様　式　Ｃ－１９、Ｆ－１９－１、Ｚ－１９　（共通）

科学研究費助成事業　　研究成果報告書

平成　３０　年　　６　月　１９　日現在

機関番号：　１２１０２
研究種目：　若手研究(B)
研究期間：　2016～2017
課題番号：　１６Ｋ１６３９７

研究課題名（和文）Development of controllable nitric oxide-releasing injectable hydrogel with ROS scavenging effect for biomedical therapies

研究課題名（英文）Development of controllable nitric oxide-releasing injectable hydrogel with ROS scavenging effect for biomedical therapies

研究代表者

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交付決定額（研究期間全体）：（直接経費）　　3,000,000円

研究成果の概要（和文）：我々は一酸化窒素（NO）制御放出インジェクタブルレドックスハイドロゲル（NO-RIG）を開発した。NO-RIGは、過剰産生された活性酸素種（ROS）を除去するポリマー鎖と局所のNO量を調整するポリマー鎖からなるフラワータイプのポリイオンコンプレックスミセルが静電的的に架橋されることで形成される。心筋梗塞後、NO-RIGで治療することにより、単純にNOを放出する機能のみを持つゲルやROS除去能のみをもつゲルに比べて、梗塞巣の大きさは顕著に減少し、心機能の改善が見られた。更にNO-RIG治療はNOの持続的放出と抗酸化作用のバランスを調節することによって、著しく血管新生を増強することを見出した。

研究成果の概要（英文）：Research Summary: In this study, we developed a controllable nitric oxide (NO)-releasing injectable hydrogel (NO-RIG) formed by the electrostatic irreversibly crosslinking between the polyion complex flower-type micelles composing of functional polymers to scavenge overproduced reactive oxide species (ROS) and regulate the local NO expression level simultaneously. Treatment with NO-RIG remarkably decreased the infarction size and improved the heart function after myocardial infarction when compared to control injectable hydrogels, such as a simple NO-releasing or ROS-scavenging injectable gels. We found that NO-RIG treatment significantly enhanced the angiogenesis in mice through the regulation of the NO sustained release and redox equilibrium. NO- RIG presents high potential in preventing and treating cardiovascular diseases.
- This work was published in Biomaterials (2018) and presented in Polymer meeting, Gelsymposium, American chemistry Society Meeting

研究分野：　Biomaterials

キーワード：　injectable hydrogel　nitric oxide　myocardial infarction

１．研究開始当初の背景

Nitric oxide (NO) possesses various functions in cardiovascular diseases; however, due to an extremely short half-life and low bioavailability, its therapeutic application is limited. In inflamed tissues, overproduced reactive oxygen species (ROS) rapidly react with the endogenous NO, reducing its bioavailability.

２．研究の目的

Here, we developed a controllable NO-releasing injectable hydrogel (NO-RIG) formed by the electrostatic irreversibly crosslinking between the polyion complex flower-type micelles composing of functional polymers to scavenge overproduced ROS and regulate the local NO expression level simultaneously, as shown in Figure 1.

３．研究の方法

NO-RIG was prepared based on the instability of polyion complex under physiological conditions. Myocardial infarction (MI) model mice were prepared to evaluate the therapeutic efficacy of NO-RIG after intracardiac injection. MI model mice were prepared by ligation of the left anterior descending artery (LAD). After the position of LAD coronary artery was determined, a 6-0 suture was passed gently underneath the LAD coronary artery, the needle was placed carefully to avoid entering the cavity of the left ventricle, but at the same time care was taken to not be too superficial, as the suture would cut through the wall of the ventricle. The suture was then tied with four knots. The LAD occlusion was confirmed by the change of color (becoming pale) of the left ventricular anterior wall. Cardiac function was determined by echocardiogram imaging and histological assessment was carried out to evaluate the infarction size.

４．研究成果

After the intracardiac injection to mice, NO-RIG converted to gel via physiological temperature-responsive character, distributed homogeneously, and retained in the myocardial tissue for more than 10 d. Treatment with NO-RIG remarkably decreased the infarction size and improved the heart function such as the ejection fraction (EF) and fraction shortening (FS), which are important parameters of cardiac function, after myocardial infarction when compared to control injectable hydrogels, such as a simple NO-releasing or ROS-scavenging injectable gels, as shown in Figure 2. Only the mice treated with NO-RIG showed a statistically significant recovery of the thickness of myocardial tissues. The infarction size of the mice treated with NO-RIG was significantly smaller than in the other treated groups, although the infarction size was still relatively large (about 40%) due to the high severity of this infarction model. Alternatively, we repeated the experiment using a moderate MI model to confirm the therapeutic efficacy of NO-RIG in this moderate model. The results showed that the moderate MI mice treated with NO-RIG had a remarkable improvement in cardiac functions and a reduced the infarction size. The obtained results indicate that NO-RIG treatment can effectively protect the mice from MI when compared to other control injectable hydrogels. Importantly, we found that NO-RIG treatment significantly enhanced the angiogenesis and new blood vessels formation in mice through the regulation of the NO sustained release and redox equilibrium. In conclusion, NO-RIG presents high potential in preventing and treating cardiovascular diseases.

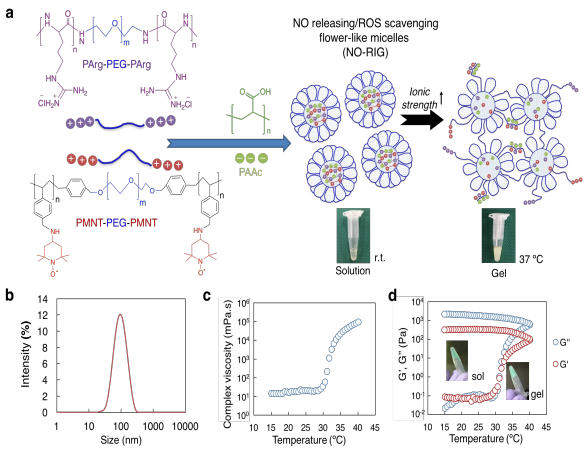

Figure 1. The schematic illustration and characterization of nitric oxide (NO)releasing/reactive oxygen species (ROS) scavenging injectable hydrogel (NO-RIG).

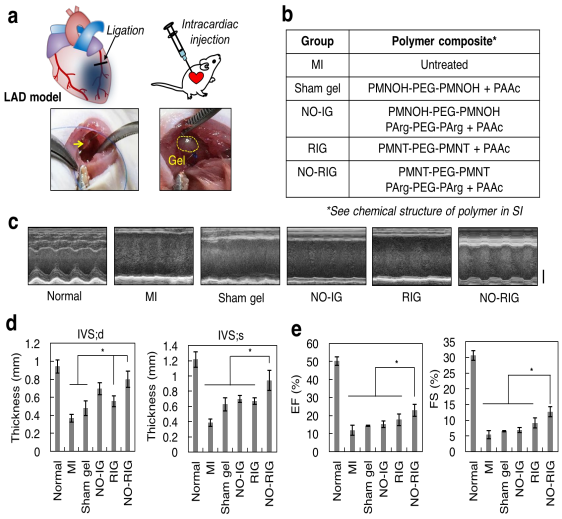

Figure 2. The therapeutic efficacy of NO-RIG in myocardial infarction (MI) mice

５．主な発表論文等
（研究代表者、研究分担者及び連携研究者には下線）

〔雑誌論文〕（計　1　件）

1. Long Binh Vong, Thang Q Bui, Tsutomu Tomita, Hiroki Sakamoto, Yuji Hiramatsu, Yukio Nagasaki. Novel angiogenesis therapeutics by redox injectable hydrogel - Regulation of local nitric oxide generation for effective cardiovascular therapy. ***Biomaterials***, 167, 143-152 (2018)

〔学会発表〕（計　6　件）

1. Long Binh Vong, Quoc Thang Bui, Hiroaki Sakamoto, Yuji Hiramatsu, and Yukio Nagasaki. Poly(arginine)-assisted redox injectable hydrogel for myocardial infarction model in mice. Gelsympo 2017
2. Long Binh Vong, Shinya Kimura and Yukio Nagasaki. Unexpectedly suppressed systemic adverse effect of oral cancer chemotherapeutics by intestinally accumulated antioxidative nanoparticle. Annual Meeting of Japanese Cancer Association 2017
3. Long Binh Vong and Yukio Nagasaki. Redox polymer nanotherapeutics: A safe and effective therapy in gastrointestinal disorder and cancer. International symposium on pure & applied chemistry (ispac) 2017
4. Long Binh Vong and Yukio Nagasaki, Maintaining the nitric oxide release by redox injectable hydrogel in myocardial infarction model mice 8th Joint Meeting of Society for Free Radical Research Australasia and Japan 2017
5. Long Binh Vong, Quoc Thang Bui, Tsutomu Tomita, Hiroaki Sakamoto, Yuji Hiramatsu, and Yukio Nagasaki, Novel Cardiovascular Therapeutics by Redox Injectable Hydrogel – Effective Maintenance of Local Nitric Oxide Generation to Induce Angiogenesis, The 3rd International Inovation in Cancer Research and Regenerative Medicine, (Ho Chi Minh city, Vietnam 2017)
6. Long Binh Vong, Thang Bui, Tsutomu Tomita, Hiroaki Sakamoto, Yuji Hiramatsu, Yukio Nagasaki, Novel Cardiovascular Therapeutics by Redox Injectable Hydrogel - Effective Maintenance of Local Nitric Oxide Generation to Induce Angiogenesis (254th American Chemical Society National Meeting, Washington DC. USA, 2017)

〔図書〕（計　1　件）

1. Long Binh Vong and Yukio Nagasaki, Redox polyion complex micelle-based injectable hydrogel as local ROS scavenging therapeutics, ACS Book chapter, under revision, 2018

〔産業財産権〕

○出願状況（計　1　件）

名称：ポリ（Ｌ－アルギニン）セグメント含有ブロック共重合体とポリアニオン性ポリマーのポリイオンコンプレックス
発明者：Nagasaki Yukio
権利者：Nagasaki Yukio, Kudo Shinpei, Hiramastu Yuji, Sakamoto Hiraki, Bui Quoc Thang, Vong Binh Long
種類：Patent
番号：PCT/JP2016/062062
出願年月日：2016/04/15
国内外の別：United States

６．研究組織

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