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The antiproliferative effects of agmatine correlate with the rate of cellular proliferation

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Adsorption and micellization behavior of novel gluconamide-type gemini surfactants

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Abstract

The adsorption and micellization behavior of novel sugar-based gemini surfactants (*N*,*N*′-dialkyl-*N*,*N*′-digluconamide ethylenediamine, Glu(*n*)-2-Glu(*n*), where *n* is the hydrocarbon chain length of 8, 10 and 12) has been studied on the basis of static/dynamic surface tension, fluorescence, dynamic light scattering (DLS) and cryogenic transmission electron microscope (cryo-TEM) data. The static surface tension of the aqueous Glu(*n*)-2-Glu(*n*) solutions measured at the critical micelle concentration (cmc) is observed to be significantly lower than that of the corresponding monomeric surfactants. This suggests that the gemini surfactants, newly synthesized in the current study, are able to form a closely packed monolayer film at the air/aqueous solution interface. The greater ability in the molecular association is supported by the remarkably (approximately 100–200 times) lower cmc of the gemini surfactants compared with the corresponding monomeric ones. With a combination of the fluorescence and DLS data, a structural transformation of the Glu(*n*)-2-Glu(*n*) micelles is suggested to occur with an increase in the concentration. The cryo-TEM measurements clearly confirm the formation of worm-like micelles of Glu(12)-2-Glu(12) at the concentration well above the cmc.

Keywords: Sugar-based gemini surfactants; Adsorption; Worm-like micelles; Surface tension

1. Introduction

Gemini surfactants, consisting of two monomeric surfactants linked with a spacer, have been synthesized with a view to developing 'next-generation' high-quality surfactants. When compared with a conventional monomeric surfactant, the corresponding gemini surfactants generally present, e.g., (i) a significantly lower critical micelle concentration (cmc), (ii) a lower surface tension recorded at the cmc and (iii) a greater ability in increasing viscosity of the diluted aqueous solution [1–3]. Indeed, a structural transformation from spherical micelles to vesicles is observed even in a diluted aqueous solution of gemini surfactants, being reflective of their larger packing parameter [4] than that of the corresponding monomeric surfactants. Although the synthetic process of gemini surfactants is generally more complicated than that of monomeric ones (and thereby, the synthetic costs are still problematic), these physicochemical properties of gemini surfactants may reduce the total consumption of substances in chemical products. Therefore, gemini surfactants themselves are deemed to be an environment-friendly material.

From the standpoint of human health and ecology, sugar-based nonionic surfactants are also an important and possible

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Phase behavior of mixed solution of a glycerin-modified cationic surfactant and an anionic surfactant

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Abstract

The phase behavior of mixed solution of newly synthesized monoglycerylcetyldimethylammonium chloride (MGCA) and sodium octyl sulfate (SOS) in water was investigated by cryo-transmission electron microscopy (cryo-TEM), dynamic light scattering (DLS), differential scanning calorimetry (DSC), and fluorescence polarizing for evaluation of the microviscosity of bilayers. No precipitate was observed in the mixed solution except at concentrations below 20 mM over all mixing ratios, and stable vesicles were formed in a considerably wide range of mixing ratio, even at the equimolar ratio. Vesicles formed in aqueous 1/1 MGCA/SOS mixture were found to exhibit no phase transition, and fluorescence polarizing measurements showed that the vesicle bilayers have a high fluidity. This flexibility allows the bilayers to have a spontaneous curvature, and thus vesicles rather than flat lamellae can be stabilized in the mixture even at the equimolar ratio. In addition, because the glycerin group of MGCA interacts strongly with water, the hydration repulsion contributes to prevent the bilayers consisting of MGCA and SOS from adhering and flocculating even though the charge neutralization between MGCA and SOS occurs at the equimolar ratio.

Keywords: Catanionic surfactant; Glycerin-modified surfactant; Thermodynamically stable vesicles

1. Introduction

Aqueous mixtures of anionic and cationic surfactants exhibit many peculiar properties that are not possessed by the other combinations of mixed surfactants. Strong synergistic interactions occur in dilute solutions of mixed cationic and anionic surfactants. The mixed system thus exhibits a drastic decrease in the critical aggregation concentration (cac) value at different mixing rations relative to the critical micelle concentration (cmc) of either of pure components. In addition, the mixture has a lowest attainable surface tension (γ_{cmc}) lower than those of single components [1–6]. The high interfacial activity of the system can be useful for its industrial applications as new detergents, emulsifiers, and dispersants.

Moreover, mixtures of oppositely charged surfactants self-assemble into a variety of aggregates [7–19] such as spherical micelles, rod-like micelles, disks, vesicles, and lamellar liquid crystals depending on the strength of intermolecular interactions, the geometrical shape of surfactant species, the mole fraction of oppositely charged surfactants, and concentration. Of particular interest for these mixtures is spontaneous formation of vesicles in dilute solutions. Since Kaler and co-workers [7] first reported such spontaneous formation of thermodynamically stable vesicles in anionic and cationic mixed surfactant systems, many researchers have investigated the microstructures and properties of spontaneously formed vesicles because they are expected to be used as a drug delivery system, model membrane, microreactor for production of colloidal assemblies, and cosmetics. When solutions of anionic and cationic surfactants are simply mixed, ion pairing of both surfactants induces vesicle formation at appropriate molar ratios even at low concentrations [7,8]. Because charge neutralization due to the ion

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Apoptosis
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Conformational change in the active center region of GST P1-1, due to binding of a synthetic conjugate of DXR with GSH, enhanced JNK-mediated apoptosis

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Abstract Treatment of cells with a synthetic conjugate of DXR with GSH via glutaraldehyde (GSH-DXR) caused cytochrome *c* to be released from the mitochondria to the cytosol following potent activation of caspase-3 and -9 by typical DNA fragmentation. This apoptosis was regulated by the JNK-signaling pathway. In the present experiment, binding of GSH-DXR to GST P1-1 allosterically led to the disappearance of its enzyme activity and activated the kinase activity of JNK without dissociation of the JNK-GST P1-1 complex. The recombinant GST P1-1 molecule with a mutation in the active center region (W38H and C47S) lost its GST activity when bound to JNK to the same degree as the wild-type, with the mutated GST P1-1 molecule failing to inhibit the activity of JNK. It has been reported that JNK-signaling is regulated by GST P1-1 via interaction with the C-terminus. We confirmed that GST P1-1 deletion mutant (Δ194–209) and a site-directed mutant (R201A) in the C-terminal region failed to bind and inhibit JNK. These results indicated that not only binding of the C-terminal region of GST P1-1 to the JNK molecule, but also the active center region of GST P1-1 play important roles in the regulation of JNK enzyme activity. The findings suggested that allosteric inhibition of GST P1-1 activity by the binding of GSH-DXR following conformational change may activate JNK and induce apoptosis via the mitochondrial pathway in the cells.

Keywords Apoptosis · c-Jun N-terminal kinase · Doxorubicin · Glutathione-Doxorubicin conjugate · Glutathione S-transferase P1-1 · Rat hepatoma cell

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Introduction

The stress-activated protein kinase, c-Jun N-terminal kinase (JNK), is predominantly activated by inflammatory cytokines and stress stimuli through phosphorylation of 183T and 185Y, and its active center consisting of an ATP-binding site formed by 55K [1–4]. The importance of the JNK pathway has also been shown in the control of cell survival and death pathways, and interference with the JNK pathway suppresses induction of apoptosis by a variety of agents [5]. Recently, the link between the redox active components of glutathione S-transferase P1-1 (GST P1-1, placental type isozyme of rat GST), and stress-activated kinases, such as JNK, has been redefined as a non-catalytic, ligand binding activity that mediates both stress and apoptotic responses [5–9]. It was important for the induction of cell proliferation, differentiation and apoptosis to activate JNK [10–14]. Strong and prolonged activation of JNK has been reported in response to lethal doses of a variety of stresses including UVC, γ radiation and cisplatin, any one of which triggers apoptosis [10–14]. It has been reported that JNK bound to several non-substrate proteins, including $p21^{WAF1}$, JIP, Rb, Hsp72 and GST P1-1 [6, 7, 15–17]. It has also been shown that $p21^{WAF1}$, Rb, Hsp72 and GST P1-1 inhibit JNK through protein-protein interactions [6, 7, 15–17], whereas JIP serves as a scaffolding protein in the JNK pathway [18]. It was addi-

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FGF-2 signaling induces downregulation of TAZ protein in osteoblastic MC3T3-E1 cells

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Abstract

Transcriptional coactivator with PDZ-binding motif (TAZ) protein is a coactivator of Runx2 and corepressor of PPARγ. It also induces differentiation of mesenchymal cells into osteoblasts. In this study, we found that FGF-2, which inhibits bone mineralization and stimulates cell proliferation, reduced the TAZ protein expression level in osteoblast-like cells, MC3T3-E1. This reduction was recovered by removing FGF-2 from the culture medium, which also restored the osteoblastic features of MC3T3-E1 cells. Furthermore, FGF-2-induced reduction of TAZ is blocked by a SAPK/JNK-specific inhibitor. These findings suggest that the expression of TAZ protein is involved in osteoblast proliferation and differentiation. This may help elucidate the discrepancies in the effect of FGF-2 and contribute to the understanding of FGF/FGFR-associated craniosynostosis syndrome etiology and treatment.

Keywords: TAZ; Fibroblast growth factor-2; Osteoblast differentiation; MAP kinase signaling

Transcriptional coactivator with PDZ-binding motif (TAZ) was first reported as a 14-3-3-binding protein in the cytoplasm [1] that interacts with a variety of transcription factors and exhibits transcriptional regulatory functions. TAZ is believed to regulate gene expression during embryogenesis [2] and development of bone [3,4], muscle [5], fat [4], lung [6], heart, and limb [7]. Furthermore, a recent study indicates that TAZ acts as a transcriptional regulator for the differentiation of mesenchymal stem cells into osteoblast cells [4]. In this case, TAZ functions as a coactivator of Runx2, which is a master regulator of osteoblast differentiation. Simultaneously, it also acts as a corepressor of PPARγ, which is a master regulator of adipocyte differentiation. These reports reveal that TAZ plays an important role in mesenchymal stem cell differentiation; however, the regulatory mechanism of TAZ expression in osteoblasts has not been elucidated.

The proliferative expansion of mesenchymal cells, osteoprogenitor cells, and preosteoblasts in response to mitotic growth factors is critical for skeletal development and bone formation. Bone matrix contains large quantities of growth factors, which modulate bone formation by stimulating osteoblast proliferation and differentiation. Among these growth factors, fibroblast growth factor-2 (FGF-2) plays an important role in the control of osteogenesis during skeletal development [8]. It has been shown that in mice with disrupted FGF-2 gene (loss of function), osteoblast proliferation and differentiation are decreased, resulting in significant reduction in bone mass with ageing [9,10]. In transgenic mice, where FGF-2 is overexpressed (gain of function), reduction of osteoblast differentiation is also observed, resulting in abnormal bone phenotype, such as shortening and flattening of long bones [11,12]. Although FGF-2 is a potential mitogen for osteoblast cell lineage and increased bone formation, continuous treatment with a high concentration of FGF-2 inhibits differentiated function of osteoblasts by suppressing synthesis of type I collagen and other proteins [13–15]. FGF-2 activates several

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LIVER CANCER

Survivin expression in early hepatocellular carcinoma and post-treatment with anti-cancer drug under hypoxic culture condition

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Abstract

AIM: To investigate the expression of survivin during the early stages of hepatocellular carcinoma (HCC).

METHODS: Immunohistochemical expression of survivin in liver tumor and non-tumor tissue specimens taken from 17 patients was compared. In addition, to determine the survivin expression in response to anti-cancer drugs in early stage HCC, the survivin expression was determined after the treatment of the HCC cells with anti-cancer drugs under hypoxic culture conditions.

RESULTS Survivin proteins were expressed in 64.7% of cells in early HCC specimens. A correlation between the survivin expression rate in the peritumoral hepatocytes and the rate of expression in the HCC specimens (low-rate groupvs high-rate group) was observed. The survivin protein concentration in HCC cells was increased by the combination of hypoxia and anti-cancer drugs.

CONCLUSION: This study suggests that survivin could be used as a therapeutic target in early HCC.

Key words: Survivin; Hepatocellular carcinoma; Hypoxia

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a major health problem worldwide. There are more than 500 000 new cases diagnosed each year, with an age-adjusted incidence of 5.5-14.9 per 100 000 people[1]. In some areas of Asia and the Middle East, HCC ranks as the most frequent cancer-related cause of death[2]. The incidence of HCC is also increasing in Europe and the United States[3]. A more effective therapy thus needs to be developed from early stages.

Survivin is a member of a family of inhibitors of apoptosis protein (IAP), which has been implicated in both the control of cell division and the inhibition of apoptosis. Specifically, its anti-apoptotic function is associated with the ability to directly or indirectly inhibit caspases. By inhibiting apoptosis and promoting mitosis, survivin facilitates cancer cell survival and growth[4-8]. Survivin is selectively expressed in the most common human neoplasms and appears to be involved in tumor cell resistance to some anticancer agents and ionizing radiation[9].

Several preclinical studies have demonstrated that the down-regulation of survivin expression/function by the use of anti-sense oligonucleotide, dominant negative mutants, ribozymes, small interfering RNAs and cyclin-dependent kinase inhibitors increased the rate of apoptosis, reduced tumor growth potential and sensitized tumor cells to various chemotherapeutic drugs and γ-irradiation in *in vitro* and *in vivo* models of various types of human tumors[9]. Moreover, YM155 is the first agent designed to inhibit survivin. Some early phase clinical studies demonstrated that this novel anticancer agent was well tolerated and shrank tumors in some patients with non-Hodgkin lymphoma and hormone-refractory prostate cancer that recurred after conventional chemotherapy. In addition, interim reports indicate that there are few side effects.

These results suggest the possible efficacy of the survivin inhibitor on HCC. It may be effective for patients with early stages of HCC. Survivin is expressed in HCC[10]. However, the expression during the early stages of HCC has not been characterized pathologically. In addition, previous results have shown that survivin gene transcription is increased in hypoxic tumor cells[11]. The well-differentiated HCC has portal blood flow and is not hypervascular[12]. In order to compare the expression of

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Useful detection of CD147 (EMMPRIN) for pathological diagnosis of early hepatocellular carcinoma in needle biopsy samples

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Abstract

AIM: To make clear whether CD147 (EMMPRIN) expression in pathological tumor samples with a fine-needle aspiration biopsy is useful for pathological diagnosis of early hepatocellular carcinoma (HCC).

METHODS: Twenty-two patients (15 men and 7 women; median age 68 years, range 56-81 years) underwent a liver tissue biopsy in order to make a diagnosis of HCC. Paraffin-embedded liver biopsy tissue samples from 22 patients were stained with anti-CD147 antibody, murine monoclonal antibody 12C3 (MAb12C3) for immunohistochemical analysis. An immunohistochemical analysis of CD147 was performed and the degree of staining compared between tumor and non-tumor tissue. In addition, the degree of staining within tumor tissue was compared according to a number of clinicopathological variables.

RESULTS: The degree of staining of CD147 was significantly higher in tumor tissues than non-tumor tissues, even in tumors less than 15 mm in diameter. The expression of this protein was significantly elevated in HCC tissue specimens from patients with a low value of serum AST and γ-GTP.

CONCLUSION: CD147 serves potentially as a pathological target for cancer detection of early HCC.

Key words: CD147; Hepatocellular carcinoma; Needle biopsy

Mamori S, Nagatsuma K, Matsuura T, Ohkawa K, Hano H, Fukunaga M, Matsushima M, Masui Y, Fushiya N, Onoda H, Searashi Y, Takagi I, Tagiri H. Useful detection of CD147 (EMMPRIN) for pathological diagnosis of early hepatocellular carcinoma in needle biopsy samples. *World J Gastroenterol* 2007; 13(21): 2913-2917

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a major health problem worldwide, involving more than 500 000 new cases yearly, with an age-adjusted incidence of 5.5-14.9 per 100 000 people[1]. In some areas of Asia and the Middle East, HCC ranks as the most frequent cancer-related cause of death[2]. The incidence of HCC is also increasing in Europe and the United States[3]. The early detection of tumors and development of therapies for HCC is likely to improve the prognosis[4]. Nevertheless, despite improvements in both diagnostic modalities and therapy, in many cases an accurate diagnosis still cannot be confirmed even with diagnostic imaging and the recognition of tumor markers in the serum. Particularly, hypovascular HCC which is often difficult to recognize by computed tomography (CT) requires ultrasound (US) examination for a definitive diagnosis. Tumor biopsy is an important method of evaluation in these cases, particularly in small tumors, less than 15 mm in diameter. Therefore, more sensitive tumor markers for pathological diagnosis are required.

CD147, also known as extracellular matrix metalloproteinase inducer (EMMPRIN) or basigin, is a transmembrane glycoprotein with two immunoglobulin-like

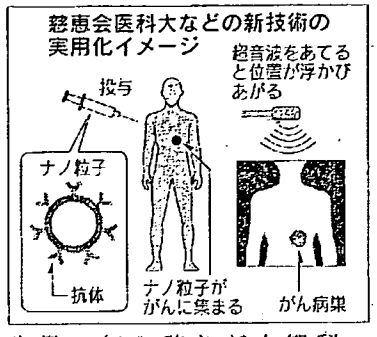
【第三種郵便物認可】

超音波照射がん識別

造影剤に微粒子活用

慈恵会医科大など 基礎技術を開発

東京慈恵会医科大学と検査装置メーカーのアロカ、東京理科大学の共同研究チームは体内に投与した微粒子に超音波をあててがんを識別する基礎技術を開発した。肝がんを模した実験装置などで基本的な機能を確かめた。マウスなどの動物実験で効果や安全性を確認し、微小ながんでも本体を正確に見つけられる造影剤として実用化を目指す。



研究チームは慈恵会医科大の大川清教授と松浦知和講師、東京理科大の上屋好司客員研究員ら。グルコースを主成分とした界面活性剤に六フッ化硫黄のガスを噴射すると、ガスを界面活性剤で包んだ最小で直径二百ナノ（ナは十億分の一）㍍の微粒子ができる。これを生体内に入れて超音波の造影剤として使う。マウスに投与する実験では副作用はみられなかった。

人工材料に肝がん細胞を培養した実験モデルを作り、造影実験をした。微粒子を流し込むと約十分後には肝がんの中に微粒子が入り込み、洗い流した後も吸着していた。従来の造影剤では吸着せずにすぐになくなってしまう。

研究チームは粒子の表面にがんで多量にみられる抗体「CD147」を付けて性能を高める。いろいろな部位のがんでみられる抗体で、がん自体の存在を見極められる見込み。悪性がんに付くため、陽電子放射断層撮影装置（PET）などでも診断ができると期待している。

見極めにくい微小がんの

を均一化する

どを開発する

骨減少・炎症を抑制

東京医科歯科大など 免疫疾患の新薬候補

東京医科歯科大学の高柳広教授と朝隈成華講師、日本ケミファなどの研究チームは関節リウマチや多発性硬化症などの新たな治療薬となる候補の物質を突き止めた。骨の減少と免疫の過剰な働きによる炎症の両方を抑

患になると骨の量が減ったり、免疫が過剰に働き炎症を起こしたりする。どちらかに効果のある物質は見つかっていたが、両方の症状を効果的に抑制する物質は見つかっていなかった。

研究チームは骨を分解

投与したところ、骨の減少が止まっただけでなく、炎症も抑えられた。

カテプシンKには免疫細胞を活性化する働きがある。試作した薬は骨の吸収を促す破骨細胞の働きを抑えるだけでなく、炎症を抑制できたとみられる。骨粗しょう症や関節リウマチなどを治療できる可能性がある。

カテプシンKの阻害薬は米ベンチャー企業と協力し、多発性骨髄腫の治療薬として臨床試験を計画中。がんが骨に転移する際に骨を壊す症状を抑制できるとみている。

さらに同阻害薬は、免疫機能を抑える働きがあり、感染症などに弱くなる可能性がある。対象となる疾病を確認しながら関節リウマチや骨粗しょう症などの治療薬を目指す。

研究成果は二月一日付の米科学誌サイエンスに掲載される。

受精卵 成長に「核小体」不可欠

理研が解明 不妊治療に応用へ

神戸大学、チェコ国立畜産研究所との共同成果で、米科学誌サイエンスに一日掲載される。

核小体はすべての細胞

働きも未解明だった。研究チームはマウスなどの卵子から核小体を取り除いたうえで様々な実験をして詳細に調べた。核小体がないまま受精させると、卵子と精子それぞれからできる前核の中で核小体がなくなっていた。

この状態では途中で発生・分化が止まるが、除去した核小体を戻すと正常に分化した。体細胞の中にある核小体を移植しても卵子由来の核小体の

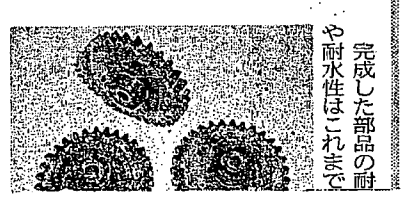
な機能を持つできていない成分や働きをれば「あらゆ

木材から歯車・ボルト

中日精工、廃材を活用 原油節約・CO_2削減

自動車部品開発の中日精工（愛知県豊川市、森久宏社長）は木材を主原料に、家電や自動車に利用できる歯車やボルトを製造する技術を開発した。従来の工業用プラスチックと同レベルの強度や耐熱性を維持できる。原油資源の節約や二酸化炭素（CO_2）の削減に役立つ新技術として実用化。

木材を細かく分断する。その後、数種類の合成樹脂を加えて強度や吸水率を調節。成形時の強度劣化を防ぐ添加剤なども混ぜて歯車やボルトに加工した。



製作した歯車はプラク並みの強度を持つ

完成した部品の耐や耐水性はこれまで

素一炭サ化ン酸セ 2キロ先の濃度も測定

情通機構 24時間利用が可

情報通信研究機構は、O_3）濃度を二十四時間、を開発した。遠距離の二酸化窒素（C測定できるセンサー装置の反射を解析

大河内記念 荏原が

大河内記念之理事長）は日、生産工学分野の研究開業績を上げた贈る大河内賞年度受賞者を

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