【発表概要】*The 105 American Association for Cancer Research Annual meeting, San Diego, 2014,4*

A novel treatment for triple-negative breast cancer using intrinsic magnetized paclitaxel

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Background: We previously reported the identification of a novel nano-organic compound, EI236, an anti-cancer agent with intrinsic magnetic property. In addition to anti-cancer effect, its ferromagnetic property contributes to unique features. 1) It can be attracted by a magnet. 2) It can be visualized by magnetic resonance imaging (MRI). Hereby, we have identified the key mechanism that contributes to magnetism by X-ray crystallographic analysis, and succeeded in generating a novel paclitaxel with intrinsic magnetism; this is a single paclitaxel compound, and is *not* a paclitaxel encapsulated in micelle with magnetic particles. Our aim is to examine its effect on triple negative-breast cancer (TNBC) cells.

Method: The magnetization of the magnetized paclitaxel was measured with a superconducting quantum interference device (SQUID) (Quantum Design MPMS7 system). Breast cancer cells, MDA-MB-453 (TNBC) and MCF7 (Non-TNBC), were obtained from RIKEN Bioresource center. Cell proliferation assay was performed using a commercially available kit, XTT Cell Proliferation Assay Kit. Apoptotic cells were stained with APC Annexin V and 7-AAD, and measured by fluorescence activated cell sorting (FACS), to evaluate early and late apoptosis. Cell cycle analysis was performed using The Cycletest™ Plus DNA Reagent Kit and assessed using FACS.

Results: Plots of magnetization versus magnetic field revealed that the magnetized paclitaxel exhibits spontaneous magnetization in SQID. Magnetized paclitaxel was easily attracted by a commercial bar magnet. Magnetized paclitaxel

exhibits greater anti-cancer effect than original paclitaxel in TNBC and Non-TNBC cells in a dose-dependent manner. Magnetized paclitaxel induced apoptosis and G2/M arrest in cell cycle analysis in a dose-dependent manner, suggesting that magnetized paclitaxel retained the original anti-cancer property. In MRI T2 -weighted imaging, signal intensity was changed in a concentration-dependent manner with magnetized paclitaxel, but not with commercial available paclitaxel.

Conclusion: These results suggested that various conventional anti-cancer drugs might be similarly magnetized, leading to novel drug development in future cancer chemotherapy.

The 105 American Association for Cancer Research Annual meeting, San Diego, 2014,4

Development of thermochemotherapy using cisplatin and ferucarbotran (Resovist®) in head and neck cancer

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Background: Radical surgery for patients with advanced head and neck cancer causes dysfunctions as well as decreases quality of life. To overcome this issue, we developed a new combination therapy of cisplatin and inductive hyperthermia using ferucarbotran (Resovist®). Ferucarbotran, which is made of superparamagnetic iron oxide, generates heat when exposed to an alternating magnetic fields (AMF). Herein, we explored whether ferucarbotran could be used as a heat source for hyperthermia upon exposure to AMF in the presence of cisplatin . Our aim is to evaluate the simultaneous therapeutic efficacy of chemotherapy and inductive hyperthermia for head and neck cancer.

Materials and Methods: OSC-19 and HSC-3, human oral cancer cell lines, were used in this study. Cell proliferation was assessed by methyl thiazolyl tetrazorium (MTT) assay. The intracellular level of reactive oxygen species (ROS) was measured using fluorescent dye 2', 7'-dichlorodihydrofluorescein diacetate. Apoptotic cells were stained with Annexin V, allophycocyanin conjugate and 7-amino-actinomycin D, and measured by fluorescence activated cell sorting (FACS), to evaluate early and late apoptosis. . Thermal images and temperature were obtained by thermograpy and thermometer. Alternating magnetic fields were generated by a transistor-driven vertical coil at a frequency of 308 KHz and electric current (EC) 250 A.

Results: Ferucarbotran generated heat in a dose- and time-dependent manner when exposed to an AMF, suggesting that ferucarbotran could be used as a heat source for hyperthermia. As we expected, Cisplatin suppressed proliferation of OSC-19 and HSC-3 cells in a dose-dependent manner, not only furucarbtran. First, we performed MTT assay and ROS generation assay to evaluate whether hyperthermia effect enhanced anti-cancer effect in the presence of cisplatin. Simply incubation at 42 °C for one hour enhanced the anti-cancer effect and ROS generation in the presence of cisplatin. Cisplatin induced apoptosis of OSC-19 and HSC-3 cells in a dose-dependent manner. Ferucarbotran further promoted cisplatin-induced apoptosis compared to cisplatin alone, when exposed to an AMF for an hour. Thus, the combination of cisplatin with ferucarbotran /AMF was more effective than cisplatin alone, suggesting that we could reduce the amount of cisplatin in clinical usage.

Conclusion: Our findings suggest that combination therapy of cisplatin and ferucarbotran in an AMF may be used to develop a new combination therapy for head and neck cancer.

第38回日本頭頸部癌学会，東京，　2014, 6

MRI造影剤フェルカルボトランを用いた新しい温熱化学療法の開発

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【目的】現在臨床で使用されているMRI造影剤フェルカルボトランは、強力な磁性を有することから交流磁場下で火炎を使用せず速やかに温度上昇を示し、組織内加温が可能な薬剤である。本研究では、頭頸部癌細胞に対してフェルカルボトランを用いた温熱療法とシスプラチンとの相乗効果について検討したので報告する。

【方法】ヒト由来頭頸部癌細胞（OSC-19、HSC-3）を用いて実験した。抗腫瘍効果は、細胞毒性試験を用いて評価した。抗癌剤や温熱によって増強される活性酸素Reactive Oxygen Species（以下ROS）をROSアッセイで評価した。アポトーシスの評価は、フローサイトメトリーを用いて測定した。われわれが開発した交流磁場発生装置 を用いて、高周波誘導加熱方式でフェルカルボトランの温度上昇を検討した。**【結果】**交流磁場下で培養細胞に添加したフェルカルボトランは、42° C以上まで温度上昇を示した。頭頸部癌細胞において、シスプラチンに交流磁場を用いたフェルカルボトランによる温熱作用を併用することでアポトーシスは増強した。また、温熱療法とシスプラチンとの相乗効果でROSの産生が増強した。

【結語】フェルカルボトランは、交流磁場下で発熱し、温熱療法のための熱源物質として応用が可能である。また、シスプラチンと併用することで抗腫瘍効果の作用を増強させ新しい頭頸部癌の治療法となることが示唆された。

The 31st Japanese Congress of Thermal Medicine, Fukui, 2014,9

Development of combination therapy with cisplatin and hyperthermia generated with ferucarbotran (Resovist®) in an alternating magnetic field for oral cancer

Itaru Sato[1, 2], Kenji Mitsudo[1], Masanari Umemura[2], Hideyuki Nakashima[1], Mitomu Kioi[1], Haruki Eguchi[3], Yoshihiro Ishikawa[2] and Iwai Tohnai[1]

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Background: Radical surgery for patients with advanced oral cancer causes dysfunctions as well as decreases quality of life. To overcome this issue, we developed a new combination therapy of cisplatin and inductive hyperthermia using ferucarbotran (Resovist®). Ferucarbotran, which is made of superparamagnetic iron oxide, generates heat when exposed to an alternating magnetic fields (AMF). Herein, we explored whether ferucarbotran could be used as a heat source for hyperthermia upon exposure to AMF in the presence of cisplatin. Our aim is to evaluate the simultaneous therapeutic efficacy of chemotherapy and inductive hyperthermia for oral cancer.

Materials and Methods: OSC-19 and HSC-3, human oral cancer cell lines, were used in this study. Cell proliferation was assessed by methyl thiazolyl tetrazorium (MTT) assay. The intracellular level of reactive oxygen species (ROS) was measured using fluorescent dye 2', 7'-dichlorodihydrofluorescein diacetate. Apoptotic cells were stained with Annexin V, allophycocyanin conjugate and 7-amino-actinomycin D, and measured by fluorescence activated cell sorting (FACS), to evaluate early and late apoptosis. Thermal images and temperature were obtained by thermography and thermometer. AMFs were generated by a transistor-driven vertical coil at a frequency of 308 KHz and electric current

(EC) 250 A.

Results: Cisplatin inhibited proliferation of OSC-19 and HSC-3 cells in a dose-dependent manner. Simply heating the medium to 42.5 °C enhanced the effect of cisplatin. Similarly, ROS production was increased in the presence of cisplatin, and was further increased upon heating. Heating to 42.5 °C was also achieved in cell culture medium to which ferucarbotran had been added and then exposing the medium to alternating magnetic fields. Ferucarbotran-induced heating enhanced both early and late cellular apoptosis. Cell cycle analysis demonstrated that cisplatin decreased G0/G1, and increased G2/M accumulation. However, no further changes in cell cycle were induced when ferucarbotran-induced heating was observed.

Conclusion: Our findings suggest that combination therapy of cisplatin and ferucarbotran in an AMF may be used to develop a new combination therapy for oral cancer.

The 73rd Annual Meeting of the Japanese Cancer Association, Yokohama, 2014,9

A novel paclitaxel with intrinsic magnetism

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Background: We succeeded in generating a novel paclitaxel with intrinsic magnetism. This is a single paclitaxel compound, and is not a paclitaxel encapsulated in micelle with magnetic particles. Our aim is to examine its effect on breast cancer cells.

Method: MDA-MB-453, MDA-MB-231 and MCF7 were used. Cell proliferation was assessed by XTT assay. Apoptosis and cell cycle were analyzed by fluorescence activated cells sorting (FACS). To examine the feasibility of magnetized paclitaxel for magnet-guided delivery, we used a mouse model, in which MCF7 were grafted onto the legs. The accumulation of this compound by a permanent magnet was examined.

Result: We found that magnetized paclitaxel inhibited the proliferation of all cell lines and also increased apoptosis. This compound retained the characteristic anti-cancer mechanism of paclitaxel itself, i.e., induction of G2/M arrest. When a magnet was used, the accumulation of magnetized paclitaxel was further increased in tumor by histological evaluation.

Conclusion: Magnetized paclitaxel may enable us to develop novel strategies in breast cancer treatment, i.e. chemotherapy with controlled drug delivery with a single-drug compound.

The 88th Annual Meeting of The Japanese Pharmacological Society, Nagoya, 2015,3

Magnetized paclitaxel derivative for novel triple negative breast cancer therapy

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Background: Recently we generated a novel paclitaxel (PTX) with intrinsic magnetism (Magnetized-paclitaxel: M-PTX). M-PTX is a single PTX compound, and is not a PTX encapsulated in micelle with magnetic particles. In this study, we are developing a novel treatment with controlled drug delivery in triple negative breast cancer (TNBC).

Material and Method: MDA-MB-453 and MCF7 were used. Cell proliferation was assessed XTT Cell Proliferation Assay. Immunohistochemistry was performed to evaluate depolymerization of microtubules with anti-alpha-tubulin antibody in the presence of M-PTX or PTX. Cell cycle and apoptosis were analyzed by flow cytometry. To examine the feasibility of M-PTX for magnet-guided delivery in tumor, we used a TNBC mouse model.

Result: We found that M-PTX exhibited anti-cancer property and inhibited the depolymerization of microtubules. Also M-PTX induced G2/M arrest in cell cycle and cellular apoptosis with similar efficacy to PTX, suggesting that M-PTX retained the characteristic anti-cancer mechanism of PTX itself. M-PTX was accumulated by a magnet in vitro and in vivo.

Conclusion: M-PTX may enable us to develop novel treatment for TNBC, i.e. chemotherapy with controlled drug delivery with a single-drug compound.

The 88th Annual Meeting of The Japanese Pharmacological Society, Nagoya, 2015,3

Magnetized methotrexate derivative for novel anti-cancer therapy

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Background: We previously reported the generation of a novel paclitaxel derivative with intrinsic magnetism. Similarly, we have synthesized a novel derivative of methotrexate, a conventional drug for cancer and rheumatic diseases, with intrinsic magnetism (M-MTX). This is a single methotrexate paclitaxel compound and is not a methotrexate encapsulated in micelle with magnetic particles. We have examined whether M-MTX has both the magnetic and the anti-cancer property with similar efficacy to methotrexate.

Materials & Methods: The magnetic property of M-MTX was measured by Electron Spin Resonance (ESR) and Superconducting Quantum Interference Device (SQUID). MCF7, breast cancer cells were used. Cell proliferation was assessed by a commercially available kit, XTT Cell Proliferation Assay Kit (ATCC). Apoptosis was analyzed using fluorescence activated cell sorter (FACS).

Results: M-MTX was easily attracted by a neodium magnet. Both ESR and SQUID showed that M-MTX has an intrinsic magnetism. Furthermore, M-MTX inhibited cell proliferation and induced cellular apoptosis in MCF7 cell lines.

Conclusion: M-MTX may provide us a new strategy for cancer therapy, i.e., chemotherapy with magnetic drug delivery with a single agent.

The 92nd Annual Meeting of The Physiological Society of Japan, Kobe, 2014,3

A novel methotrexate derivative with intrinsic magnetism

Mayumi Katsumata[1], Masanari Umemura[1], Itaru Sato[1], Makoto Ohtake[1], Kayoko Oda[1], Akane Nagasako[1], Ayako Makino[1], Haruki Aoyama[1], Haruki Eguchi[2], Yoshihiro Ishikawa[1]

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Background: We have recently reported a novel anti-cancer compound with intrinsic magnetism (EI236). In addition to anti-cancer effect, EI236 has three features 1) EI236 is attracted by a magnet, i.e., magnetic drug delivery, 2) generating heat in an alternating current magnetic field, i.e., hyperthermic effect, and 3) a new contrast agent in magnetic resonance imaging (MRI), because of its magnetism. Based on these properties of EI236, we succeeded in generating a novel methotrexate derivative with intrinsic magnetism (m-MTX). It is well known that MTX is a commercially available and has been used as conventional drug for cancer and rheumatic diseases. In this study, we examined whether m-MTX has an intrinsic magnetism and the anti-cancer effect.

Materials & Methods: The magnetic property of m-MTX was measured by ESR (Electron Spin Resonance) and SQUID (Superconducting Quantum Interference Device). VX2, rabbit squamous cancer cells and MCF7, breast cancer cells, were used. To evaluate the m-MTX-induced cytotoxicity, cell proliferation was measured using commercially available kit (ATCC).

Results: M-MTX was easily accumulated by a permanent magnet in water. ESR and SQUID showed that m-MTX has an intrinsic magnetic property. Furthermore, m-MTX inhibited cell proliferation in both cells in a dose dependent manner.

Conclusion: M-MTX may enable us to develop novel strategies in cancer treatment, i.e., chemotherapy with controlled drug delivery with a single drug compound.

The 92nd Annual Meeting of The Physiological Society of Japan, Kobe, 2014,3

Transient receptor potential cation channel 3 (TRPC3) regulates proliferation and migration via phosphorylation of STAT5 in human melanoma

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Background: It is well known that melanoma has a poor prognosis due to its rapid progression and high metastatic ability. TRPC is activated upon changes in temperature or membrane voltage, and thus triggers various intracellular responses via cationic flux. Here, we have investigated whether TRPC3, which is universally expressed in human melanoma cells, regulates proliferation and/or migration of human melanoma cells.

Material: C8161 cells, a BRAF wild type human melanoma cell line, were used in this study. TRPC3 was inactivated either genetically by siRNA encoding TRPC3 or pharmacologically by Pyr3, a pyrazole compound that is known to selectively inhibit TRPC3.

Result: Genetical knockdown of TRPC3 significantly inhibited proliferation of C8161 cells ($p<0.0001$). Pharmacological inhibition with Pyr3 suppressed cell proliferation with a IC50 value of 12.99μM. Both knockdown of TRPC3 and Pyr3 significantly decreased path length of cell migration ($p<0.01$, $p<0.01$ respectively). Pyr3 also inhibited phosphorylation of signal transducer and activators of transcription (STAT) 5, suggesting that TRPC3-induced proliferation and migration were regulated by, at least in part, the JAK/STAT signaling pathway.

Conclusion: Inhibition of TRPC3 suppressed cell proliferation and migration in C8161 cells, suggesting that TRPC3 may be a novel target in human melanoma therapy in the future.

科研費報告書 必要書類

磁性パクリタキセル使用実験まとめ

2014年4月～2015年3(2)月分

M2 牧野紋子

2015/02/27

実験種類(2014,4～2015,3)

① 磁性パクリタキセルの実験 乳がん

※使用細胞　MCF7, MDA-MB-453, MDA-MB-231

・XTT assay…濃度・時間依存的に抗腫瘍効果あり。

・ Apoptosis 誘導評価…濃度依存的に誘導効果あり。(MCF7 だけ評価し難い結果)

・Cell cycle 変動評価…G2/M 期で細胞分裂が停止した。

・チューブリン蛍光染色…チューブリンが脱重合手前で停まっているのを観察。

・チューブリンアッセイ…重合度は上がったが、DMSO と同程度。手技ミス発見。

・磁石集積 in vivo…磁石に集まることが示唆された。

② 磁性パクリタキセルの実験　舌癌

※使用細胞　OSC-19

・XTT assay…濃度依存的に抗腫瘍効果あり。しかし、市販パクリタキセルと比較すると、その効果はとても低い。

1. 磁性パクリタキセルの抗腫瘍効果

※使用細胞: MDA-MB-453（ヒト由来トリプルネガティブ乳がん細胞), MDA-MB-231（ヒト由来トリプルネガティブ乳がん細胞), MCF7（ヒト由来エストロゲン受容体陽性乳がん細胞), OSC-19（ヒト由来扁平上皮癌細胞）

<背景>

先行実験に於いて、ヒト由来トリプルネガティブ乳がん細胞である MDA-MB-453、MDA-MB-231 とヒト由来エストロゲン受容体陽性（非トリプルネガティブ）乳がん細胞である MCF7 に対して、磁性パクリタキセルの抗腫瘍効果が XTT assay を用いて示されている。

<目的>

ヒト由来の乳がん細胞（トリプルネガティブのセルラインも非トリプルネガティブのセルラインも含める）に対する磁性パクリタキセルの抗腫瘍効果を示す。同時に、比較対象の市販のパクリタキセルの抗腫瘍効果と有意な差がないことを示す。(磁性化してもパクリタキセルの性質を保持できていることの証明)

磁性パクリタキセルの濃度や刺激時間を他の細胞種と揃えた実験を行い、論文の figure 用にする。

また、ヒト由来扁平上皮癌細胞 OSC-19 を用いて、乳がんだけでなく、舌癌にも効くことを証明する。

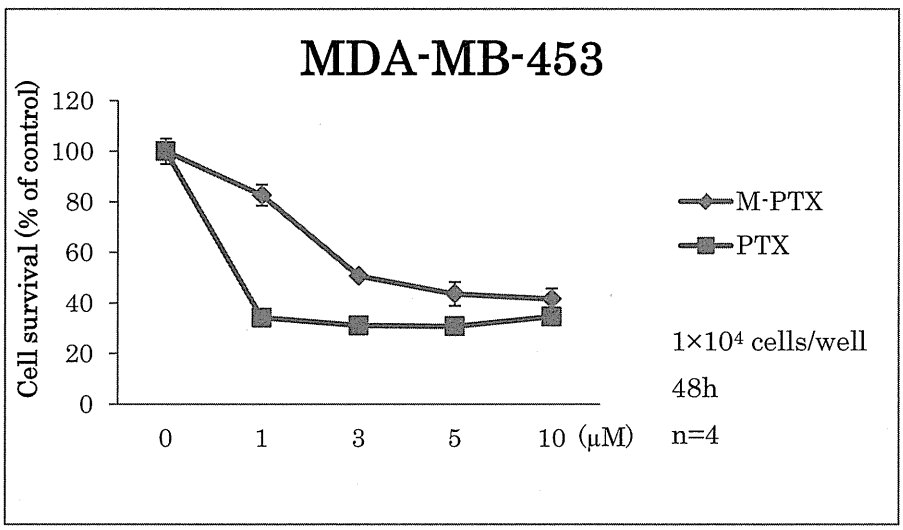
<方法>

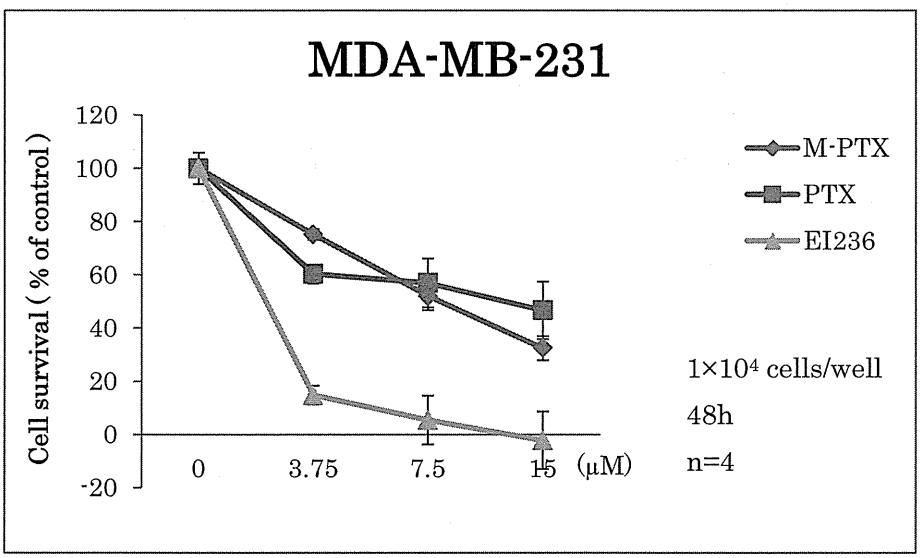
MDA-MB-453、MDA-MB-231、MCF7 の細胞を 96well plate に撒いた（n=4)。翌日、磁性パクリタキセルとパクリタキセルを細胞に投与した。その 24～48 時間後、activated-XTT 試薬を加え、2 時間後にプレートリーダーで吸光度を測定した。

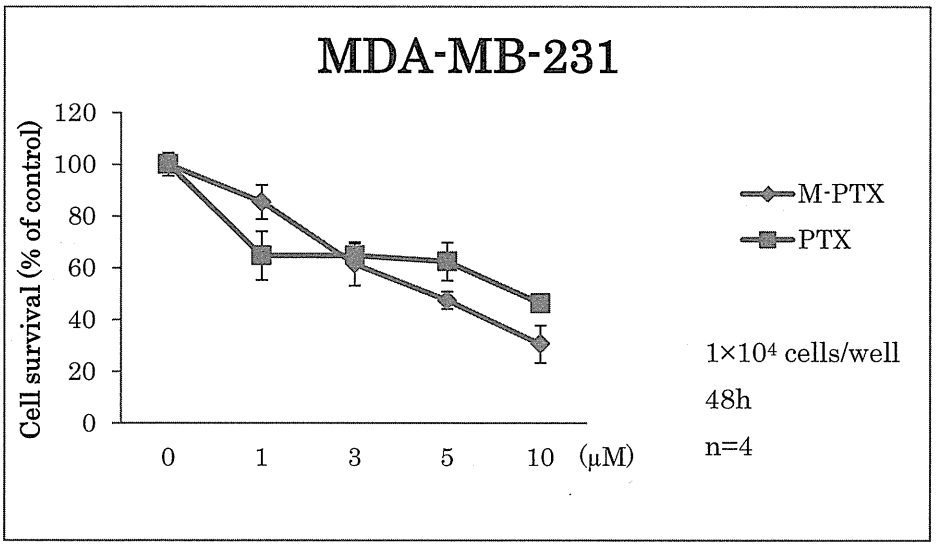
実験は複数回に分けて行い、濃度・時間・細胞数を検討した。

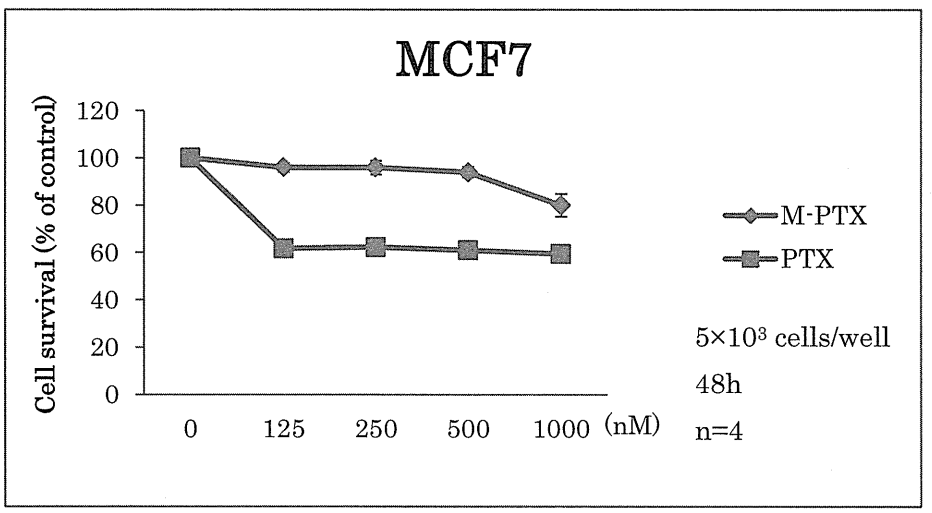
〈結果・考察〉

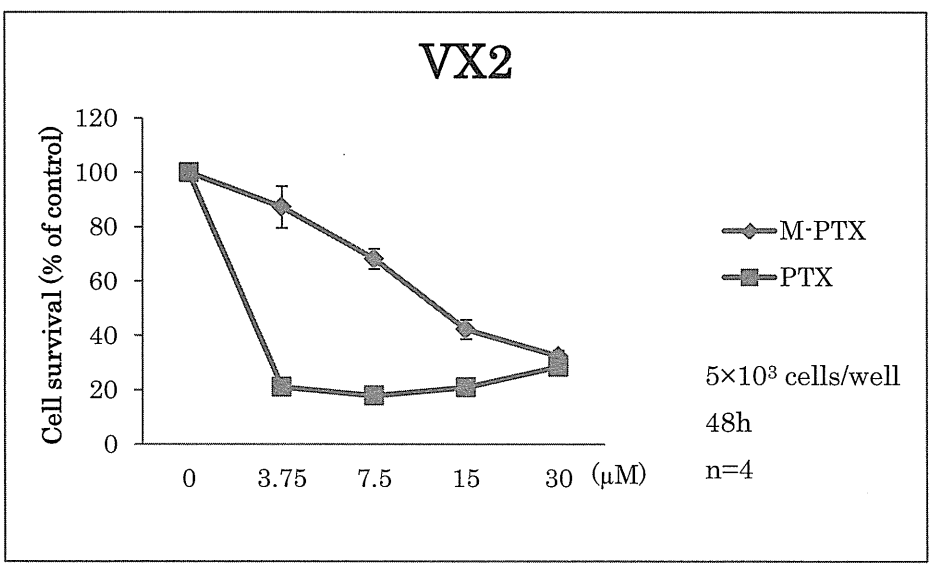
磁性パクリタキセルは市販のパクリタキセルと同様、乳がん細胞（トリプルネガティブ乳がんも非トリプルネガティブ乳がんも）と扁平上皮癌細胞に対して抗腫瘍効果を示した。条件検討した結果、濃度依存的に効果を示す傾向にある。また、低濃度でも効果が示せたが、濃度を低くすると、市販のパクリタキセルとの効果の差が顕著にひらく。






MDA-MB-231
Cell survival (% of control)
120
100
80
60
40
20
0
0
1
3
5
10
(μM)
M-PTX
PTX
1×10⁴ cells/well
48h
n=4


MCF7
Cell survival (% of control)
120
100
80
60
40
20
0
0
125
250
500
1000
(nM)
M-PTX
PTX
5×10³ cells/well
48h
n=4


VX2
Cell survival (% of control)
120
100
80
60
40
20
0
0
3.75
7.5
15
30
(μM)
M-PTX
PTX
5×10³ cells/well
48h
n=4

2. 磁性パクリタキセルの

アポトーシス誘導

※使用細胞: MDA-MB-453（ヒト由来トリプルネガティブ乳がん細胞), MDA-MB-231（ヒト由来トリプルネガティブ乳がん細胞), MCF7（ヒト由来エストロゲン受容体陽性乳がん細胞）

〈背景〉

乳がん細胞 MCF7、MDA-MB-453、MDA-MB-231 の細胞において、磁性パクリタキセルがアポトーシスを誘導していることが示唆された。

〈目的〉

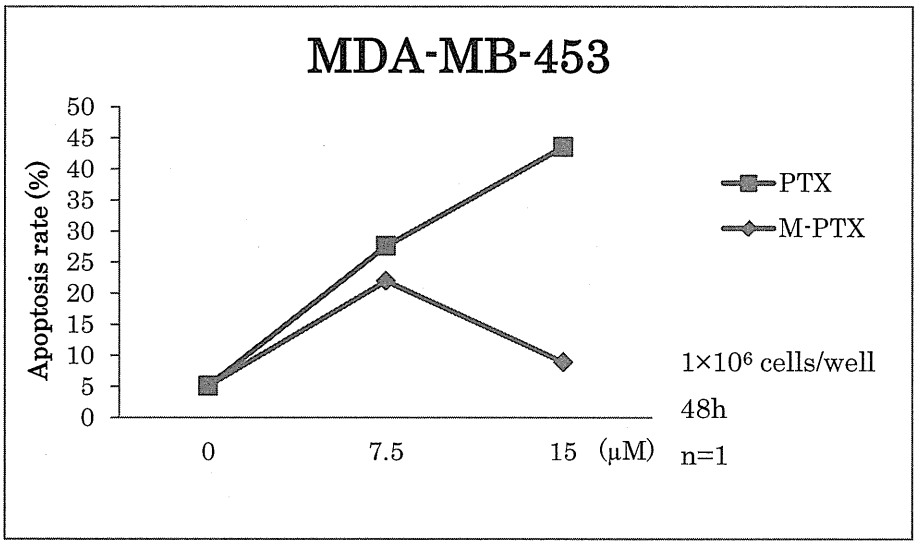
トリプルネガティブ乳がん細胞である MDA-MB-453 と MDA-MB-231、そしてエストロゲン受容体陽性乳がん細胞である MCF7 において、磁性パクリタキセルが市販のパクリタキセルの作用と同様に、アポトーシスを誘導することの再現性をとる。

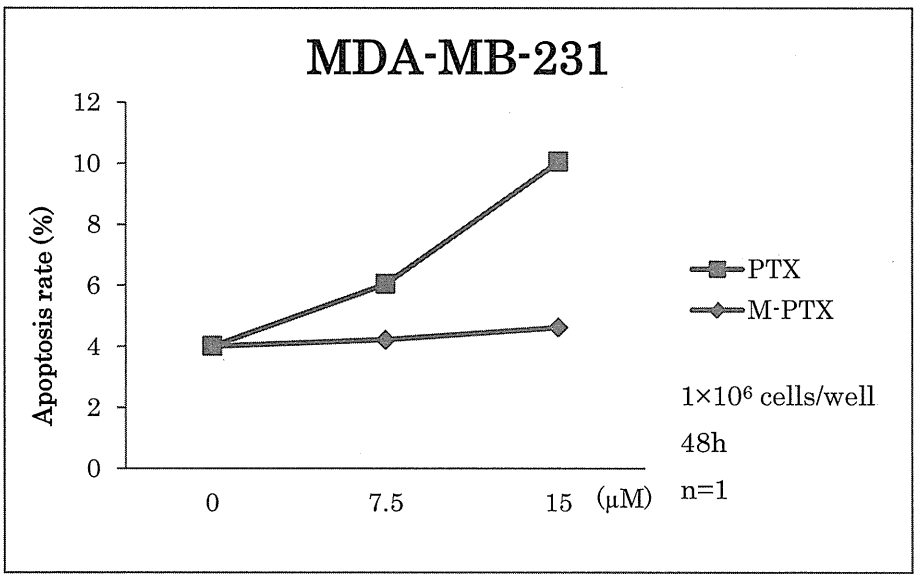
〈方法〉

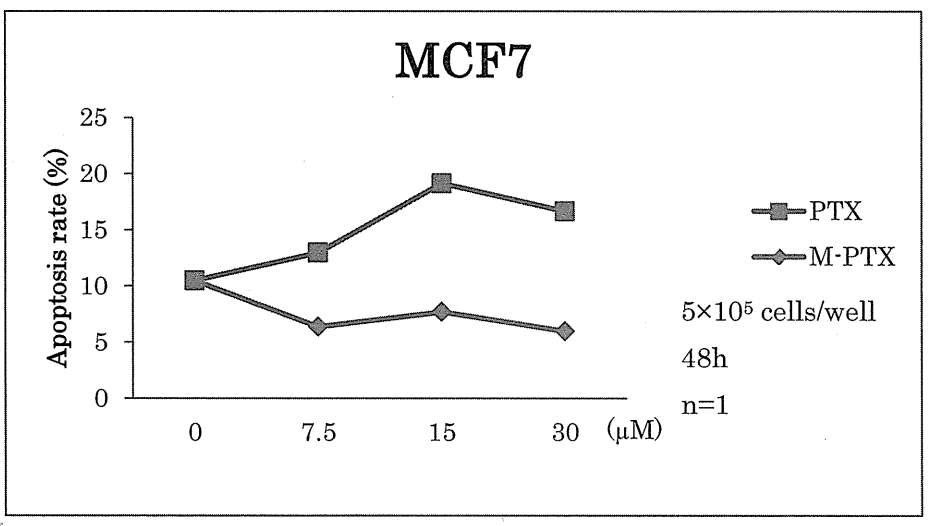
乳がん細胞を T-flask または 6cm dish に撒いた。翌日、磁性パクリタキセルと比較対象の市販のパクリタキセルを細胞に投与した。48 時間後、細胞をそれぞれ回収した。PBS で洗い、AnnexinV buffer で懸濁し、染色試薬 AnnexinV と 7AAD を加え、室温でインキュベーションした。（ネガティブコントロールは AnnexinV のみ、7AAD のみ、AnnexinV と 7AAD の両方を加えたものの 3 種類用意した）それぞれのサンプルに AnnexinV buffer を加え、フィルターにかけた。FACS でアポトーシスを起こしている細胞を分離し、カウントした。

〈結果・考察〉

MDA-MB-453、MDA-MB-231、MCF7 細胞において、磁性パクリタキセルも市販のパクリタキセルもアポトーシスを誘導した。但し、磁性パクリタキセルは市販のパクリタキセルと比較して有意に効果が低いことが示された。また MDA-MB-453 と MCF7 においては、n=4 で濃度依存的にアポトーシス率が上昇した。しかし、MDA-MB-231 においては、濃度依存的にはアポトーシスが誘導されなかった。濃度が濃すぎて細胞が死んでしまった可能性が考えられる。


MDA-MB-453
Apoptosis rate (%)
50
45
40
35
30
25
20
15
10
5
0
0
7.5
15 (μM)
PTX
M-PTX
1×10⁶ cells/well
48h
n=1


MDA-MB-231
Apoptosis rate (%)
12
10
8
6
4
2
0
0
7.5
15 (μM)
PTX
M-PTX
1×10⁶ cells/well
48h
n=1


MCF7
Apoptosis rate (%)
25
20
15
10
5
0
0
7.5
15
30 (μM)
PTX
M-PTX
5×10⁵ cells/well
48h
n=1