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Surface Topographical Modification of Coronary Stent: A Review

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Abstract. Driven by the urge of mediating the inflammatory response from coronary stent implant to improve patency rates of the current coronary stent, concern has been focusing on reducing the risk of in-stent restenosis and thrombosis for long-term safety. Surface modification approach has been found to carry great potential due to the surface is the vital parts that act as a buffer layer between the biomaterial and the organic material like blood and vessel tissues. Nevertheless, manipulating cell response in situ using physical patterning is very complex as the exact mechanism were yet elucidated. Thus, the aim of this review is to summarise the recent efforts on modifying the surface topography of coronary stent at the micro- and nanometer scale with the purpose of inducing rapid in situ endothelialization to regenerate a healthy endothelium layer on biomaterial surface. In particular, a discussion on the surface patterns that have been investigated on cell selective behaviour together with the methods used to generate them are presented. Furthermore, the probable future work involving the surface modification of coronary stent were indicated.

1. Introduction

Cardiovascular diseases (CVD) are the leading cause of death globally, in 56 million deaths occurred worldwide during 2012, 17.5 million deaths was caused by cardiovascular diseases which are 31% of total deaths [1]. In other words, this statistic shows approximately one in every four deaths is caused by CVD worldwide. Therefore, currently, this issue is a global active issue as everyone is aiming on reducing the overall mortality from CVD. Generally, CVD is caused by the deposition of fatty material called plaque beneath the endothelium that comprises the innermost layer of a vessel, this condition called atherosclerosis [2,3]. This caused arterial narrowing and an inhibition of blood flow called stenosis. Currently, for stenosis cases a preferable treatment is angioplasty with stent placement; because this approach is the least invasive treatment after all compare to bypass surgery [4].

Stent is a scaffolding device that is introduced to cooperate with plain balloon angioplasty, in order to re-establish vascular patency and prevent elastic recoil of the vessel occur after plain balloon angioplasty that leads to restenosis [5]. However, as time passed it become apparent that bare metal stents too are restenotic due to intimal proliferation, thus ever since it has evolved to incorporate



biological functionality in order to mitigate the risk of restenosis by inhibiting the Neointimal hyperplasia and decrease immune responses initiated by injury caused by stent implantation [4,6].

The invention of coronary stenting has transformed the treatment of coronary artery disease to be safer and ultimately save a lot of life or at least extent the patient life successfully. However, there were still a lot of room for improvement in order to overcome the current limitation. For example, although the introduction of Drug Eluting Stent (DES) has successfully reduced the risk of restenosis but due to the delayed healing that causes by the anti-proliferation drug, it also increases the risk of late stent thrombosis [7]. Therefore, this has led to rapid innovation over the past decade in order to optimise the stent performance.

This review aims to provide valuable insight into the recent work on enhancing the attachment and proliferation of endothelial cells by modifying the surface topography of coronary stent. In particular, a discussion on the techniques that has been explored to develop the surface topography and those surface topographies that has been investigated are presented to aid the future research directions. Prior to this, an overview of the rationale of physical surface modification to attain in situ endothelialization will be presented.

2. Rationale of surface topographical modification

Restenosis and late-stent thrombosis remain as the most challenging limitation after stent placement. Restenosis is the event of re-narrowing of blood vessel which occurs when the excessive proliferation of smooth muscle cells in the response to acute vessel wall injury induced by angioplasty and stenting [8]. Thrombosis is the event of blot clot on the surface of implanted medical device due to the surface electrical charge differences between stent surface and the blood elements, and other surface properties might contribute to this such as surface topology that determine the binding properties between the stent surface and blood cells [9]. Drug-eluting stent has been invented in order to overcome the restenosis issue by locally releasing anti-proliferation agent to control and inhibit the proliferation of smooth muscle cells [10]. While this has successfully reduced the risk of restenosis, the use of DES has caused the late-stent thrombosis risk increases due to the delayed healing of the vessel wall as the anti-proliferation drug also inhibit the proliferation of endothelial cells which is a desire for healing purposes [5,11–13]. Moreover, all patient with DES placement needs to undergo dual antiplatelet therapy, which has unwanted complication such as the risk of bleeding [14]. Thus, the current research direction has shifted from inhibiting the proliferation of smooth muscle cells as shown by DES to stimulate healing by enhancing the adhesion and proliferation of endothelial cells. A lot of research have proven the value of functional and intact endothelium in the prevention of restenosis and thrombosis [15–17]. Thus, the current priority was to modify the stent in term of function that will induce the adhesion and proliferation of healthy endothelial cells.

In conjunction, surface topographical modification attempt to alter the surface properties and equip the surface with specific functions while not disturb or damage the bulk material properties which normally is the valuable mechanical properties of the material. The specific functions aforementioned are referred to the surface that has better biocompatibility which should show selective cell growth on those favourable cells and simultaneously prevent the rejection response by the immune system on a foreign object. In other words, the surface topographical modification is capable of minimising the thrombogenicity of the material while stimulating vessel wall healing by enhancing the adhesion, proliferation and migration of endothelial cells.

Therefore, the current active area of research on improving the performance of stent was on manipulate the surface topography such as surface roughness, surface pattern and feature size in order to optimise the biological responses. This has led to the efforts on developing non-thrombogenic surface modifications that facilitate vascular wall healing in a manner that leads to the generation of an intact and functional endothelium layer. Despite the fact that various biomaterial like 316L stainless steel, AISI 310, nitinol or biodegradable material is publicly regarded to be biocompatible, it is still needed to modify its surface properties such as surface roughness and feature size in order to improve their performance as vascular stent materials [18,19].

3. Methods of surface topographical modification

Surface topographical modification should just intent on minimal alteration to the topmost layer of the surface without affecting the bulk material properties. There are a vast variety of methods to perform surface topographical modification with the ultimate aim of achieving better blood compatibility and rapid endothelialization can be grouped into 2 categories. The categories are surface roughening approach and surface patterning approach, which are illustrated in figure 1 below. In general, surface roughening means to roughen the stent surface by creating uneven structure across the surface structure randomly and unspecific as illustrated in figure 1(a). On the other hand, Surface patterning approach is a modify the surface with specific tailor patterns that are more organised and almost identical throughout the surface as illustrated in figure 1(b) and 1(c) which is the cross-section view of surface patterning with arrays of spikes and grooves respectively. Table 1 demonstrated those common surface topographical modification methods.

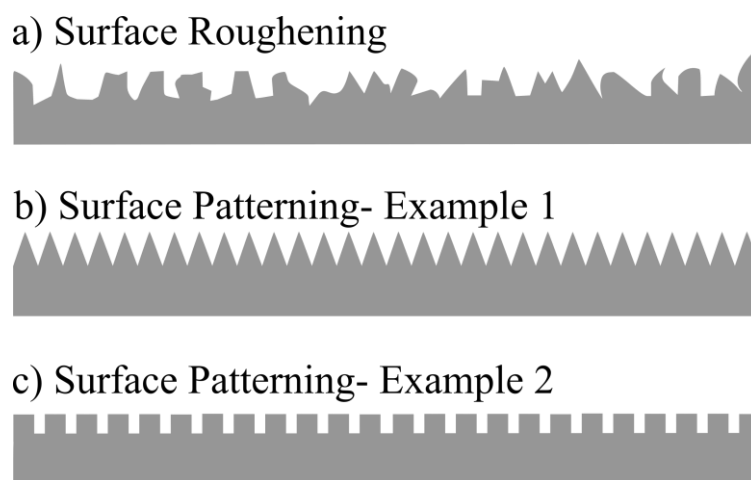


Figure 1. Illustration of the surface modification approaches.

4. Recent development of surface topographical modification

A vast variety of surface structures and methods have been explored to enhance the biocompatibility of coronary stent by developing nano/microstructure on the stent structure. Thus, this paper summarise the methods and the surface topographies that has been investigated and highlight the important and more recent studies. A summary table of all studies that have been reviewed in this paper is provided in 1.

In 2008, Lu et al. [20] speculated that rationally design surface structure with an elongated and aligned morphology which mimic the natural structure of a healthy vessel wall would enhance rapid endothelialization. Thus, they has introduced a novel plasma-based dry etching technique to modify surface structure into periodic arrays of grooves with high precision and reproducibility on titanium, and had compare the endothelial cell response on surfaces with the width of grooves equal to the ridge that is ranging from 750 nm to 100 μm [20].

In vitro study showed endothelial cell proliferated faster on the surface with the smallest feature size that is the grooves with 750 nm. Moreover, the cell guidance effect can be clearly noticed when the groove width is below 10 μm that show cellular alignment and elongated along the grooves. They also suggested that there is a potential for even smaller feature size on enhancing endothelial cell proliferation [20].

However, the effects of competitive adhesion and proliferation of smooth muscle cells should be assessed in order to draw a more conclusive finding. Besides, the surface modification of plasma-based dry etching process has altered not only the surface topology but also other surface properties such as the surface wettability and surface chemistry. Thus, it is hard to conclude that the smaller features have obvious effects on cell guidance from above studies.

Table 1. Fabrication methods employed to develop surface topographical features.

Approaches	Methods	Description
Surface Roughening - This method is to create a random surface structure to roughen surface that has low reproducibility and cannot form a specific surface pattern.	Chemical pickling [21]	Chemical pickling is an acid etching process, which can be used to roughen the surface and produce micropores on the surface when the acid solution is selected properly.
	Anodization [22]	An electrochemical process that used to coat the surface with an anodic oxide. With proper parameter control, nanotube surface structure can be developed.
	Sandpaper one-directional grinding [21]	Sandpaper grinding is being used to roughen surface by creating micro scratch on the surface.
Surface Patterning – develop well define surface structure with specific patterns. Normally have high reproducibility and precision.	Chemical vapour deposition [23]	A chemical process often used in the semiconductor industry to produce high-quality thin films. With a proper parameter control, the surface structure generated could be in nanoscale or microscale.
	Photo-lithography	Utilise the ultraviolet light to expose light sensitive photoresist and form patterns on the following the mask patterns then follow by direct etching to remove the substrate material then lastly the removal of the resist. Normally only at microscale level due to the limit of light diffraction.
	Electron-beam lithography and hot embossing [24]	Extent version of photolithography that utilises the high energy electrons to expose the electron sensitive resist. Widely used to create nanoscale surface features.
	Plasma dry etching [20]	Advanced micromachining techniques with high precision and reproducibility that can be used to create define and uniform patterns surface, popular in microelectronic fabrication. A Periodic array of microgrooves is one of the examples that can be produced using this method.
	Reactive ion etching [25]	A dry etching technology uses chemically reactive plasma to remove material. Widely used in microfabrication. Can be used to form predefine patterns with high precision.
	Laser Surface Engineering [19,25]	Nanosecond laser and femtosecond laser has been widely used to develop micro and nanostructure on the surface. Either direct write surface patterning or laser induces periodic surface structuring.

Therefore, in 2009, Shen et al. [21] had tried to study the solo effect of surface feature sizes on endothelialization by controlling the surface wettability and surface chemistry by using nano-coating approach. They developed micropores and microgrooves surface features on biomedical nitinol alloy by using chemical pickling approach and sandpaper one-directional grinding approach respectively and the combination of both approaches was used to create the surface structure that composes of both micropores and microgrooves [21]. They also found out that micro-pores surface showed better cell adhesion than the surface patterned with micro-grooves, while surface patterned with both micropores and micro-grooves showed even better cell adhesion among all [21]. Moreover, the plasma nano-coating that had enhanced the surface hydrophilicity also showed better cell adhesion results compared with the surface without nano-coating. In contrary, Aktas et al. [27] found that there was no correlation between the wetting behaviour of substrate and cell adhesion behaviour.

Likewise, in 2012, Aktas et al. [27] highlighted the need to investigate the effects of each individual surface properties separately on endothelialization, this is because normally the surface modification technique not only alters the surface topography but also made changes to the surface chemistry and/or surface free energy at the same time. Thus, they have developed Al_2O_3 nanowires surface structure of different density by using chemical vapour deposition technique and investigated the selecting cell behaviour of both endothelial cells and smooth muscle cells [27]. They claimed that the chemical vapour deposition technique have the ability to develop surface topography of different roughness with the identical surface chemistry and wetting behaviour [27]. The nanowires having diameters in the range of 20 to 30 nm, the two surfaces density developed were having an average roughness (R_a) and maximum roughness (R_{max}) of 21 and 187 nm; and 29 and 272 nm respectively. Through the in-vitro studies, Aktas et al. [27] found that microstructured Al_2O_3 plates have better cell growth compare to nanostructured Al_2O_3 for both endothelial cells and smooth muscle cells. However, the low-density nanowires structured Al_2O_3 demonstrated the desired cell selective behaviour, which is favouring the adhesion and proliferation of endothelial cells while inhibiting the growth of smooth muscle cells. Since the low-density nanowires structure is showing lower aspect ratio when compare with high-density nanowires structure. Thus, Aktas et al. [27] suspected that the endothelial cells are favouring lower aspect ratio surface structure while smooth muscle cells are favouring high aspect ratio surface structure. This finding suggesting that surface topography plays an important role in manipulating the cell responses.

On the other hand, since the stent will be contacted with blood inside the vessel thus it is important to investigate the effect of the surface feature's changes onto blood cells too and compare its adhesion rate with the healing endothelial cells. Thus, in 2010, Csaderova et al. [24] has demonstrated that the nano-pillars surface structure on poly- ϵ -caprolactone (PCL) has a strong cell-selective effect on two different cell lines, which inhibiting the proliferation of fibroblast while enhancing the proliferation of the endothelial cell. They suggested that the cell-selective effect is caused by the reduction of available surface area generated by nano-pillars [24]. The nano-pillars with a diameter of around 105 nm, a depth around 116 nm and a pitch of 300nm were fabricated on silicon master by utilising the technique of electron-beam lithography and transferred to PCL substrate by a hot embossing technique.

Furthermore, in 2014, Lee et al. [12] has investigated the effects of surface morphology of nanotubular structure on cell selecting behaviour which include the cell spreading, proliferation and migration. These surface features were created through anodization onto Nitinol biomaterial as a coating. This nanotubular surface structure has shown it could enhance re-endothelialization by improving the spreading and migration of endothelial cells and diminish the neointimal hyperplasia by decreasing the proliferation, ECM production, and migration of smooth muscle cells. In addition, the nanotubular surface did not induce inflammation by observing the ICAM-1 expression in smooth muscle cells as compare to a flat surface. However, there was no proliferation of endothelial cells shown on the nanotubular structure by analysing the cell numbers. Thus, Lee et al. [22] suggested that further studies on optimising the diameter of the nanotube can be conducted in the future in order to improve the endothelial cells proliferation. Although the surface structure generated in this studies is not exactly the same with the surface structure developed by Csaderova [24] as mention above, but it clearly showing the same cell response which can be deduced that the nanotube-like structure does improve endothelialization. However, more studies have to be done on comparing this surface features with those with an array of grooves patterns in order to elucidate more conclusive results.

Moreover, at the same year, Vandrangi et al. [25] intended to fill the knowledge gap of how endothelial cells response towards with micrometre to sub-micrometre groove-based feature on titanium and silicon substrate. Thus, they employed the Ti Deep Reactive Ion Etching method and conventional Silicon micromachining techniques to develop periodic groove feature on titanium and silicon substrate respectively [25]. A highly uniform periodic groove array were precisely formed with nearly rectangular groove profiles that have groove width ranging from 0.5 to 50 μm with a groove depth of 1.3 μm and groove pitch equal to twice the groove width. In the thorough in-vitro studies, Vandrangi et al. [25] found that endothelial cells have shown favourable response on cell proliferation,

adhesion, function, and morphology with decreasing feature size on both patterned titanium and silicon substrate just that the titanium substrate is showing better cell response over silicon substrate at comparable feature size. Although this study has shown the most comprehensive in-vitro study on the effects of patterned substrate produced so far, it does suffer from a major drawback that it does not take account of smooth muscle cells nor does examine the cell response of smooth muscle cell compare to endothelial cells. This is very important in order to show the cell selective capability of the patterned surface features as the desired cell response is to inhibit the growth of smooth muscle cells will enhancing the proliferation of endothelial cells.

On the other hand, laser surface modification approach had been widely employed to develop surface topography with cell selective behaviour. Generally, those studies employed laser surface modification approach can be divided into two categories that are a direct-write modification and self-organizing effects modification. Direct-write modification approach is almost like laser milling which the surface patterns output is greatly depends on path of laser movement the generate defined pattern, while the self-organizing effects modification approach is an implicit process that the surface structure is being altered by using ultrashort pulse laser that normally develops induced surface structure where the dimension of the patterns is independent of the focused laser spot size such as cone-like protrusions and laser surface induced periodic structure.

The study of the endothelial cells' behaviour on surface features created by using nanosecond laser was first carried out by Li et al. [26] in 2013. They demonstrated that there was a significant increase in adhesion and proliferation of endothelial cells on laser treated surface with defined surface pattern and surface chemistry [26]. Besides, they showed that surface chemistry is one of the factors that have great influence on cell behaviour as from the in-vitro study showed when nitrogen assisted gas is employed during the laser surface structuring process, there were obvious changes in the surface chemistry and which ultimately contribute to the significant effects on cell response [26]. Similarly at the same year, Oberringer et al. [28] reported the use of femtosecond laser on creating direct write patterns of laser pulse spots array on 316L stainless steel which composed of micro and nano features and investigated the cell-surface interaction of endothelial cells and fibroblast with the ultimate aim of reducing the risk of thrombosis. They demonstrated that the surface with more nanofeatures had better performance on decreasing the proliferation of myofibroblast proliferation while not affecting the proliferation of the endothelial cell [28]. This study has led the priority focus of future study to focus on nanoscale features.

While for laser-induced surface structures, in 2015, Nozaki et al. [29] demonstrated that the nitinol surface composed of both periodic micro and nanostructures that were induced by femtosecond laser was capable of improving the morphology of endothelial cells and inhibit the adhesion of platelets cells. They showed that there was a contradiction on the surface wettability between the periodic microstructured surface and periodic nanostructured surface that induced by femtosecond laser [29]. Where the Nanostructures surface was hydrophilic and have successfully improved the morphology of endothelial cells, while the micro/nanostructures surface was hydrophobic and successfully prevent the adhesion of platelets cells. Similarly, in 2016, Liang et al. [19] has investigated on how to enhance rapid in-situ re-endothelialization of 316L stainless steel coronary stent by altering the surface features using femtosecond laser with the goal of mimicking the native micro and nano structure of vascular smooth muscle cell (SMC) wall. The biomimetic stent has been tested in-vivo in the iliac artery of the rabbit and the results showed that the bionic surface patterns do regulate the growth orientation and enhance the adhesion, proliferation, and migration of endothelial cells through cell guidance effect. Liang et al. [19] have demonstrated that the microgrooves of around 24 μm do enhance the stability of HUVECs on the surfaces by controlling the cell growth orientation, and the nanometer surface fibrillary structure of about 700 nm have guides the migration of the HUVECs. In the other words, this patterned surface has the potential for enhancing the re-endothelialization process and ultimately reduce the incident of restenosis and thrombosis. As this result has also been supported by McDaniel et al. [30], where the laser-induced surface structure by femtosecond laser was able to reduce the adhesion of monocytes cells.

Table 2. Summary of previous works on developing surface topographical features.

Methods	Substrate	Pattern & Dimension	Description	Author (year) [ref.]
Chemical vapour deposition (CVD) with nanosecond laser treatment	Al ₂ O ₃	Nanostructure with micro-craters. Micro-craters diameter: 45-50 µm with 100 nm depth and the spacing between craters is 150 µm.	Chemical vapour form nanostructures and nanosecond laser form micro-craters. Both surface structure managed to promote the adhesion and proliferation of endothelial cells and successfully reduced the adhesion of smooth muscle cells.	K Kiefer et al. (2016) [23]
Ti deep reactive ion etching (Ti DRIE)	Silicon and Titanium	Groove-based topography (micron to submicron). Groove widths: 0.5-50 µm, depth: 1.3 µm, pitch: twice the groove width	Successfully demonstrated the significant improvement in cellular adhesion, proliferation and morphology with decreasing feature size on patterned Ti substrates	P Vandrangi et al. (2014) [25]
Anodization	Nitinol	Upright nanotubular structure. Outer Diameter ≈ 110 nm	Successfully demonstrated the increased of endothelial cell spreading and migration and decreased of smooth muscle cell proliferation.	P P Lee et al. (2014) [22]
Chemical Vapour Deposition	Al ₂ O ₃	Nanostructured surface with nanowires feature Nanowire diameter: 20-30 nm	Low-density nanowires structured surface have cell selective behaviour of endothelial cells over smooth muscle cells.	C Aktas et al. (2012) [27]
Electron-beam lithography and hot embossing	Poly-ε-caprolactone	Nano-pillars Diameter: 105±5 nm, depth: 116±5 nm, pitch: 300 nm	The nano-pillars structures have shown cell selective behaviour of enhancing endothelial cells proliferation and inhibiting the proliferation of fibroblast.	L Csaderova et al. (2010) [24]
Chemical Pickling, Sandpaper grinding and plasma nano-coating	Nitinol	Micro-pores, micro-grooves, Surface roughness, Ra: 10 to 600 nm	Better cell adhesion on feature with both structure and with better hydrophilicity.	Y Shen et al. (2009) [21]
Plasma-based dry etching	Titanium	Mimic native vessel endothelial cell wall Periodic arrays of grooves. Groove and ridge: 750 nm to 100 µm	Nanometer- scale grooves structure has shown better performance on endothelialisation compares to micrometer-scale grooves structure as well as the random nanostructure control.	J Lu et al. (2008) [20]
Femtosecond laser	316LSS	Mimic native SMC structure: Microgrooves (≈24 µm) and nanometer fibrillary structure (≈700 nm).	Successfully promote adhesion, proliferation and migration of endothelial cells on the bionic surface with patterns of vascular smooth muscle cells wall.	C Liang et al. (2016) [19]
	Platinum stainless steel (Pt: SS) and 316LSS	Laser-induced periodic surface structure (LIPSS) with roughness ranging from 29 nm to 50 nm.	Alter surface topology with chemical composition together. LIPSS successfully decreased the adhesion of monocytes that shows it's capable on reducing thrombosis occurring.	C McDaniel et al. (2015) [30]
	Nitinol	Laser-induced periodic surface structure (LIPSS), Hierarchical periodic nanostructures and micro/nanostructures surface.	Nanostructures surface was hydrophilic and has successfully improved the morphology of endothelial cells. While the micro/nanostructures surface was hydrophobic and successfully prevent the adhesion of platelets cells.	K Nozaki et al. (2015) [29]
	316LSS	Array of pulsed laser scan with different hatch distance, composed of micro and nanostructured surface.	Successfully decrease the proliferation of myofibroblast on laser treated surface while there are no significant effects on endothelial cells proliferation.	M Oberringer et al. (2013) [28]
	Stainless steel 304	Laser-induced periodic structure with linear and circular polarisation.	Successfully demonstrated that the laser treated surfaces have better biocompatibility than untreated surface.	C Y Lin et al. (2012) [31]
Nanosecond Laser	316LSS	Array of pulsed laser scan with different hatch distance, composed of micro and nanostructured surface.	Manage to alter the surface topography and surface chemistry in a single step with the help of nitrogen assist gas that has shown improvement in endothelialisation	L Li et al. (2013) [26]

5. Conclusions and future prospects

Overall, these reviews highlight the viability of manipulating cells-substrate response by surface topographical modification. Despite intensive research, the ideal stent surface topography with optimal cell response remain to be achieved. There were an obvious contradiction in the literature regarding the surface features dimension as some suggesting that nanoscale features were better than microscale features on modulating the selective cellular behaviour while others suggesting the other way round, thus further investigation is needed to refine the optimum features dimension and structure. From the literature, those bionic surface that mimics the native vascular wall is the quite promising approach, but either mimicking the endothelial cell wall or the smooth muscle cell wall has greater performance has to investigate further. Besides, in term of surface topography, many studies have investigated the width of groove and ridge, however, no study has been done on investigating the effects of the groove depth and the groove profile. In addition, the effect of surface topography on cell selective response have to be studied further on other widely used biomaterials of stent to proof its viability.

Besides, although plenty of surface topographical modification methods has been assessed on developing a better stent surface, the ideal surface topography method yet to be identified. This is because, almost all modification methods that alter the surface features is always accompanied with other surface properties changes such as surface chemistry, surface wettability, surface charge distribution etc. Thus, it is very difficult to investigate and elucidate the independent contribution of surface topography effects on collective cell growth. Some literature suggesting that applying a coating on top of different surface topography were able to isolate the surface topography effects by homogenised others surface properties. Thus, further research is needed in this particular area. Moreover, regarding the cell culture and assays, other than the responses of endothelial cells and smooth muscle cells, it is a must to investigate the thrombogenicity of the surface topography in order to demonstrate the cells-substrate response in details. Lastly, in vivo study is crucial as the complex in vivo environment may induce different result as in vitro study.

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