workers for the fabrication of polymer multilayers constructed mainly through electrostatic interaction [1]. We have extended the scope and applicability of this LbL assembly by introducing molecularly regular conformations of polymers or proteins by employing for the first time weak interactions, such as der Waals interactions [2] and biological recognition [3] (**Figure 1**). Since these weak interactions are the sum of the attractive or repulsive forces between parts of the same molecule, they allow macromolecules to be easily arranged into the most stable conformation in a LbL film. We have achieved stereocomplex LbL formations of stereoregular polymers and their application for stereospecific template polymerization and nanomaterials [4,5]. We have also reported for the first time extracellular matrix (ECM) multilayers focused on fibronectin (FN) using biologically specific recognition. By using the ECM multilayers, three-dimensional (3D) cellular multilayers could be developed to apply for tissue engineering and pharmaceutical application [6].

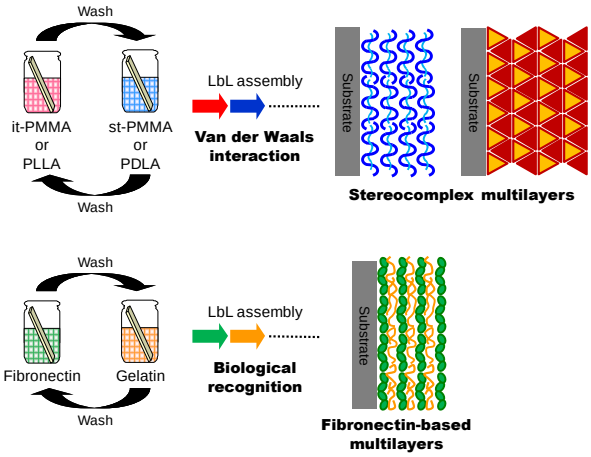

Figure 1. Schematic illustration of the LbL assemblies using van der Waals interactions and biological recognition [7].

ECM Nanofilms for 3D-Cell Chips

We have developed a simple and unique bottom-up approach, hierarchical cell manipulation technique, using nanometer-sized LbL films consisting of fibronectin and gelatin (FN-G) as a nano-ECM (**Figure 2**) [3]. The FN-G nanofilms were prepared

directly on the cell surface, and we discovered that at least 6 nm thick FN-G films acted as a stable adhesive surface for adhesion of the second cell layer. The multilayered constructs like a blood vessel wall structure indicated almost the same drug response as *in vivo* natural blood vessel, suggesting the possibility to use as an *in vitro* blood vessel model to analyze drug response [6b]. Recently, we also developed a rapid bottom-up approach, cell-accumulation technique, by a single cell coating using FN-G nanofilms, because the fabrication of two-layers (2L) was limitation through the above technique due to the time required for stable cell adhesion [6a]. This rapid approach easily provided approximately ten to twenty-layered (over 100 μm) 3D-tissues after only one day of incubation. Moreover, fully and homogeneously vascularized tissues of 1 cm width and 100 μm height were obtained by a sandwich culture of the endothelial cells. These hierarchical cell manipulations will be promising to achieve one of the dreams of biomedical field, *in vitro* creation of artificial 3D-tissue models [8].

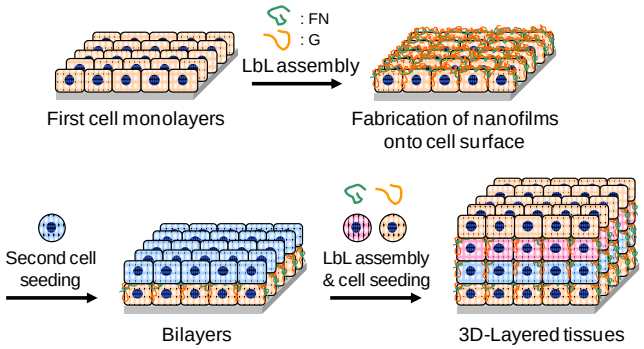

Figure 2. Fabrication of 3D-tissue models by hierarchical cell manipulation.

References

[1] a) Decher, G., Hong, J. D. *Makromol Chem Macromol Symp* **1991**, *46*, 321; b) Decher, G. *Science* **1997**, *277*, 1232; [2] a) Serizawa, T., Hamada, K., Kitayama, T., Fujimoto, N., Hatada, K., Akashi, M. *J. Am. Chem. Soc.* **2000**, *122*, 1891; b) Serizawa, T., Yamashita, H., Fujiwara, T., Kimura, Y., Akashi, M. *Macromolecules* **2001**, *34*, 1996; [3] a) Matsusaki, M., Kadowaki, K., Nakahara, Y., Akashi, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 4689; b) Nakahara, Y., Matsusaki, M., Akashi, M. *J. Biomater. Sci. Polymer Edn.* **2007**, *18*, 1565; [4] a) Serizawa, T., Hamada, K., Akashi, M. *Nature* **2004**, *429*, 52; b) Ajiro, H., Kamei, D., Akashi, M. *Macromolecules* **2009**, *42*, 3019; c) Akagi, T., Fujiwara, T., Akashi, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 5493; [5] a) Kida, T., Mouri, M., Akashi, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 7534; b) Kondo, K., Kida, T., Ogawa, Y., Arikawa, Y., Akashi, M. *J. Am. Chem. Soc.* **2010**, *132*, 8236; [6] a) Nishiguchi, A., Yoshida, H., Matsusaki, M., Akashi, M. *Adv. Mater.* **2011**, *23*, 3506; b) Matsusaki, M., Amemori, S., Kadowaki, K., Akashi, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 7557; [7] Matsusaki, M., Ajiro, H., Kida, T., Serizawa, T., Akashi, M. *Adv. Mater.* **2012**, *24*, 454; [8] Matsusaki, M. *Bull. Chem. Soc. Jpn.* **2012**, *85*, 401.