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The wingless-related integration site-5a/secreted frizzled-related protein-5 system is dysregulated in human sepsis

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Summary

Sepsis and type 2 diabetes exhibit insulin resistance as a common phenotype. In type 2 diabetes we and others have recently provided evidence that alterations of the proinflammatory wingless-related integration site (wnt)-5a/anti-inflammatory secreted frizzled-related protein (sFRP)-5 system are involved in the pathogenesis of insulin resistance. The aim of the present study was to investigate whether this novel cytokine system is dysregulated in human sepsis, which may indicate a potential mechanism linking inflammation to metabolism. In this single-centre prospective observational study, critically ill adult septic patients were examined and proinflammatory wnt5a and wnt5a inhibitor sFRP5 were measured in serum samples by enzyme-linked immunosorbent assay (ELISA) at admission to the intensive care unit (ICU) and 5 days later. Sixty sepsis patients were included, and 30 healthy individuals served as controls. Wnt5a levels were found to be increased significantly in septic patients compared to healthy controls ($2{\cdot}21 \pm 0{\cdot}33$ *versus* $0{\cdot}32 \pm 0{\cdot}03$ ng/ml, $P < 0{\cdot}0001$). In contrast, sFRP5 was not altered significantly in septic patients ($19{\cdot}72 \pm 3{\cdot}06$ *versus* $17{\cdot}48 \pm 6{\cdot}38$ ng/ml, $P = 0{\cdot}07$). On admission to the ICU, wnt5a levels exhibited a significant positive correlation with the leucocyte count ($r_s = 0{\cdot}3797$, $P = 0{\cdot}004$). Interestingly, in patients recovering from sepsis, wnt5a levels declined significantly within 5 days ($2{\cdot}17 \pm 0{\cdot}38$–$1{\cdot}03 \pm 0{\cdot}28$ ng/ml, $P < 0{\cdot}01$). In contrast, if sepsis was worsening, wnt5a levels increased in the same time-period by trend ($2{\cdot}34 \pm 0{\cdot}59$–$3{\cdot}25 \pm 1{\cdot}02$ ng/ml, $P > 0{\cdot}05$). sFRP5 levels did not change significantly throughout the study period. The wnt5a/sFRP5 system is altered in human sepsis and might therefore be of interest for future studies on molecular pathophysiology of this common human disease.

Keywords: cytokines, human, inflammation

Introduction

Inflammation and metabolism are necessities for life. At the same time, chronic inflammatory and chronic metabolic disorders display two of the greatest threats to human health and welfare worldwide [1]. Evolutionary perspectives have helped understanding of why these two systems seem to be not only closely related but also to interact very effectively with each other [2]. Pathogens and injuries induce a type of classical and high-grade inflammation enhancing the inflammatory response and causing metabolic disturbances. Conversely, metabolic abnormalities, such as excess intake of energy, lead to complications such as type 2 diabetes [3], which many studies suggest is mediated by a state of so called 'low-grade inflammation'.

Both classical high-grade inflammation (also called 'hot inflammation') and low-grade inflammation (also called 'cold inflammation') lead to insulin resistance [4]. Insulin resistance and consequent hyperglycaemia in sepsis at the severe end of the 'hot inflammation' spectrum are detrimental for the clinical outcome [5]. The same holds true for patients with insulin resistance in type 2 diabetes mellitus [6], a clinical example for 'cold', low-grade inflammation. However, there is no rational intervention available for targeting this pathophysiological interaction of inflammation and metabolism. Therefore, it is of importance to define

innovative anti-inflammatory strategies for the therapy of severe systemic hot and cold inflammation and their life-threatening metabolic complications. Instead of focusing upon the known inflammatory players, exploration of para-inflammatory processes [7], induced by macrophages, may suggest novel ways to address this problem.

Para-inflammation describes the cross-talk between a 'secondary' adaptive immune response, local tissue stress or (metabolic) malfunction and vice versa, all aimed at restoring tissue functionality [7]. We have shown that the secreted glycopeptide wingless-related integration site (wnt)-5a exerts such a 'restoring' effect in human obesity. In that model of cold inflammation, we have demonstrated that wnt5a is secreted by adipose tissue macrophages and alters adipocyte function [8,9]. Interestingly, in rodents, in chronic low-grade inflammation, wnt5a signalling is balanced by its inhibitor secreted frizzled-related protein (sFRP)-5 which is secreted, for example, by healthy adipocytes [10–12]. The wnt signalling pathway is highly conserved [12], as is the immunometabolic system. This suggested that our previous findings regarding wnt signalling in cold inflammation may also be relevant to hot inflammation, where an initial study reported that wnt molecules might be important [13]. Therefore, the aim of the present prospective clinical study was to investigate whether the wnt5a/sFRP5 system is dysregulated in human sepsis and might thereby serve as a molecular link between inflammation and metabolism.

Subjects and methods

This prospective observational study was approved by the local ethics committee [no. A161/11, Ethik Kommission der Universität zu Kiel, 24105 Kiel (Germany)]. Written informed consent was obtained from each subject or their legal representative before inclusion into the study.

Study population

Between January and December 2012, 60 consecutive critically ill patients with sepsis were recruited either at the medical or the anaesthesiological/surgical intensive care unit (ICU) (Table 1). Sepsis was defined in accordance with the 'Sepsis Guidelines 2010 of the German Sepsis Society' [14] and 'The international sepsis forum consensus conference on definitions of infection in the intensive care unit' [15]. An age- and sex-matched control cohort of 30 human individuals (basic characteristics in Table 2) was collected in the same time-period by the same department and the same personnel from the cross-sectional FoCus cohort, a population-based study in the North of Germany to study metabolic inflammation (http://www.focus.uni-kiel.de). The sepsis was treated according to standard guidelines. Subjects were included into the study in the morning within 24 h after diagnosis of sepsis, and serum samples were

Table 1. Basic characteristics, dropouts, focus of infection and antibiotic treatment applied of sepsis patients.

	Sepsis improved ($n = 38$)	Sepsis not improved ($n = 10$)	P-value
Male : female	21:17	8:2	0·2762
Age (years)	66·06 ± 2·29	69·8 ± 3·5	0·5263
Weight (kg)	77·71 ± 3·09	79·4 ± 5·9	0·6542
Height (m)	171·2 ± 1·19	175·4 ± 2·4	0·1193
BMI (kg/qm)	26·54 ± 1·15	25·7 ± 1·66	0·8689
Dropout			
Death	7		
Discharge	5		
Focus of infection			
Lungs	9	1	
Liver	0	2	
Kidney	3	2	
Git	11	2	
Lower extremity	1	0	
Unknown	14	3	
Antibiotics			
Vancomycin	6	4	
Erythromycin	5	3	
Piperacillin and tazobactam	8	2	
Ceftriaxone	3	2	
Metronidazol	11	4	
Ciprofloxacin	10	1	
Meropenem	9	1	
Cefotaxim	2	3	
Clarithromycin	5	0	
Sulphamicillin	1	0	
Imipenem	1	1	
Clindamycin	2	0	
Cefuroxim	1	0	
Gentamycin	1	1	
Rifampicin	1	0	
Neomycin	1	0	
Ceftazidim	1	0	
Diflucan	1	1	

Data are given as means ± standard error of the mean; $P > 0·05$ = not significant. BMI = body mass index.

Table 2. Basic characteristics of sepsis patients and age-, sex- and body mass index (BMI)-matched healthy controls of wingless-related integration site (wnt)-5a and secreted frizzled-related protein (sFRP)-5 serum concentration measurements.

	Control ($n = 30$)	Sepsis ($n = 48$)	P-value
Male : female	13:17	29:19	0·8149
Age (years)	67·17	66·92	0·9216
BMI (kg/m^2)	26·04	26·36	0·3688
CRP (mg/l)	5·04	199·7	<0·0001

Data are given as means ± standard error of the mean; $P > 0·05$ = not significant. CRP = C-reactive protein.

conserved (= baseline). Wnt5a and sFRP5 serum levels were measured at the time-point of inclusion into the study and 5 days later. Based on the changes of the classical inflammatory infection parameters [leucocytes, C-reactive protein (CRP), procalcitonin (PCT)] within the 5 days of observation, patients were divided into two groups: patients with a clinical improvement and an at least 30% decrease in at least one of the classical inflammatory markers between days 0 and 5 of the observational period were classified as 'sepsis improved'; $n = 38$ patients (Table 1). Conversely, no change or increase of classical inflammatory parameters suggested no sepsis improvement, and patients were thus assigned to the 'sepsis not improved' category; $n = 10$ patients (Table 1). Seven patients died and five were referred to other hospitals within 5 days of admission (dropouts). Inclusion criteria were: male and female patients aged 20–80 years, sepsis, informed consent of patient or legal representative and Caucasian descent. Exclusion criteria were: known HIV, hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. The number of patients suffering from type 2 diabetes was overall low (<20%), and was not statistically significant between controls and sepsis patients ($P = 0{\cdot}230$).

Biochemical analysis

Blood samples were taken during the morning hours at baseline and on day 5 of follow-up. Blood cell count was measured using automatic bead cell count (Sysmex, Kobe, Japan; Modell XE-5000). Serum was centrifuged at 677 ***g*** for 5 min, aliquoted and stored at −80°C. The following enzyme-linked immunosorbent assays (ELISA) for wnt-signalling molecules and sFRP5 proteins were used: wnt5a [Uscn Life Science Inc. Wuhan, China; order number E83549Hu (analytical-sensitivity: 0·051 ng/ml)]; sFRP5 [Uscn Life Science Inc.; order number E92842Hu (analytical-sensitivity: 0·64 ng/ml)]. The ELISAs were performed according to the manufacturer's instructions. According to the manufacturer, the wnt5a ELISA and the sFRP5 ELISA had excellent specificity for detection of human wnt5a and sFRP5 and no significant cross-reactivity or interference with analogues was observed. The specificity of the antibodies was confirmed by Western blot experiments. For the wnt5a antibody, two cell line lysates were tested by the manufacturer. HeLa cells produced a positive signal, while HEK293 cells were negative. For the sFRP5 antibody, tissue homogenates from human pancreas and liver tissue were tested separately (personal communications with the supplying company). Insulin and glucose were determined in serum using automated analysers in the Department of Clinical Chemistry of the University Hospital of Schleswig-Holstein in Kiel (Germany). The Homeostatic Model Assessment index (HOMA) was calculated as follows: fasting insulin (μU/ml) × fasting glucose (mg/dl)/405 [16]. The HOMA index is widely used to estimate insulin resistance, whereby normal insulin sensitivity is associated with values below 3, moderate insulin resistance is associated with values between 3 and 5 and severe insulin resistance is associated with values greater than 5 [17].

Statistical analysis

Statistical analysis was performed using GraphPad Prism version 5·01 and SPSS version 22 software. Associations between categorical variables were assessed by χ^2 test. Continuous data were analysed for normality of distribution using Kolmogorov–Smirnov and Shapiro–Wilk tests. In the case of independent-samples group comparison, Student's *t*-test was applied for normally distributed data and the Mann–Whitney *U*-test was used if non-parametric data in one or both groups was present. In the case of group comparison of paired samples the paired *t*-test was applied for normally distributed data, and Wilcoxon's signed-rank test was used if non-parametric data in one or both groups was present. For correlation analysis, Spearman's correlation coefficient was used. Values of $P < 0{\cdot}05$ were considered statistically significant.

Results

Clinical manifestations

Patient characteristics are outlined in Table 1. In total, 60 critically ill patients with sepsis were enrolled into the study. During follow-up, seven patients died and five were referred to other hospitals, meaning a follow-up dropout rate of 20%. In 17 patients the concurrent source of sepsis remained unclear. The focus had been diagnosed in the gastrointestinal tract for 13 patients, in the lung for 10 patients, in the kidney/urogenital tract for five cases, in the liver for two patients and one affected lower extremity. Antibiotics were administered in different combinations (Table 1). In the 'sepsis improved' group CRP levels exhibited a reduction from $200{\cdot}4 \pm 18{\cdot}1$ to $84{\cdot}9 \pm 10{\cdot}3$ mg/l ($P < 0{\cdot}001$), while in the 'sepsis not improved group' CRP levels raised from $197{\cdot}2 \pm 33{\cdot}8$ to $258{\cdot}8 \pm 37{\cdot}5$ mg/l ($P = 0{\cdot}046$). With regard to the leucocyte count, a reduction was observed from $13{\cdot}9 \pm 1{\cdot}0$ to $10{\cdot}5 \pm 0{\cdot}8 \times 10^9$/l ($P = 0{\cdot}008$) in the 'sepsis-improved group', while the 'sepsis not-improved group' exhibited the following parameters: day 0, $16{\cdot}1 \pm 2{\cdot}4 \times 10^9$/l; day 5, $18{\cdot}7 \pm 2{\cdot}5 \times 10^9$/l ($P = 0{\cdot}401$). Finally, the PCT levels were falling in the 'sepsis-improved group' from $15{\cdot}1 \pm 5{\cdot}8$ to $1{\cdot}7 \pm 0{\cdot}5$ ng/ml ($P = 0{\cdot}089$) during the 5-day observational period, while in the 'sepsis not-improved group' the PCT changed from $37{\cdot}0 \pm 31{\cdot}6$ to $22{\cdot}7 \pm 18{\cdot}9$ ng/ml ($P = 0{\cdot}7618$).

Wnt5a serum levels are elevated in sepsis patients

In a previous report, we have shown elevated wnt5a levels in morbidly obese subjects with low-grade

inflammation compared to age- and sex-matched lean controls [18]. In the present study we measured wnt5a serum levels by ELISA in sepsis patients in order to examine whether wnt5a is related specifically to low-grade inflammation of adipose tissue, or whether wnt5a might also be a proinflammatory factor in the much more severe condition of hot inflammation. Therefore, we compared wnt5a serum levels on administration to ICU of sepsis patients to those of age- and sex-matched controls. This analysis revealed a sevenfold increase in wnt5a serum levels in sepsis patients compared to controls (Fig. 1).

Wnt5a serum levels are associated with insulin resistance in sepsis patients

In order to examine whether wnt5a is associated with the degree of insulin resistance in sepsis patients, we measured glucose and insulin levels at admission to the ICU and calculated the HOMA. In the first analysis, we divided the cohort into individuals with mild insulin resistance (HOMA <5) and severe insulin resistance (HOMA >5) and compared serum wnt5a concentrations. In agreement with the hypothesis that wnt5a might be involved in metabolic inflammation, in that analysis individuals with severe insulin resistance exhibited significantly higher wnt5a levels compared to individuals with mild insulin resistance ($P < 0{\cdot}05$, Fig. 2). In addition, we performed correlation analysis of wnt5a and HOMA showing a significant positive correlation of wnt5a and HOMA in severe insulin-resistant sepsis patients ($r_s = 0{\cdot}46$, $P = 0{\cdot}014$).

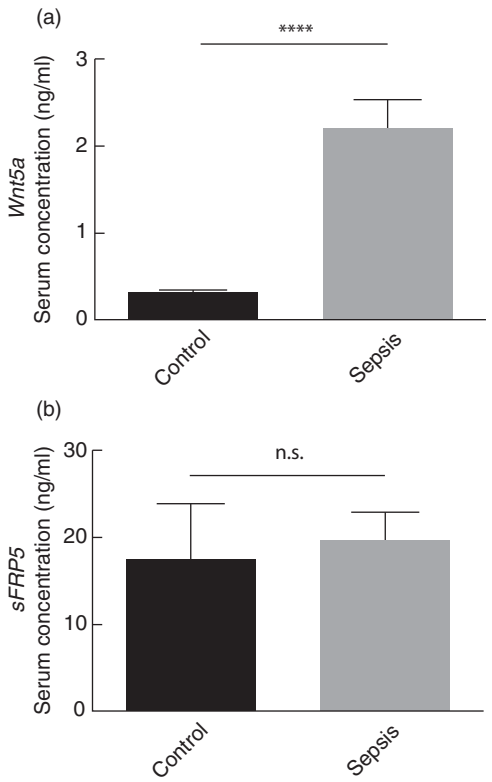

Fig. 1. Wingless-related integration site (wnt)-5a and secreted frizzled-related protein (sFRP)-5 serum concentrations in sepsis patients and age-, sex- and body mass index (BMI)-matched healthy controls. (a) Levels of wnt5a, (b) levels of secreted frizzled-related protein (sFRP)-5. For group comparison, the Mann–Whitney *U*-test was applied. Data are given as means ± standard error of the mean; ****$P < 0{\cdot}0001$, n.s. = not significant.

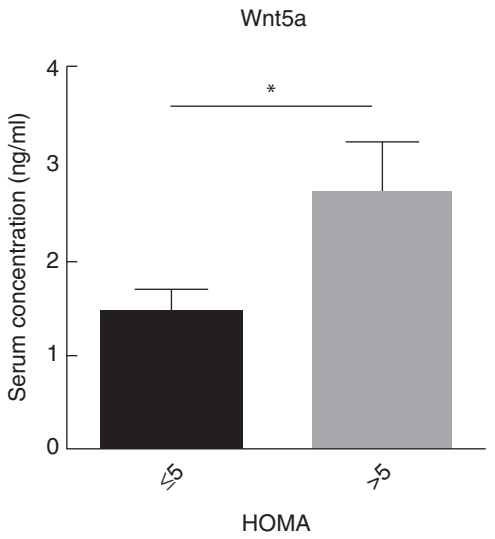

Fig. 2. Wingless-related integration site (wnt)-5a serum concentrations in sepsis patients and controls with normal glucose tolerance or mild insulin resistance [Homeostatic Model Assessment index (HOMA) ≤ 5] *versus* severe insulin resistance [HOMA > 5]. For group comparison, the Mann–Whitney *U*-test was applied. Data are given as means ± standard error of the mean; *$P < 0{\cdot}05$.

Wnt5a serum levels are correlated positively with the leucocyte count

As was found in previous studies, leucocytes are supposed to be a major source of wnt5a in humans in low-grade inflammation [9] and in hot inflammation (sepsis) [13]. Therefore, we performed correlation analysis of several cellular and humoral inflammatory factors and serum wnt5a concentrations at admission to the ICU (Table 3 and Fig. 3). Strikingly, only the leucocyte count was correlated significantly positively with increasing serum concentrations of wnt5a ($r_s = 0{\cdot}3797$, $P = 0{\cdot}0039$) (Table 3 and Fig. 3).

Wnt5a serum levels decrease if sepsis is improved

In the next step, we compared wnt5a levels at admission to the ICU between 'sepsis-improved' (2·17 ± 0·38 ng/ml) and 'sepsis not-improved' (2·34 ± 0·59 ng/ml) groups. In that analysis, no significant difference could be observed (Figs 4 and 5) at baseline. The degree of insulin resistance given by the HOMA index was also not different between these two

Table 3. Correlation analysis of wingless-related integration site (wnt)-5a and secreted frizzled-related protein (sFRP)-5 with common cellular and humoral markers of inflammation.

	Day 0: correlation coefficient	*P*-value	No. of XY pairs	Day 5: correlation coefficient	*P*-value	No. of XY pairs
wnt5a *versus* leucocytes	0·3797	0·0039	56	0·2264	0·1493	42
wnt5a *versus* CRP	0·0172	0·9059	50	0·1433	0·3906	38
wnt5a *versus* PCT	0·3550	0·0638	28	0·4048	0·3268	8
sFRP5 *versus* leucocytes	0·2128	0·1154	56	–0·0986	0·5344	42
sFRP5 *versus* CRP	0·0879	0·5437	50	–0·2011	0·2260	38
sFRP5 *versus* PCT	0·1629	0·4077	28	–0·4524	0·2675	8

Spearman's r_s, $P < 0{\cdot}05$ = significant, $P > 0{\cdot}05$ = not significant. CRP = C-reactive protein; PCT = procalcitonin; (wnt)-5a = wingless-related integration site; (sFRP)-5 = secreted frizzled-related protein.

groups at baseline ($P = 0{\cdot}493$). Furthermore, we analysed the wnt5a serum levels between days 0 and 5 in the sepsis patients. In the 'sepsis-improved' group wnt5a serum levels decreased significantly (Fig. 4) between days 0 ($2{\cdot}17 \pm 0{\cdot}38$ ng/ml) and 5 ($1{\cdot}03 \pm 0{\cdot}28$ ng/ml, $P = 0{\cdot}002$). In contrast, the wnt5a levels in the 'sepsis not-improved' group tended to increase (Fig. 5) [day 0 ($2{\cdot}34 \pm 0{\cdot}59$ ng/ml) and day 5 ($3{\cdot}25 \pm 1{\cdot}02$ ng/ml, statistically not significant].

Failure of compensatory sFRP5 induction in sepsis patients

We next measured anti-inflammatory sFRP5 in the same serum samples, as this wnt5a inhibitor was found to show compensatory up-regulation in human chronic low-grade inflammation [19]. sFRP5 levels at baseline were $19{\cdot}72 \pm 3{\cdot}06$ ng/ml. This was not significantly different to those in age- and sex-matched healthy controls (Fig. 1), indicating no induction of sFRP5 in sepsis patients. Patients in whom sepsis worsened during the time–course of the study tended to exhibit lower sFRP5 serum levels at the beginning ($14{\cdot}49 \pm 3{\cdot}43$ *versus* $21{\cdot}10 \pm 3{\cdot}75$ ng/ml); however, this effect did not reach statistical significance. At the end of the study period, sFRP5 serum levels accounted to $18{\cdot}54 \pm 3{\cdot}63$ ng/ml in the subjects were sepsis-improved and $15{\cdot}57 \pm 5{\cdot}18$ ng/ml in the subjects with no improvement, which was not statistically significant different from baseline.

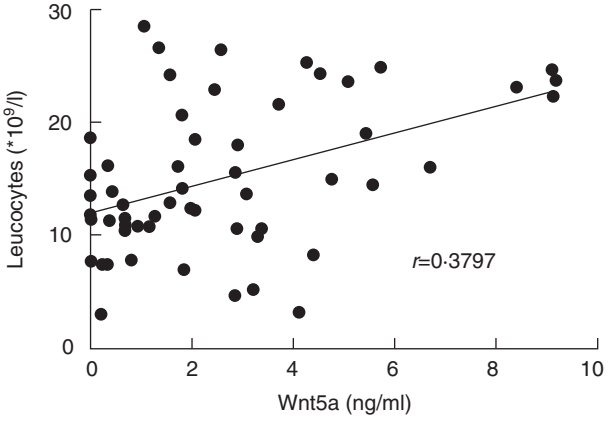

Fig. 3. Correlation analysis of serum wingless-related integration site (wnt)-5a levels and leucocyte count at baseline (day 0). Spearman's correlation was applied. Data are given as Spearman's correlation coefficient $r_s = 0{\cdot}3797$, $P = 0{\cdot}0039$.

Discussion

Several high-profile clinical trials of new forms of sepsis treatment have published negative results during recent years, leading researchers to the conclusion that sepsis studies require new directions [20]. Important reasons for the failures of new investigative drugs have been suggested to lie in problems in design and implementation of those trials [21–26]. It is thought that key pathophysiological mechanisms that drive sepsis have not been understood fully [27]. Most concepts and understandings of mechanisms and treatment targets in sepsis are based on the idea of the involvement of the classical immune system and cytokine storms. New ideas include the wider use of biomarker-guided therapeutic approaches and immune-adjuvant therapies [28], while suppression of apoptosis has also been suggested as a new therapeutic target [29].

It is well recognized that sepsis confers a high risk of morbidity and mortality and also features concomitant endocrine and metabolic disturbances [4]. In particular, insulin resistance and hyperglycaemia seem to have a causal link to adverse outcomes in sepsis [5]. Therefore, there is an unmet clinical need to describe para-inflammatory mechanisms in the time–course of sepsis, potentially inducing the link to metabolism. In an earlier study we identified wnt5a to be secreted by adipose tissue macrophages [9]. Expression of wnt5a was also reported in haemophagocytic macrophages of sepsis patients [13]. Interestingly, in the same study, Pereira *et al.* detected wnt5a in peripheral blood samples of sepsis patients by immunoprecipitation and Western blot [13]. Together, these findings suggest that wnt5a might serve as a novel proinflammatory factor in hot and cold inflammation. Therefore, in the present study in a larger independent cohort we aimed to measure wnt5a serum levels at different time–points during the course of human sepsis to gain further insights into

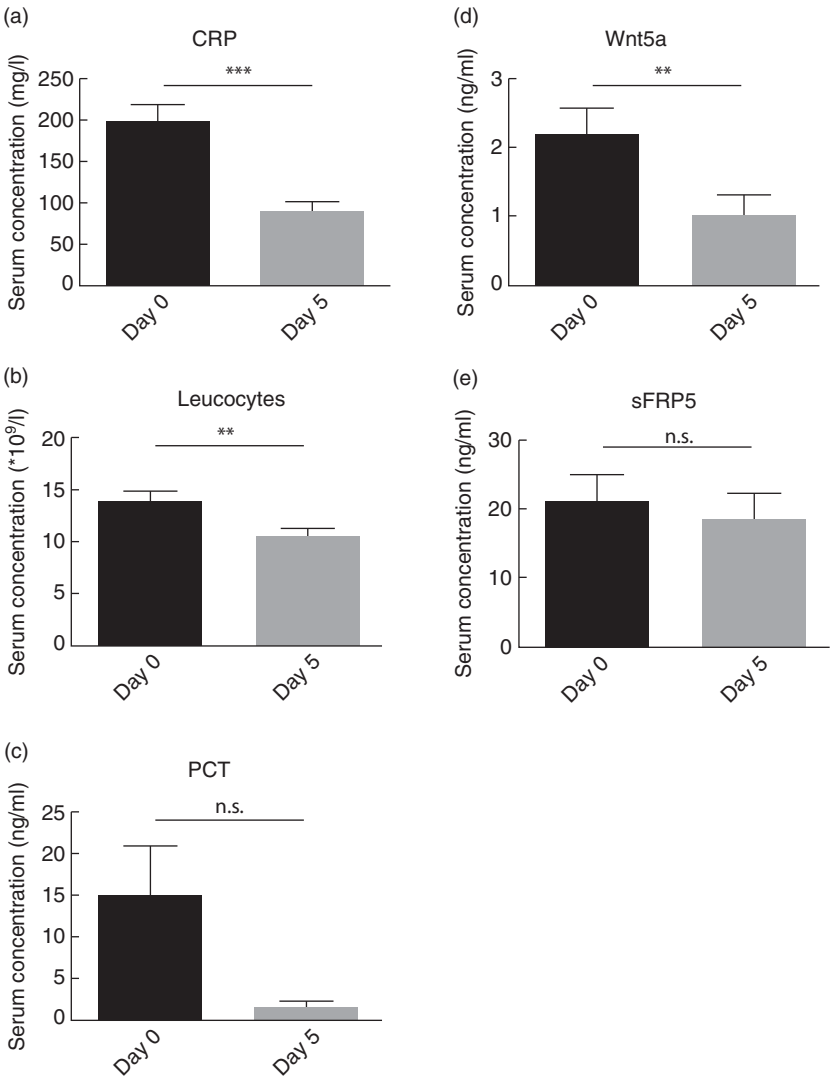

Fig. 4. Changes in wingless-related integration site (wnt)-5a, secreted frizzled-related protein (sFRP)-5 and common cellular and humoral inflammatory markers in critically ill septic patients in whom sepsis improved between days 0 and 5. (a) C-reactive protein (CRP); (b) leucocytes; (c) procalcitonin (PCT); (d) wingless-related integration site (wnt)-5a; (e) secreted frizzled-related protein (sFRP)-5. For group comparison, the paired *t*-test was applied in the case of normal distribution of data and Wilcoxon's signed-rank test in the case of non-parametric data in one or both groups. Data are given as means ± standard error of the mean; $^{***}P < 0{\cdot}001$, $^{**}P < 0{\cdot}01$, $^{*}P < 0{\cdot}05$, n.s. = not significant.

wnt5a biology. In contrast to the earlier report by Pereira *et al.*, we used a quantitative approach by ELISA instead of a semi-quantitative analysis by Western blot. In parallel, for the first time we measured the wnt5a inhibitor sFRP5 in the same serum samples. In that analysis we observed wnt5a induction in human sepsis *in vivo*, fitting with the hypothesis that wnt5a is a proinflammatory molecule, which could be causally involved in the pathogenesis of this systemic inflammatory disease. Furthermore, we observed that measurements of wnt5a levels at baseline do not predict the outcome (improvement *versus* non-improvement/worsening) of the sepsis; however, wnt5a serum levels reflect the course of the disease with decreased levels of wnt5a when sepsis is improved.

Which tissue is the major source of wnt5a cannot be concluded from our clinical study. However, several findings suggest that leucocytes might be a major contributor to the increased serum wnt5a levels: (i) we and others have shown earlier that human monocytes and macrophages express wnt5a *in vivo* [9,13]; (ii) leucocytes are major cellular effectors in inflammatory processes in early sepsis [30]; and (iii) wnt5a serum levels were found to be correlated positively with the leucocyte count in the present study.

Wnt5a might be important in the link between metabolic and inflammatory reactions in the context of human sepsis, as previous reports suggest wnt5a to inhibit insulin receptor signalling [10]. In agreement with these data, in the present study we detected increased levels of wnt5a in sepsis patients with severe insulin resistance compared to subjects with only a mild insulin resistance. This finding underlines the hypothesis that wnt5a is a potential factor in the development of the so-called metabolic inflammation.

A significant decrease in classical proinflammatory markers within the first 5 days of the diseases indicates an improvement of the sepsis (Fig. 4). In parallel, we found that wnt5a serum levels also decline significantly when sepsis improved (Fig. 4). As the major source of wnt5a are

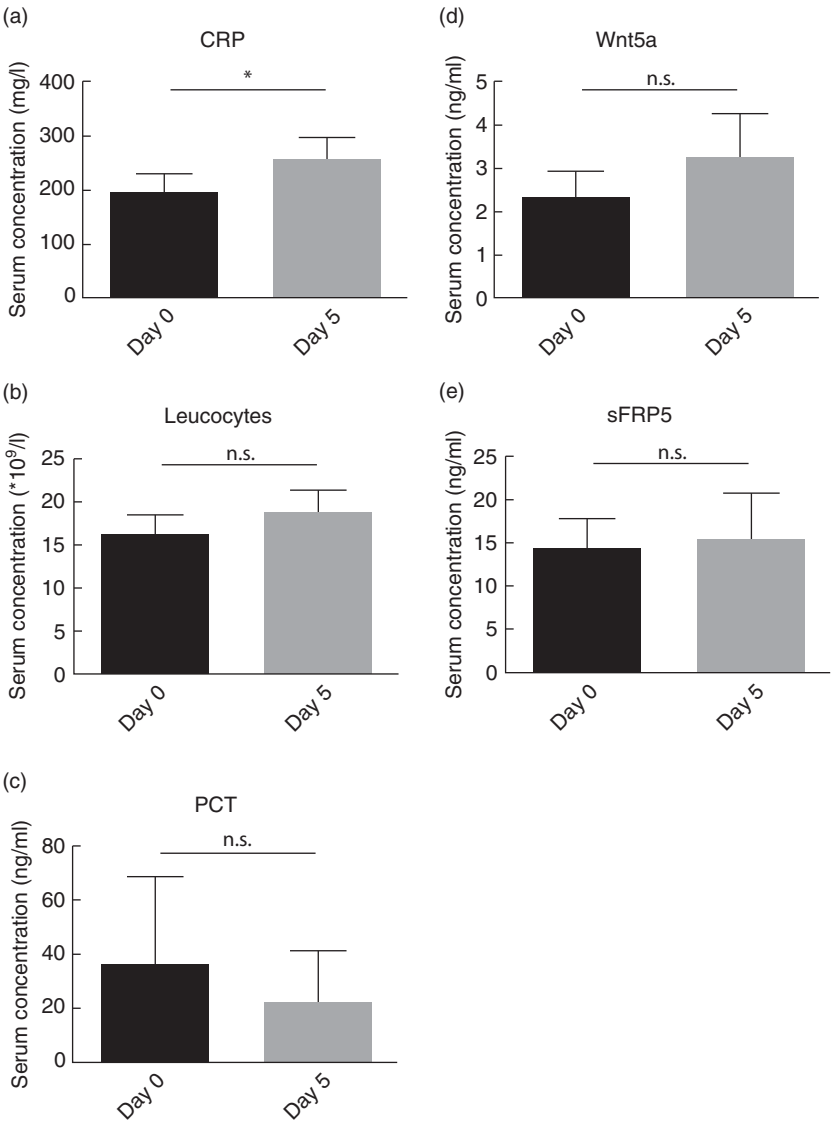

Fig. 5. Changes in wingless-related integration site (wnt)-5a, secreted frizzled-related protein (sFRP)-5 and common cellular and humoral inflammatory markers in critically ill septic patients in whom sepsis did not improve between days 0 and 5. (a) C-reactive protein (CRP); (b) leucocytes; (c) procalcitonin (PCT); (d) wingless-related integration site (wnt)-5a; (e) secreted frizzled-related protein (sFRP)-5. For group comparison, the paired *t*-test was applied in the case of normal distribution of data and Wilcoxon's signed-rank test in the case of non-parametric data in one or both groups. Data are given as means ± standard error of the mean; $^*P < 0{\cdot}05$; n.s. = not significant.

supposed to be leucocytes, together these findings indicate that wnt5a might serve as a novel cytokine in the human innate immune system.

In contrast to proinflammatory wnt5a, the serum concentrations of anti-inflammatory sFRP5 were neither increased at the time-point of the diagnosis nor did they change significantly during the time–course of sepsis (Figs 1, 4 and 5). This is in contrast to what we found in a model of chronic inflammation: in a present report from our group wnt5a was found to be elevated in serum samples of human subjects with psoriasis, a chronic inflammatory disease known to be associated with severe metabolic complications. In this study, increased sFRP5 concentrations were detected in serum samples of psoriasis patients, suggesting that under chronic inflammatory circumstances the human organism is, at least in part, able to prevent overwhelming wnt5a activity [19]. Taking these findings into consideration, it might be speculated that under chronic inflammatory conditions the human organism is able to prevent overwhelming wnt5a activity by producing sFRP5 and that this compensatory mechanism is not activated in the early stages of acute high-grade inflammation.

Interestingly, sFRP5 has been patented recently to restore normal metabolic function (US20110274689), and might therefore be a novel therapeutic option for metabolic abnormalities associated with acute inflammatory diseases to mimic the compensatory sFRP5 up-regulation found under chronic inflammatory conditions [19]. Thus, the wnt5a/sFRP5 system might be of clinical relevance in the future, suggesting that more research should be carried out into this novel cytokine system.

In conclusion, the data reported in the present study suggest that the wnt5a/sFRP5 system might be an interesting subject for future studies of the pathogenesis of human sepsis and the development of novel therapies targeting it.

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Disclosure

None of the authors has something to disclose.

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