

# Coating of Single Cells towards Biomedical Applications



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## Introduction

In 2002, a pioneering work on single cell coating with macromolecules through layer-by-layer (LbL) method was published in Langmuir [1]. Yeast cells were alternately coated with cationic and anionic macromolecules. Even after coating, the cells still survived. Inspired by the work, multilayered macromolecules have been used for coating various types of microbial cells and endospores [2]. Although the survival of microbial cells in the artificial coat was interesting of itself, the impact of works was under evaluated in the biomedical fields because the method was limited to microbial cells and the macromolecular coating had no particular roles. The two limitations have been gradually solved by developing functional coating materials and applying the method to mammalian cells. The function of coating materials was mainly improved by shifting from organic macromolecules to inorganic materials, in other words, from soft to hard materials Tang et al. [3-6]. crystalized calcium phosphate on the multilayer-coated yeast cells, leading to rigid artificial shells [7]. Choi et al. synthesized silica on the multilayer-coated yeast cells in a biomimetic manner, which was the first report on coating living cells with covalent bonded inorganic materials [8-10]. And chrollera cells were coated with Titania using catalytic peptides [11].

The strong coating has provided native cells with superior properties which were beneficial for protecting the cells and changing inherent cellular behaviors. For instance, coated cells survived longer than native cells under unfavorable conditions and the artificial shell protected the cells from foreign aggressions. The cell division could be retarded presumably because a physical barrier caused by the shell suppressed the cell division and decrease permeability of nutrients across the coats. Although organic macromolecules are mostly weaker than inorganic materials, strong organic materials also have been developed to coat yeast cells. For example, polydopamine inspired by adhesive proteins in mussels and iron ion-tannic acid complex inspired by wine staining were successfully applicable to coating microbial cells [12,13]. The organic coats were capable of protecting cells and changing cellular behaviors.

On the other hand, cell-coating methods have been modified to be more biocompatible and applied to mammalian cells which were considered more difficult to manipulate with chemical treatments because the cells are more fragile than microbial cells. Despite the disadvantage, various types of LbL multilayers were used for coating mammalian cells such as red blood cells [14], fibroblasts [15], mesenchymal stem cells [16], breast cancer cells [17], and lymphocytes [18]. Chaikof et al. successfully coated pancreatic islets with poly-L-lysine linked to poly (ethylene glycol) [19,20]. The report showed us a strategy that toxic materials are also applicable to mammalian cells through the redaction of their toxicity by manipulating the materials biocompatibly. Akashi et al. coated human fibroblast cells, human umbilical vein endothelial cells, human hepatocellular carcinoma cells with multilayers composed of fibronectin (FN) and gelatin (G) through biospecific interactions [21]. By taking benefit of biocompatibility of biomaterials, the mammalian cells were coated without damage. The coated cells were packed into tissues with high density, which are applicable to tissue engineering. The coated cells were used for fabrication of artificial tissues with vascular networks, constructed by co-cultivation of human umbilical vein-derived vascular endothelial cells between normal human dermal fibroblasts [22]. The artificial tissue was implanted into nude mice, resulting in connectivity between host and implanted tissue. Choi et al. expanded biomimetic silica synthesis to HeLa cells, which was useful for protection and control of the cells [23]. While native HeLa cells are grown by attaching onto the surface of cell culture flask, silica-coated cells were floated in culture media. The cell in an adhesive nature was changed to be a floating cell, which implies that the coating changed an inherent nature of the cells. Human Jurkat T cells were coated with titania while maintaining their viability and inherent functions [24]. The iron ion-tannic acid complex was also applied to coating mammalian cells [25].

There are useful biomedical applications for coating of virus although the virus is not a living thing. Virus is considered as a promising vector for gene therapy because of their inherent

immunogenicity and strong transgene expression. However, it has some obstacles including preexisting antivector immunity and low efficiency of viral gene delivery. Tang et al. [26] coated Adenovirus serotype 5 with calcium phosphate and preexisting anti-Ad5 immunity was suppressed by the coating [26]. The other advantage of coated virus is increased thermal tolerance. The virus stabilized by silica coating was prolonged its infectivity by ~10-fold at room temperature while a similar result was obtained by storing native ones at 4°C [27]. Prolonged infectivity was mainly obtained by restricting molecular mobility of virion structure with silica nanoanchors. The enhanced thermal stability is practically important for long-term storage of virus vaccine. In commercial viewpoints, coated virus needs no refrigeration in its delivery, which is beneficial to save the cost in worldwide spread of vaccine. Human enterovirus 71 was also coated with alumina, which enhanced thermostability and immunogenicity [28].

Single cell coating is still approaching to more practical way towards biomedical applications. The coated cell has potential in the field of biomedical sciences. a) Protection of the cell would improve success rate of tissue implantation [3,4,6]. b) Enhanced viability gives a time enough to settle down implanted cells in a tissue of host body. The coating can also reduce immune-rejection by blocking direct contact between implanted cells and host tissue. c) Control of cell-cycle is beneficial to build up cell-based sensors which are integrated with electronic circuits and cells [9,12]. Durability of the sensors is mostly depended on viability of the cell and cell-cycles because cell death or cell growth will cause malfunction and bust the device. d) Coated virus could be used for a carrier for gene therapy because of high infectivity and low immune-rejection [26]. And stabilized virus is practically useful for long-term storage of vaccines because of its high thermal tolerance [27,28]. e) Coated cells have great potential in fundamental biological researches. For instance, the cells could be used for studying single cell behavior and cell-to-cell communication because the cells are isolated from outer environments including other cells [3,6]. Although there are still challenging issues on use of coated cells for biomedical applications, the strategies are evolving to more practical and biocompatible ways.

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