外国語要旨

学位論文題目　Study of fluorine-doped diamond like carbon films for application to intravascular devices.

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The coronary artery stent used for treatment of coronary artery disease is associated with stent thrombosis and restenosis. Stent thrombosis is a thrombotic occlusion and neointimal hyperplasia is the major cause of restenosis at the site of stent placement. In order to prevent these problems, a drug-eluting stent (DES) that is coated with a drug on the surface of the stent has been developed, but new problems, such as very late stent thrombosis occurring more than one year later, arose. Therefore, we focused on fluorinated diamond-like carbon (F-DLC) coatings, which is known to have antithrombotic properties, as a better coronary artery stent with the ability to prevent thrombotic and inflammatory events.

F-DLC films has fluorine added to diamond-like carbon (DLC) films. DLC is an amorphous carbon film having sp^3 bonds with a diamond-like structure of carbon and sp^2 bonds with a graphite-like structure. DLC has superior abrasion resistance, high hardness, and chemical inertness. It is known that F-DLC films inhibit platelet adhesion, and this can be applicable to medical devices.

A biomaterial that is placed in a blood vessel requires anti-thrombotic, anti-inflammatory, and cell proliferative properties. In this study, these functions were evaluated using platelets, leukocytes and vascular endothelial cells.

1. F-DLC films

Using radio frequency plasma-enhanced chemical vapor deposition (RF-PECVD), fluorine-incorporated diamond-like carbon (F-DLC) films were deposited on a stainless steel (SUS) 316L alloy, which is widely used as a substrate for medical equipment. a-SiC:H/a-C:H:Si film was deposited as an intermediate layer to prevent peeling and cracking.

F-DLC films were analyzed by XPS and Raman spectroscopy. The surface of the film contained a large amount of fluorine and had sp^2 bonds and sp^3 bonds like DLC.

2. Evaluation of antithrombogenicity using platelets

Platelets were exposed to F-DLC-coated and -uncoated SUS discs. Compared to F-DLC-uncoated SUS discs, the number of platelets adherent and the CD62P expression in reaction to F-DLC-coated SUS was significantly lower. CD62P is the platelet activation marker most closely associated with increased thrombotic risk and promotion of thrombus formation. In addition, CD62P binds to leukocyte P-selectin glycoprotein ligand-1 (PSGL-1) and activates the leukocytes that trigger the inflammatory response. It may imply inhibition of leukocyte accumulation, rolling, adhesion, and transmigration through interaction

with activated platelets by the F-DLC-coating, consequently preventing thrombosis and inflammation.

3. Evaluation of anti-inflammatory features using white blood cells

When granulocytes were exposed to F-DLC-coated and -uncoated SUS discs, the number of granulocytes adherent to the surface of disc coated with F-DLC was significantly decreased compared to F-DLC-uncoated SUS discs. Adhesion of leukocytes is the beginning of the inflammatory reaction, and anti-inflammatory features of F-DLC-coated materials are thus expected to suppress neointimal hyperplasia and prevent restenosis.

Leukocytes (lymphocytes, monocytes, and granulocytes) were exposed to FDLC-coated and -uncoated SUS discs, and the concentration levels of various cytokines in their supernatants were measured. The level of interleukin (IL)-8, a cytokine with potent neutrophil-activating and angiogenic activities, was found to be significantly increased in the supernatant from leukocytes exposed to FDLC-coated discs compared to those exposed to uncoated SUS discs. A higher level of IL-8 is thought to enhance inflammation, while promoting early coverage of the stent surface after stent placement.

4. Evaluation of cell proliferation using HUVECs

HUVECs (human umbilical vein endothelial cells) were seeded on F-DLC-coated and -uncoated SUS discs. F-DLC-coated SUS discs inhibited cell adhesion, although adherent cells continued to grow for four weeks. The supernatants of HUVECs cultured on F-DCL-coated and -uncoated SUS discs were collected, and the cytokine levels were measured. The levels of IL-10, an anti-inflammatory cytokine, were significantly elevated in the supernatant from HUVECs cultured on F-DLC-coated SUS discs compared to those cultured on F-DLC-uncoated ones.

The present study revealed that F-DLC had anti-thrombotic and anti-inflammatory properties, and affected the ability of cells to proliferate on the F-DLC-coated SUS discs. Development of devices, not only coronary artery stents but also intravascular devices, with high biocompatibility can be expected with F-DLC coatings.