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Fundamental study on cancer therapy by blocking newborn blood vessels by magnetic force control

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Abstract

In this study, a cancer treatment by accumulating and aggregating ferromagnetic particles in newborn blood vessels was examined. It is necessary for this treatment to control dispersion-aggregation property of ferromagnetic particles. Ferromagnetic particles required in this method disperse at low magnetic field, aggregate at high magnetic field and maintain the aggregation even after removal of the magnetic field. In order to control the dispersion-aggregation property, the surface of magnetite particles was modified with higher fatty acids having different lengths. As a result, we succeeded to prepare propionic acid-modified magnetite particles that form irreversible aggregation by magnetic field. The model experiments simulating newborn blood vessels showed that these particles can block the flow by the magnetic field, and the blockage was maintained after removal of the magnetic field.

Keywords : cancer therapy, magnetite particles, surface modification, particle dispersion, particle aggregation

1. INTRODUCTION

The cancer treatment such as surgery, anticancer drug treatment and radiation therapy has been developed. However, we find some problems in those, for instance, invasiveness, side effects, and damage around cancer tissues [1, 2]. This motivates us to develop cancer therapy with less invasive side effects.

Fig. 1 shows a conceptual diagram of a cancer therapy by blocking newborn blood vessels with magnetic force control we have proposed. For cancer growth, it is necessary to develop the blood vessels carrying nutrients and oxygen. The blood vessels formed are called newborn blood vessels and they cause cancer metastasis [3]. In the cancer therapy by magnetic force control, ferromagnetic particles are accumulated and aggregated in the newborn blood vessels using an external magnetic field, resulting in blockage of the newborn blood vessels. Blocking newborn blood vessels prevents the cancer growth and metastasis.

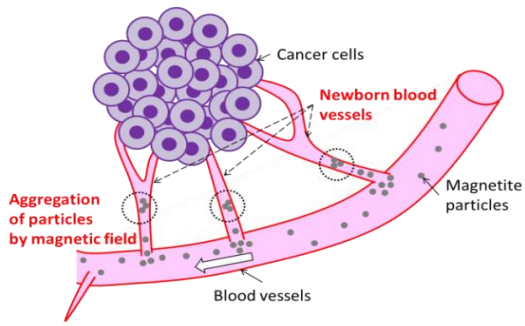

Fig. 1. Conceptual diagram of cancer therapy by blocking newborn blood vessels.

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The dynamics state of magnetite particle can be controlled by the external magnetic fields from outside of the patient's body. Furthermore, the magnetite particles are biocompatible that are used as a contrast medium of MRI (Magnetic Resonance Imaging). The proposed cancer treatment should have a lower side effect and provide the less invasive therapy.

In this therapy, it is necessary to aggregate particles in the blood vessel to block newborn blood vessels of which inner diameter is 10-40 μm [4]. On the other hand, since the minimum inner diameter of normal blood vessels is 10 μm, the particles should not form aggregation over 10 μm that may obstruct the normal blood vessels. So particle dispersion is necessary in normal blood vessels. Consequently in this therapy, dispersion and aggregation of the particles should be controlled in the blood vessels.

The procedure of the cancer therapy proposed in this study is described as follows. The treatment of the therapy is carried out in following 3 states. As the 1st step, magnetite particles are injected from the upstream of cancer tissues by a catheter. In the 2nd, the injected magnetite particles are accumulated in newborn blood vessels around cancer. In the 3rd, these accumulated particles are aggregated by a magnetic field to promote the blockage of the newborn blood vessels. The aggregation is to be maintained even after removal of the magnetic field. Considering a frequency of cancer treatment, the period for maintaining the aggregation is about 1 week.

In order to realize this therapy, there are three tasks. Task Ⅰ is to prepare ferromagnetic particles that can be controlled in dispersion and aggregation by magnetic force. Task Ⅱ is to design magnetic field for particle accumulation. Task Ⅲ is to design magnetic field for particle aggregation. In the cancer therapy, it is necessary

to apply a magnetic field to the deep part of the human body, which can be realized only with a superconducting magnet. Therefore, task Ⅱ and task Ⅲ include the design of superconducting magnet.

This study is positioned as a study on task I, and here we aimed to design the magnetite particles whose dispersion and aggregation can be controlled.

2. METHODOLOGY

In order to design magnetite particles whose dispersion and aggregation can be controlled by magnetic force, we utilized repulsive force originated from surface modifying group and magnetic attractive force. Fig. 2 shows dispersion and aggregation behavior of the ideal magnetite particles for this therapy.

The particles are dispersed by the surface modification lower than the threshold magnetic field H_0. On the other hand, the particles are aggregated by the magnetic interaction between particles higher than H_0. The threshold magnetic field H_0 can be controlled by the length of modifying group and the diameter of magnetite particles. In order to prevent aggregation in normal blood vessels, it is necessary to accumulate the particles in the newborn blood vessels in the dispersing state. In other words, it is necessary to accumulate particles in the newborn blood vessels without aggregation. So, the magnetic field for accumulation should be lower than H_0.

According to our previous study about the particle accumulation [5], the magnetite particles of 100 nm in diameter can be accumulated by applying the magnetic field around 250 mT. Thus, the threshold of magnetic field H_0 was set at 300 mT that is slightly larger than 250 mT.

Furthermore, it is necessary for this therapy to maintain the blockage of newborn blood vessels until cancer tissues undergo necrosis. The magnetite particles should maintain aggregation irreversibly even after removal of the magnetic field. It is considered that this irreversible aggregation can be realized by utilizing entanglement of modifying groups [6]. We aimed to design the surface the modified magnetite particles suitable for this cancer therapy and examined the effect of length of modifying group on the dispersion and aggregation behavior and formation of irreversible aggregation by application of magnetic field.

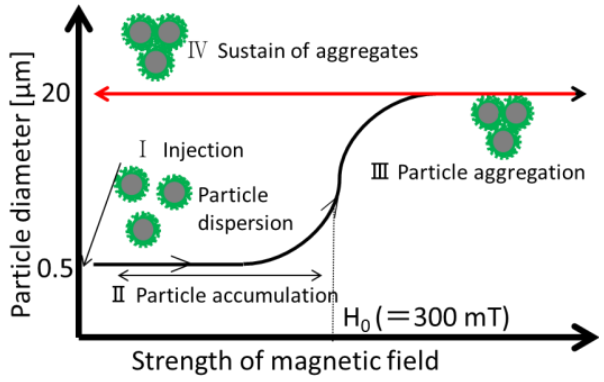

Fig. 2. Aggregation-dispersion dynamics of ideal particles.

3. EXPERIMENTAL METHOD

3.1. Surface modification with fatty acids

In order to investigate the effect of the length of the surface modifying group on the dispersion and aggregation behavior of magnetite particles, the surface modification of the particles was carried out with two kinds of fatty acids as shown in TABLE.1. The length of these modifying groups was calculated from the bond length and angle in Chemical Handbook [7].

The procedure for preparing the two surface modified particles is as follows. 2.2×10^{-4} mol of each fatty acid salt was dissolved in 100 mL of distilled water and the temperature was raised to 90℃ using a temperature controlled bath.

While stirring the fatty acid solution with a stirring blade, 0.10 g of magnetite particles (0.10 μm in diameter, MITSUI Mining & Smelting, Japan) was added and reacted for 1 hour at 90℃. The particle suspension was evenly divided into four centrifuge tubes and then each suspension was diluted to 50 mL with distilled water. The suspensions were cooled to room temperature and the solid was separated by centrifugation (3500 rpm, 10 min.). The supernatant was discarded and the particles were washed once with ethanol and toluene. After washing with toluene, the particles were dried at room temperature to obtain fatty acid modified magnetite particles. The prepared particles were dispersed in distilled water (5.0×10^2 ppm). These particle suspensions were used in the experiments described below.

3.2. Dispersion and aggregation behavior

The effect of the length of the modifying group was examined by comparing dispersion-aggregation behavior of the particles with different modifying groups. The particle size distribution was compared for 3 conditions that is without magnetic field, after application of magnetic field, and after 10 min. of ultrasonic irradiation followed by the two processes. Since the shear force of blood flow is smaller than that by ultrasonic irradiation, the aggregation which withstands ultrasonic water could be maintained in blood flow. The concentration of particle suspension was 500 ppm and the strength of the applied magnetic field were 200 mT and 400 mT, whereas the threshold H_0 was around 300 mT. A laser diffraction scattering particle size distribution analyzer (LA-920, HORIBA, Japan) was used for particle size measurement, and ultrasonic cleaner (CPX 1800-J, BRANSON Ultrasonies, USA) with output of 70 W and frequency of 40 kHz was used for ultrasonic irradiation.

3.3. Capillary blockage

In order to investigate the effectiveness of flow blockage by irreversible aggregation, the experiments were

TABLE 1
CHEMICAL FORMULA OF FATTY ACID USED FOR SURFACE MODIFICATION.

Fatty acid	Carbon number	Chemical formula	Molecular weight	Moleculer length
Propioric acid	3	CH_3CH_2COOH	74.1	0.45 nm
Stearic acid	16	$CH_3(CH_2)_{16}COOH$	284.5	2.25 nm

conducted using surface modified particles. Fig. 3 shows the flow path used in the experiment. The flow path consists of four glass tubes with inner diameter of 500 μm, that is 10 to 50 times larger than the newborn blood vessel. Three of them, A, B, and C simulate normal vessels, and the other D simulates a newborn blood vessel. PVA solution of whose viscosity 4.7 mPa·s simulating blood, and a static magnetic field of about 300 mT was applied by setting a neodymium magnet (φ30 mm×40 mm) under the glass tube which simulates the newborn blood vessel. This experiment was performed to confirm if a magnetic field makes the particles accumulate and aggregate in the newborn blood vessel. The flow rate in the glass tube was set about 1.8 mm/s simulating blood flow in capillary blood vessels.

25 mL of suspension of surface modified magnetite particles (5.0×10^2 ppm) was injected from the upstream of glass tube by syringe. They were successfully accumulated and aggregated in the glass tube. After that, methylene blue solution was flowed into the entire flow path at a flow rate of 1.8 mm/s, in order to confirm the blockage of the flow path. After confirming the blockage, the magnetic field was removed. The duration of the blockage was measured.

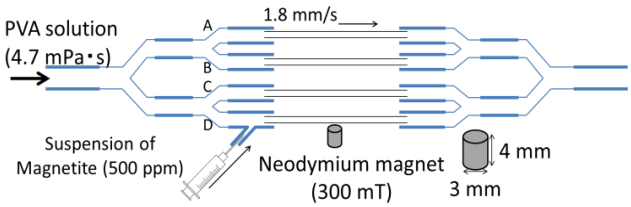

Fig. 3. Flow path simulating blood vessels used in the blockage experiment.

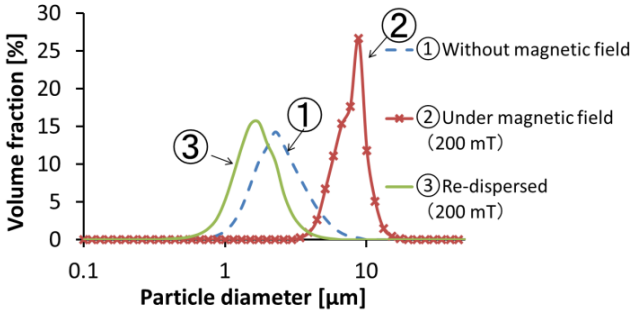

Fig. 4. Change in size distribution of propionic acid modified magnetite particles. (Magnetic field: 200 mT)

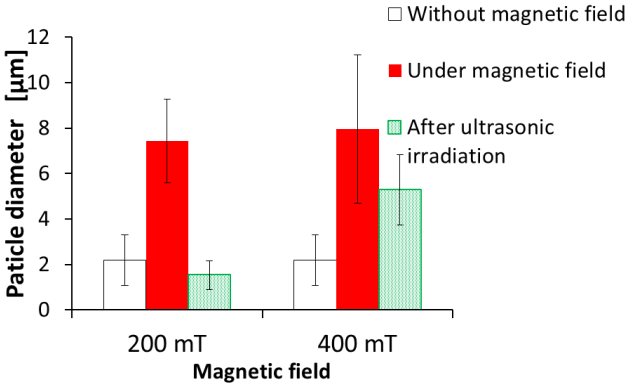

Fig. 5. Change in particle median diameter of propionic acid modified magnetite particles.

4. Result and Discussion

4.1. Influence of length of modifying group

Fig. 4 shows the change in the size distribution of propionic acid modified magnetite particles when the applied magnetic field is 200 mT. The particle diameter immediately after the application of magnetic field is larger than that before the application. It indicates that the propionic acid modified magnetite particles form aggregates when a magnetic field is applied. However, the size after ultrasonic irradiation is almost the same as that before magnetic field application. It means that the aggregation formed by applying the magnetic field was re-dispersed by ultrasonic irradiation.

Fig. 5 shows dispersion and aggregation behavior of propionic acid (carbon number: 3) modified magnetite particles (primary particle diameter: 0.10 μm) having relatively short molecular length when the applied magnetic field is 200 and 400 mT. The vertical axis is the median diameter, and the error bar is the standard deviation of the arithmetic average value. When the applied magnetic field is 200 mT, the median diameter after ultrasonic irradiation is close to that without magnetic field. This result shows that aggregation formed under 200 mT of magnetic field were easily redispersed by ultrasonic irradiation. On the other hand, when the applied magnetic field is 400 mT, the median diameter immediately after magnetic field application and that after ultrasonic irradiation were consistent with each other within the error range. These results indicate that the propionic acid modified magnetite particles form irreversible aggregation at 400 mT. This suggests the effectiveness of propionic acid modified magnetite particles for maintining of the blockage even after removal of magnetic field.

On the other hand, Fig. 6 shows the experimental results of stearic acid (carbon number: 18) modified magnetite particles (primary particle diameter: 0.10 μm) having a relatively long molecular length. It can be seen that the average particle size before magnetic field application is almost the same as that after ultrasonic irradiation at both the magnetic field of 200 mT and 400 mT. These results show that the stearic acid modified magnetite particles do not form irreversible aggregation, so the aggregation formed by applying magnetic field can disperse by ultrasonic irradiation. According to the experimental results above, surface modified magnetite particles with short modifying groups are more likely to form irreversible aggregation by application of magnetic field.

It is considered that the interparticle magnetic force among propionic acid modified magnetite particles is larger than that among stearic acid modified ones because the interparticle distances in the former particles are smaller than that of the latter ones.

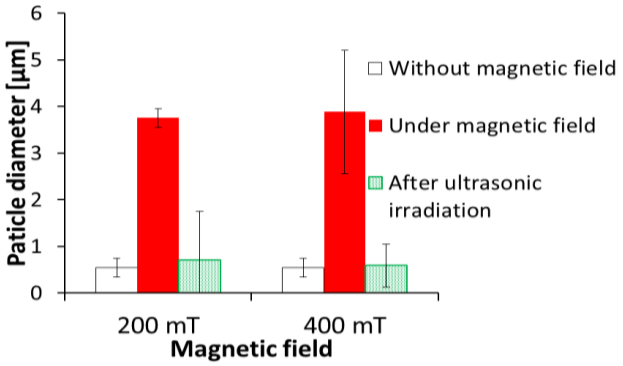

Fig. 6 Change in median particle diameter of stearic acid modified magnetite particles.

4.2. Blockage with irreversible aggregation

Based on the results, the effectiveness of irreversible aggregation of the flow blockage was investigated. Experiments were conducted with stearic propionic acid modified magnetite particles.

Fig. 7 shows the experimental results with the stearic acid modified magnetite particles. The blockage of flow was tested by flowing methylene blue solution into the flow path, in Fig. 7(a), methylene blue solution flows into A, B, and C simulating normal blood vessels, whereas does not into the D where the magnetic field was applied. This shows that the aggregation of the stearic acid modified magnetite particles blocked the flow path. However, three minutes after removal of the magnetic field shown in Fig. 7(b) indicates that methylene blue solution also flows into the D. It can be seen that stearic acid modified magnetite particles, did not form irreversible aggregation, and they couldn't keep the blockage of flow path.

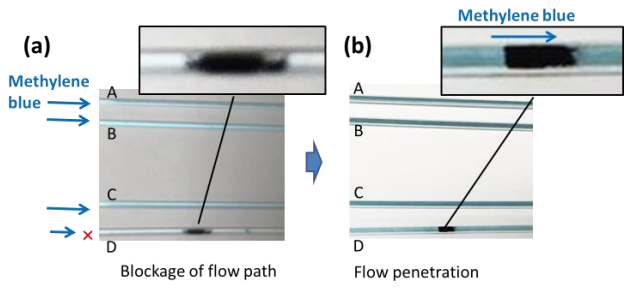

Fig. 7. Flow blockage with stearic acid modified particles, (a) after 0 min., (b) after 3 min. removal of magnetic field.

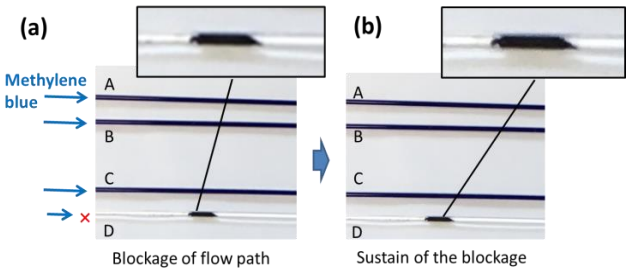

Fig. 8. Flow blockage with propionic acid modified particles (a) after 0 min., (b) after 60 min.

Fig. 8 shows the results with the propionic acid modified magnetite particles. In Fig. 8(a), the blockage of the flow path D was confirmed as same as the stearic acid modified magnetite particles. Furthermore, it was confirmed by Fig. 8(b) that methylene blue did not flow into path D even after 60 minutes removed of magnetic field. This suggests the effectiveness of irreversible aggregation on keeping the blockage of newborn blood vessels even after removal of the magnetic field.

5. SUMMARY

In this study, we proposed a new cancer therapy by accumulating and aggregating the magnetite particles in the newborn blood vessels around the cancer by magnetic force control. In order to realize this method, it is necessary to control dispersion and aggregation of the magnetite particles and to design the magnetic fields.

Firstly, the influence of the length of the surface modifying group on the dispersion and aggregation behavior was investigated in order to control dispersion and aggregation of magnetite particles by a magnetic field. Experimental results indicated that the magnetite particles modified with short modifying groups are more likely to form irreversible aggregation under the magnetic field. Based on the results, the model experiments simulating blood vessels with glass tubes were conducted, we confirmed that the blockage of the flow path was maintained even after removal of the magnetic field when the particles were modified by the short modifying groups.

The aim of this study was to prepare the particles dispersing lower than 300 mT as the threshold, whereas forming irreversible aggregates higher than 300 mT. It was concluded that propionic acid modified magnetite particles are more suitable for flow blockage that can form irreversible aggregates at a magnetic field of 400 mT, whereas re-dispersing at 200 mT.

In this study, we examined the blockage of blood vessels located close to the source of magnetic field, but in practical treatment it is necessary to block the newborn blood vessels existing deep inside the body in maximum 100 mm from the surface. According to previous study, it was calculated that particles can be accumulated to the diseased part deep in the body by using a rotating magnetic field [9]. For this control, a superconducting magnet or multiple ones are necessary. In the future, design of magnetic field for particle accumulation followed by aggregation in newborn blood vessels will be conducted with the superconducting solenoidal magnet.

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