Progranulin Regulates Gene Networks Involved in the Antimicrobial Response and May Serve as a Biomarker for Sepsis

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Parameter	Healthy (n=45)	Localized Infection (n=47)	Sepsis [a] (n=111)
Age (y)	50 (39 - 53)	51 (35.5 - 64)	68 (57 – 77)
BMI (kg/m^2)	25.2 (23.6 - 26.0)	26.3 (23.4 - 28.7)	25.39 (22.0 – 29.3)
APACHE II	-	4 (3 – 5)	24 (16.25 – 31)
qSOFA	-	0	2 (2 – 3)
SOFA	-	-	12 (8 – 14)
Lactate (mmol/L)	-	1.1 (1 – 1.6)	2.5 (1.6 – 3.6)
Norepinephrine (µg/kg/min)	-	0	0.32 (0.12 – 0.67)
Acute renal failure (%)	-	8.5 (n = 4)	52.3 (n = 58)
ARDS (%)	-	0	34.2 (n = 38)
ICU stay required (%)	-	2.1 (n = 1)	95.5 (n = 106)
Duration of ICU therapy (d)	-	7	13 (8 – 31.75)
Mortality (%)	-	0	23.4 (n = 26)

Data are median (p_{25}-p_{75})
[a]Thirty-one patients had sepsis, 80 patients were in septic shock (Sepsis-3 criteria)

Table 1

Introduction. Progranulin (PGRN) is a pleiotropic growth factor with a central role in the early protective and antiinflammatory host response to bacterial infections (1,2). PGRN deficiency results in severe inflammation and lung injury in experimental animals after a lipopolysaccharide (LPS) challenge (3). We delineated the molecular network involved in the regulation of PGRN expression in early sepsis and tested the hypothesis that PGRN concentrations in plasma could serve as a novel biomarker for sepsis.

Methods. We calculated Area Under Curve (AUC) and Receiver Characteristic Curves (ROC) for PGRN alone, and in comparison with the established biomarkers procalcitonin (PCT), C-reactive protein (CRP) and interleukin-6 (IL-6) in 111 patients with sepsis (Sepsis-3 criteria), 47 patients with severe localized infections (e.g. large peripheral abscesses) at high risk for sepsis, and 45 healthy volunteers (s. Table 1 for demographic and clinical data). Additionally, we performed comprehensive untargeted high-throughput sequencing of miRNAs and mRNAs isolated from blood cells of patients with septic shock (n=7) and healthy volunteers (n=7) to identify the canonical gene network involved in the antimicrobial response of PGRN followed by qPCR confirmation in an independent and larger sample (n=39 for septic shock and n=23 for controls).

Results. Sepsis prediction by PGRN (AUC=0.89±0.03, 95% CI=0.84-0.94) for localized infection was comparable to PCT (AUC=0.87±0.03, CI=0.81-0.93 for PCT, p=0.67 for AUC difference to PGRN, paired DeLong test) and to CRP (AUC=0.86±0.04, CI=0.78-0.94, p=0.56) and significantly better than IL-6 (AUC=0.57±0.05, CI=0.48-0.69, p<0.001) (Figure A).

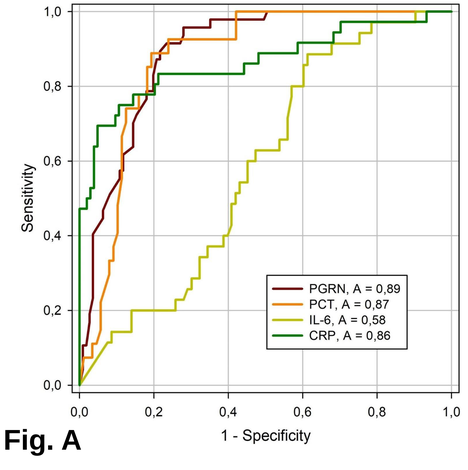

Fig. A

High-throughput sequencing in patients with septic shock and healthy controls revealed 82 significantly regulated miRNAs (40 upregulated) and 2,918 paired target mRNAs (1,385 upregulated). Using in-silico analyses, we constructed a transcriptomic network involved in the early antimicrobial response to septic shock, which verified an upregulated PGRN (GRN gene) expression ($log_2FC=1.16$, $p_{adj}=3.46E-8$). Further genes involved in the network were sortilin, an important regulator of PGRN plasma levels (4), ($log_2FC=2.47$, $p_{adj}=1.38E-8$) as well as Toll-like Receptor 4 (TLR4, upregulated, $log_2FC=2.83$, $p_{adj}=6.56E-3$), known to recognize LPS in early sepsis (5), and Tumor Protein 53 (TP53, downregulated, $log_2FC=-2.45$, $p_{adj}=1.37E-11$), which has potential roles in cellular division, repair, and metabolism in septic shock (6). Downregulated sepsis-related miR-16-5p ($log_2FC=-2.40$, $p_{adj}=1.19E-3$), miR-150-5p ($log_2FC=-2.41$, $p_{adj}=2.14E-6$) and others were found to regulate mRNA expression within the network (Figure B).

Conclusion. PGRN is part of a key network involved in the early antimicrobial response, is regulated by sepsis-associated miRNAs, and may represent a novel and sensitive risk biomarker for the development of sepsis in the presence of a severe localized infection.

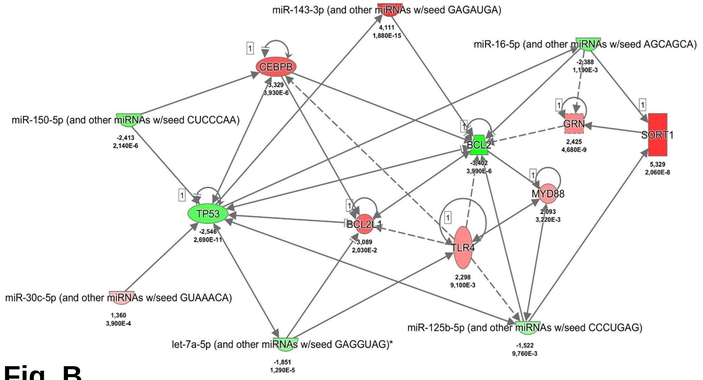

Fig. B

References. (1) Am J Respir Crit Care Med 194 (10), 2016, 1219-32, (2) J Leukoc Biol 93 (2) 199-208, (3) J Cell Mol Med 20 (3) 506-17, (4) Am J Hum Genet 87 (6) 890-7, (5) Curr Opin Immunol 44 14-19, (6) Am J Respir Crit Care Med 194 (4) 494-501