Colloquium on Polymer Science and Molecular Engineering Zhejiang University and the University of Chicago
12-16 April 2017

Mechanical adaptability of the MMP-responsive film improves the functionality of endothelial cell monolayer

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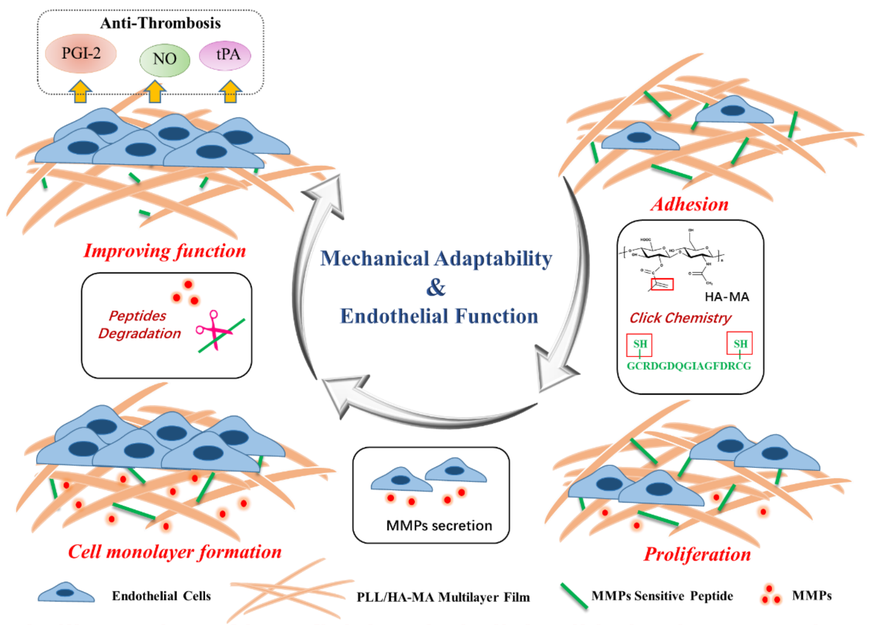
Abstract:

Extracellular matrix and cells are inherently in coordinating and adapting to each other during all physiological and pathological processes. Synthetic materials, show rarely reciprocal and spatiotemporal responses to cells, and lacking self-adapting properties as well. Here, polyelectrolyte multilayer films with mechanical adaptability are prepared through matrix metalloproteinase(MMP)-sensitive peptides crosslinked poly-lysine and methacrylated hyaluronic acid (PLL/HA-MA) multilayer films. The stiffness of the substrates can dynamically changed with cell-secreted MMPs. Compared with substrates with static stiffness, such stiffness-adaptive substrates shows the cell-controlled manner to benefit endothelial cell growth and consequent endothelial function of endothelial cell monolayer.

Introduction:

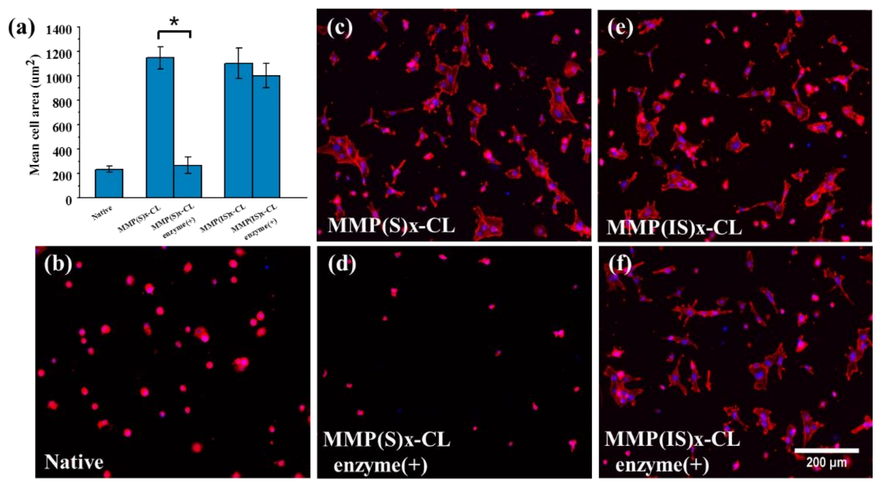


➢ **Schematic illustration of beneficial endothelial cell behaviors on substrate with mechanical adaptability.**

ECs have different biophysical demands from their residing microenvironment during different cellular stages. At early stage, substrates with increasing stiffness can promote EC adhesion, spreading and proliferation. However, the increasing stiffness was demonstrated by recent studies to lead to endothelium dysfunction or impairment, such as increasing permeability and decreasing NO release. In this work, a mechanical adaptability of thin polyelectrolyte film satisfying the process of endothelial progression was clarified. The adaptive stiffness was achieved by taking advantages of EC-secreted MMPs.

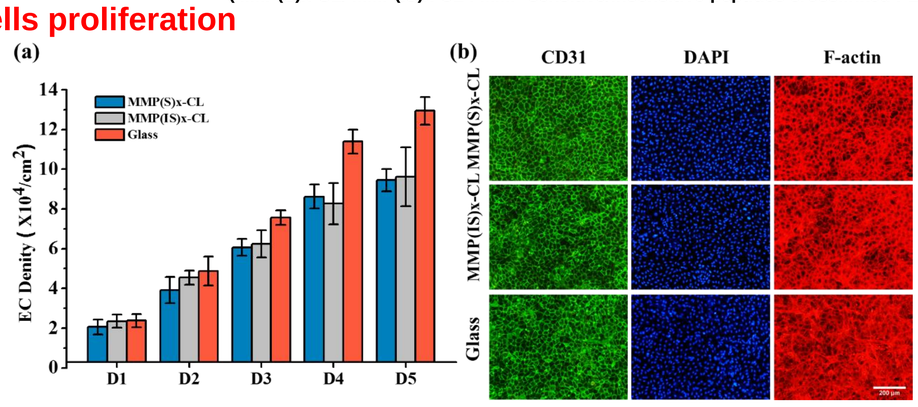
Results and Discussion:

➢ Cells adhesion



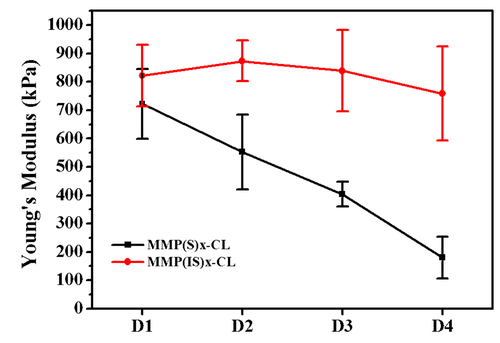
(MMP(S)x-CL/ MMP(IS)x-CL : MMP-sensitive/insensitive peptides crosslinked PLL/HA-MA film)

➢ Cells proliferation



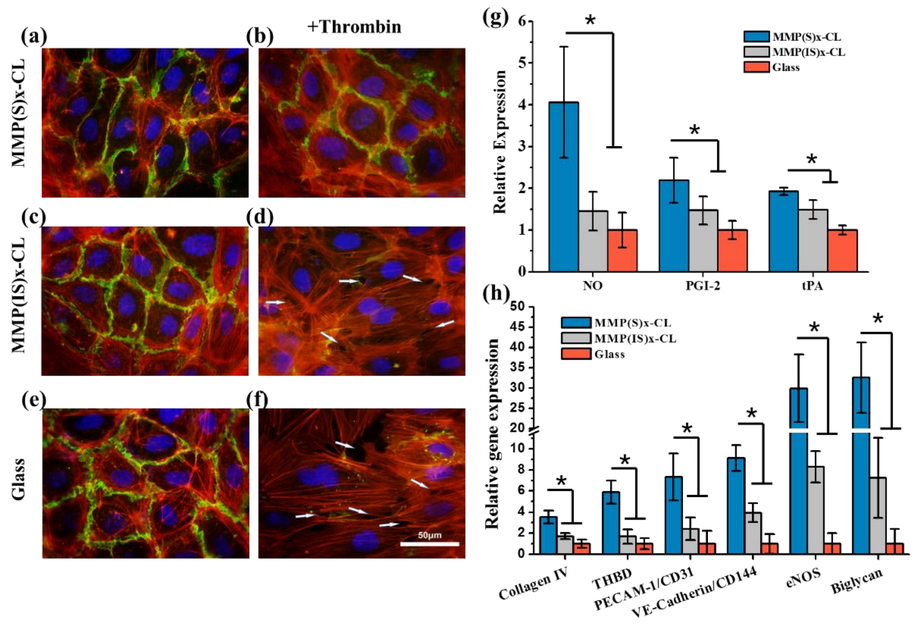
1. **ECs exhibited effective adhesion and proliferation.**
2. **Both MMP(S)x-CL and MMP(IS)x-CL films formed integrated EC monolayer.**

➢ Young's modulus variation during cell culture



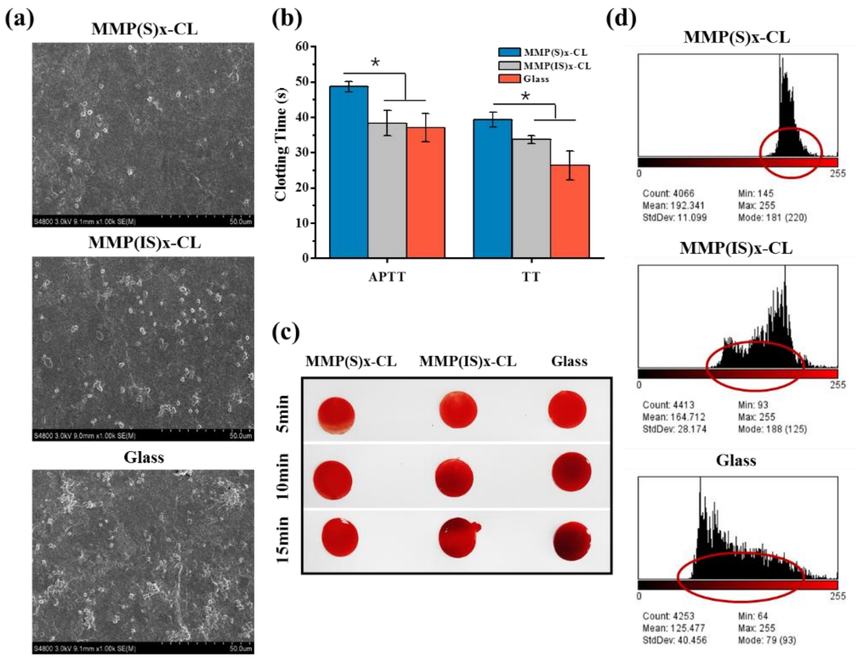
1. **During EC monolayer formation, the stiffness of MMP(S)x-CL film decreased.**
2. **While the stiffness of MMP(IS)x-CL films remained about the same level.**

➢ Fundamental work of EC monolayer



1. **Intact EC monolayer formed on MMP(S)x-CL films in response to thrombin.**
2. **Production of NO, PGI-2 and tPA was higher compared with the control.**
3. **Functional related genes expression increased on MMP(S)x-CL films .**

➢ Anticoagulant and antithrombotic function of EC monolayer



MMP(S)x-CL film with adaptive stiffness led to much less platelet adhesion and prolonged blood coagulation time compared with the control.

Conclusion:

A substrate with mechanical adaptability was developed by employing the PLL/MA-HA film and following crosslink with the MMPs-sensitive peptides via the thiol-ene click chemistry. The film was favoring the EC adhesion and growth, and forming intact EC monolayer. More important, significantly improved endothelial function of EC monolayer was demonstrated. Our concept work suggests very importance of mechanical adaptability of substrate on cell behaviors and the reciprocal and spatiotemporal dialogue between cells and biomaterials, which shed a light on a new design strategy for materials in the field of tissue engineering and regenerative medicine.

Acknowledgement

Financial support from Zhejiang Provincial Natural Science Foundation of China under Grant No. LR15E030002, the National Key Research and Development Program of China (2016YFC1102203), the National Natural Science Foundation of China (51333005, 21374095, 51573162), Research Fund for the Doctoral Program of Higher Education of China (20120101130013), and the Fundamental Research Funds for the Central Universities (2016QNA4031).

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