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平成24年度分担研究報告書

血清 Progranulin の慢性炎症性疾患病態への関連

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研究要旨

Progranulin (PGRN)は炎症、免疫や感染防御などに対して多彩な機能を有している。本年度炎症性筋疾患における血清 PRGN 濃度を測定したところ、炎症性筋疾患、特に皮膚筋炎で血清 PGRN 濃度が上昇していた。皮膚筋炎を間質性肺炎の種類で分類すると急性／亜急性間質性肺炎合併例では慢性間質性肺炎合併例に対し血清 PRGN 濃度が有意に上昇していた。また、血清 PRGN 濃度は血清フェリチン、CRP、LDH と有意な相関を示した。健常人 PBMC を用いた PGRN の機能解析では、PGRN は CpG 存在下でのみ IL-6 産生を増強した。以上、PRGN は TLR9 を介して炎症性筋疾患における炎症の惹起及び維持に関与している可能性が示唆された。今後、TRAPS などの自己炎症疾患における血清 PGRN 濃度の測定、病態への関与を検討する必要がある。

A. 研究目的

Progranulin(PGRN)は細胞外の糖タンパクであり 7 個半の cysteine-rich domain を有している。PGRN は活性化した上皮細胞、白血球、軟骨細胞、ニューロンで産生されている。PGRN は炎症や免疫、感染防御に多彩な作用を有することが明らかになってきた。また TNF との関連では、TNF 受容体に対する TNF の結合を競合的に結合することで TNF のシグナル伝達を阻害する作用を有することが近年明らかにされた（Tang et al. Science 2011）。Toll-like receptor 9 (TLR9) は微生物由来の CpG-DNA の受容体であり自然免疫に関わるが、PGRN は CpG-DNA、TLR9 双方に結合してこれら分子の会合を促進する作用も報告されている。このような多彩な機能を考えると、PGRN が炎症性疾患でどのような動態を示すかを明らかにすることは、炎症疾患の病態解明、治療法の開発に意義が大きいと思われる。しかしながら本研究の開始時点では炎症性疾患でPGRNの動態を検討した報告はほとんど見られなかった。昨年度の本研究において我々は慢性炎症性疾患の代表といえる関節リウマチ患者の血清 PGRN 濃度を測定し、関節リウマチ患者では血清PRGN濃度が健常人に比し有意に上昇している事を報告した。本年度は炎症性筋疾患における血清PRGN濃度を測定した。我々の実験系は今後 TRAPS を含めた自己炎症性疾患やその他のさまざまな炎症性疾患の診断や病態解明に応用できると思われる。

B. 研究方法

1. 検体

九州大学病院免疫・膠原病・感染症内科に通院中の皮膚筋炎患者（50 名）、多発性筋炎(21 名)ならびに健常人（60 名）に研究への同意を書面で得て採血し、分離した血清を検討の対象とした。血清は測定時まで−20℃に保存した。

2. 倫理的な配慮

本研究は九州大学倫理委員会の承認を得て行った。

3. PGRN の測定

血清 PGRN の測定は、ELISA kit (R&D Systems)を用いて行った。血清を希釈し、マウス抗ヒトPGRNモノクローナル抗体をコートした microtiter well で反応させ、洗浄後、二次抗体としてペルオキシダーゼを結合させたマウス抗ヒトPGRN抗体を反応させた。基質として Tetramethylbenzidine を加えて発色させて吸光度を測定した（ThermoFisher SCIENTIFIC 社製)。標準曲線から血清中の PGRN 濃度を算定した。

4. PGRN の健常人 PBMC への作用

健常人の末梢血から得られた PBMC（$4x10^6$ cells）を無血清培地で 250ng/mL のヒト組み換え PGRN の存在下または非存在下に、10nmol/L の CpG-B（Invitrogen）または poly(I:C)、LPS、Imiquimod で刺激し、24 時間後に培養上清中の IL-6 濃度を測定した。IL-6 濃度の測定は、ELISA kit (R&D Systems)を用いて行った。

5. 統計解析

2 群間の比較は Student's *t*-test で解析した。血清 PRGN 濃度と臨床検査値の相関には Spearman の順位相関係数を用いた。

C. 研究結果

皮膚筋炎患者、多発性筋炎および健常人の平均血清 PGRN 濃度はそれぞれ 130.3 ng/mL、66.9 ng/mL、49.3 ng/mL であり有意に炎症性筋疾患患者、特に皮膚筋炎患者で上昇していた（皮膚筋炎 vs 健常人 $p<0.0001$、皮膚筋炎 vs 多発性筋炎 $p<0.01$、多発性筋炎 vs 健常人 $p<0.01$)。皮膚筋炎患者を急性／亜急性間質性肺炎合併例、慢性間質性肺炎合併例、間質性肺炎非合併例に分類するとそれぞれの平均血清 PRGN 濃度は 230.5ng/mL、96.5ng/mL、93.5ng/mL であり急性／亜急性間質性肺炎合併例で有意に高値を示した(いずれも $p<0.001$)。間質性肺炎合併例において血清PRGNは血清フェリチン(rs=0.71 $P<0.001$)、LDH(rs=0.59 $P<0.001$)、CRP(rs=0.57 $P<0.001$)と有意な相関を認めた。

健常人 PBMC に対する PGRN の効果を検討した（図１)。CpG-B 刺激では培養上清中に IL-6 濃度の上昇を認め、PGRN 存在下でさらに有意に IL-6 濃度は上昇した ($p<0.05$)。

TLR3,4,7 のリガンドである poly(I:C)、LPS、Imiquimod 刺激でも培養上清中の IL-6 濃度の上昇を認めたが、PRGN による増強効果は認められなかった。

D. 考察

本年度の研究で炎症性筋疾患、特に皮膚筋炎で血清PGRN濃度が上昇していることが初めて明らかになった。皮膚筋炎を間質性肺炎の種類で分類すると急性／亜急性間質性肺炎合併例では慢性間質性肺炎合併例に対し血清PRGN濃度が有意に上昇していた。また、血清 PRGN 濃度は血清フェリチン、CRP、LDH と有意な相関を示した。この結果はPRGNの炎症惹起物質としての側面を支持する。一方、急性／亜急性間質性肺炎合併例で血清PRGNが上昇する機序に

ついては今後の検討を有する。

今回の研究では、PRGN による健常人 PBMC の IL-6 産生増強が TLR9 特異的である事を明らかにした。TLR9 が起動しうる状態、すなわち微生物感染などで非メチル化 CpG が増加している病態において、PGRN は CpG と協働して IL-6 産生を増強すると考えられる。

TRAPS において、あるいはその他の家族性地中海熱やメバロン酸キナーゼ欠損症などの自己炎症性疾患では周期的に発熱する原因は明らかになっていない。細菌感染などで非メチル化 CpG が増加する状態にあるときに、PGRN と協働して IL-6 などの炎症性サイトカインが誘導されるために、周期的な発熱や臨床症状出現の原因になっていることが推測される。

E. 結論

炎症性筋疾患、特に皮膚筋炎で血清 PGRN 濃度が上昇していることを初めて明らかにした。健常人 PBMC を用いた PGRN の機能解析では、PGRN は CpG 存在下でのみ IL-6 産生を増強した。

TRAPS などの自己炎症疾患における PGRN の役割を解明するために、血清濃度の測定、患者 PBMC を用いた機能解析が必要である。

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G. 知的財産権の出願・登録状況

（予定を含む.）

1. 特許取得

なし.

2. 実用新案登録

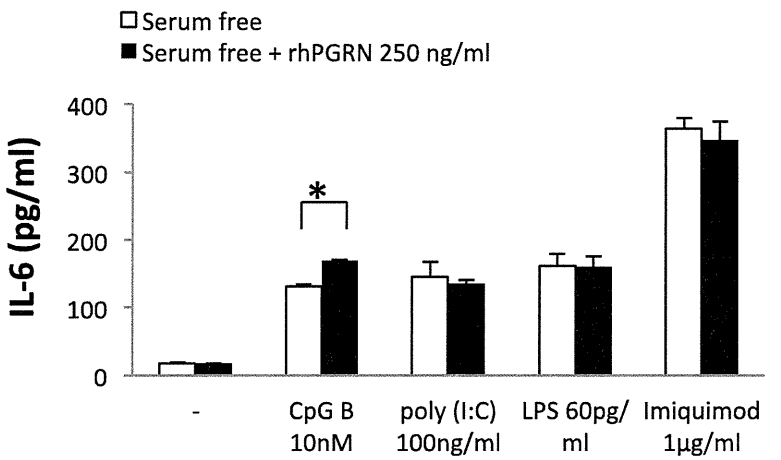
なし.

3. その他

なし.

図 1. PGRN augments the IL-6 production by human PBMCs only via TLR9 signaling.

PBMCs from healthy control individuals were incubated for 24 hr in serum-free medium with or without 10 nM CpG-B, 100 ng/ml poly (I:C), 60 pg/ml LPS or 1 μg/ml imiquimod and purified PGRN (250 ng/ml). The supernatant IL-6 levels were measured by ELISA. The data are representative of three independent experiments (average and SEM).



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研究成果の刊行に関する一覧表

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REVIEW ARTICLE

Review Series: Advances in Consensus, Pathogenesis and Treatment of Urticaria and Angioedema

Guideline for Hereditary Angioedema (HAE) 2010 by the Japanese Association for Complement Research - Secondary Publication

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ABSTRACT

This guideline was provided by the Japanese Association for Complement Research targeting clinicians for making an accurate diagnosis of hereditary angioedema (HAE), and for prompt treatment of the HAE patient in Japan. This is a 2010 year version and will be updated according to any pertinent medical advancements.

KEY WORDS

allergic inflammation, angioedema, complement, guideline, Japan

PURPOSE OF THIS GUIDELINE

This guideline was provided by the Japanese Association for Complement Research targeting clinicians for making an accurate diagnosis of hereditary angioedema (HAE), and for prompt treatment of the HAE patient.

HAE is caused by a deficiency or improper function of the inhibitor of complement component protein C1 (C1-INH), which affects the blood vessels. Patients with HAE can develop rapid swelling of the hands, feet, limbs, face, intestinal tract, larynx or trachea. HAE is relatively easy to diagnose if you are familiar with the disease and it may be treated efficiently. The lack of an accurate diagnosis can have serious consequences. Patients with misdiagnosed HAE may un-

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Conflict of interest: No potential conflict of interest was disclosed.

* This article is a second publication of the Guideline for Hereditary Angioedema (HAE) 2010 published by The Japanese Association for Complement Research, which is available at http://square.umin.ac.jp/compl/HAE/HAEGuideline2010.pdf(in Japanese).

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Table 1 Treatment during an episode

Treatment During an Episode	Laryngeal Edema	Subcutaneous Edema-Excluding Face and Cervical Region	Subcutaneous Edema-Face and Cervical Region	Abdominal Symptoms
Follow-up	-	+	+	+
Tranexamic acid	-	+	+	+
C1-INH	+	+/-	+	+
Intubation in ICU	+	-	-	-

dergo unnecessary medical procedures (e.g. appendectomy, exploratory laparotomy). We all hope that patients suffering from the disease will be immediately diagnosed with HAE and treated appropriately. We will update this guideline according to any pertinent medical advancements.

GENERAL INFORMATION ON HAE

a) Epidemiology: one in every 10,000 to 150,000 people (mostly reported as one in every 50,000).
b) Types of HAE
   i) Type 1, autosomal dominant inheritance (85% of all HAE): Low amount of C1-INH protein and low level of C1-INH activity.
   ii) Type 2, autosomal dominant inheritance (15% of all HAE): Normal or increased amount of C1-INH protein and low level of C1-INH activity.
   iii) Type 3 is very rare and not reported in Japan, occurring mostly in females (estrogen-dependent). Details of the pathogenesis are unknown, and the mutation of coagulation factor XII is detected in some families. Both C1-INH protein and C1-INH activity are normal.
   iv) Sporadic cases not related to family history are observed in approximately 25% of all HAE.

DIAGNOSIS

HAE is often unrecognized or misdiagnosed because it is rare, and its symptoms are similar to many other more common angioedema.

a) Differential diagnosis for HAE: acquired angioedema (AAE), drug-induced angioedema, etc.
b) Symptoms of suspected HAE
   i) Angioedema can be caused in any tissues and its symptoms may vary in each organ.
      • Laryngeal edema - the fatality rate is 30% when not appropriately treated. Rare in children under 3 years old.
      • Subcutaneous edema, submucosal edema (not associated with itching, can be seen all over the body, swelling is sometimes below the surface of the skin).
      • Digestive symptoms (abdominal pain, nausea, vomiting, diarrhea).
   ii) Angioedema attacks may be induced by psychological stress, physical stress such as trauma, tooth extraction, surgical operation, overwork, pregnancy, menstruation, drugs, etc.
   iii) Angioedema usually peak within 24 hours and subside within 72 hours, however, they may continue for more than 72 hours in some cases.
   iv) Approximately 75% of HAE patients have family histories.
   v) Attacks can occur in all ages.
c) Laboratory serum test
   C1-INH activity is low in all HAE patients. Therefore, C1-INH activity is the most important measurement for the diagnosis of HAE and this test is covered by health insurance in Japan. During an angioedema episode, the level of complement component C4 decreases in 98% of HAE patients, and therefore may be a good marker for the diagnosis of HAE during its episode.
d) Determination of HAE types
   To determine the type of HAE, quantification of C1-INH protein is required, although the cost is not covered by Japanese health insurance.
      • Low C1-INH protein - Type 1 HAE
      • Normal C1-INH protein - Type 2 HAE
e) When there is no family history, diagnosis should be differentiated from AAE. When the level of C1q (not covered by the Japanese health insurance) is low, it can generally be diagnosed as AAE. However, in rare cases, low levels of C1q can be detected in HAE and genetic analysis is required for accurate diagnosis.
f) When Type 3 HAE is suspected, a mutation of Factor XII may be identified.

TREATMENT DURING AN EPISODE (Table 1)

a) Laryngeal edema
   i) C1-INH replacement therapy (for less than 50 kg, 500 units and for more than 50 kg, 1,000 to 1,500 units, intravenous injection).
   ii) Intra-tracheal intubation or tracheotomy in Intensive Care Unit for respiratory distress by airway stenosis.
b) Subcutaneous edema (excluding face and cervical region)
   i) Follow-up first.
   ii) If no improvement is seen, give the following treatment: Tranexamic acid 15 mg/kg every 4

hours. For severe cases in which symptoms do not improve by tranexamic acid treatment alone, C1-INH replacement therapy is required (for less than 50 kg, 500 units and for more than 50 kg, 1,000 to 1,500 units, intravenous injection).

c) Subcutaneous edema (face and cervical region)
   i) Tranexamic acid (15 mg/kg every 4 hours).
   ii) C1-INH replacement therapy (for less than 50 kg, 500 units and for more than 50 kg, 1,000 to 1,500 units, intravenous injection).
d) Abdominal symptoms
   i) Tranexamic acid (15 mg/kg every 4 hours).
   ii) C1-INH replacement therapy (for less than 50 kg, 500 units and for more than 50 kg, 1,000 to 1,500 units, intravenous injection).

SHORT-TERM PROPHYLAXIS

a) Cases with minimal stress: dental treatment (less invasive), etc. Treatment for prevention is not required, but C1-INH replacement should be ready for use.
b) Cases with intensive stress: highly invasive dental treatment, surgical operations, etc. Give C1-INH replacement therapy (for less than 50 kg, 500 units, and for more than 50 kg, 1,000 to 1,500 units, intravenous injection) an hour prior to the operation. Furthermore, a second C1-INH replacement therapy should be prepared.

LONG-TERM PROPHYLAXIS

The following treatment is recommended for patients with a history of laryngeal edema, those who develop symptoms once or more a month, and/or suffered from symptoms for more than 5 days a month.

a) Tranexamic acid
   i) 30-50 mg/kg/day administered in divided doses 2-3 times a day.
   ii) Adverse reactions: muscle ache, muscle weakness, fatigue, and reduction in blood pressure.
b) Danazol
   i) 2.5 mg/kg/day(maximum 200 mg/day) will be administered for one month, if it is not effective, 300 mg/day will be administered for one month, and if it is still not effective, 400 mg/day will be administered for one month. If 200 mg/day is effective, 100 mg/day will subsequently be administered for one month and the amount will be reduced to 50 mg/day or 100 mg/every second day.
   ii) Contraindication: children, pregnant women, lactating women, and cancer patients.
   iii) Adverse reactions: virilization, hepatic disorder, hypertension, lipid abnormality, polycythemia, and hemorrhagic cystitis.
   iv) Follow-up: Blood testing is required every 6 months. For patients treated with more than 200 mg/day Danazol, an abdominal ultrasonography is required every 6 months and for cases treated with less than 200 mg/day an abdominal ultrasonography is required every year, due to a possibility of hepatic tumorigenesis.

REFERENCE MATTERS FOR DIAGNOSIS

a) For the initial screening for HAE, a serum C4 measurement during attacks should be considered.
   i) Low C4 level → Conduct C1-INH activity measurement.
   ii) Normal C4 level → HAE can basically be ruled out.
b) Measurement of the C1-INH activity is essential for making an accurate diagnosis of HAE
   i) Low C1-INH level → It can be diagnosed with angioedema caused by a deficiency of C1-INH. Differentiate the types as follows.
      • With a family history → It can be diagnosed as HAE. → Conduct quantitation of C1-INH. → If the level is low, it can be diagnosed as Type 1, and if the level is normal or increased, it can be diagnosed as Type 2.
      • No family history → Conduct serum C1q measurement and if the level is low, it can be diagnosed as AAE. However, it should be taken into account that low C1q can occur in some HAE patients. → A genetic analysis is desired in order to make an accurate diagnosis.
   ii) Normal C1-INH level → Suspect of Type 3 or drug-induced angioedema. → Confirm his/her medication history (especially, antihypertensive drugs, estrogen preparations). In addition, Type 3 has not been reported in Japanese; however, according to reports in Caucasians, it is related to family history and occurs mostly in women.

NOTES

Please contact us if you have any opinions about this guideline. Contact: Takahiko Horiuchi, Steering Committee, The Japanese Association for Complement Research. E-mail: horiuchi@intmed1.med.kyushu-u.ac.jp.

Please refer to our website at http://square.umin.ac.jp/compl/ if you have any concerns about C1-INH activity measurement, protein quantitation, and genetic analysis.

C1-INH formulation is provided as Berinert P (trade name) (CSL Behring) in Japan. Information on hereditary angioedema can be obtained from homepage of CSL Behring at http://www.cslbehring.co.jp, or a dedicated website for hereditary angioedema "HAE Information Center" at http://www.hae-info.jp. For example, you can find information like "Tranexamic acid is provided as Transamin (trade name)

(Daiichi Sankyo), etc.", and "Danazol is provided as Bonzol (trade name) (Mitsubishi Tanabe Pharma), etc.".

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