Identification of Endothelial Cell Protein C Receptor by Urinary Proteomics as a Novel Prognostic Marker in Non-recovery Kidney Injury

Chih-Hsiang Chang MD[1], Chen-Chia Lee MD[1], Yung-Chang Chen MD[1], Pao-Hsien Chu MD, PhD[2], Lichieh Julie Chu PhD[3], Jau-Song Yu PhD[3], Hsiao-Wei Chen[3], Chih-Wei Yang MD[1], Yi-Ting Chen* PhD[3]

[1]Department of Nephrology, Kidney Research Center, Chang Gung Memorial Hospital, Taiwan
[2]Department of Cardiology, Chang Gung Memorial Hospital, Taiwan; [3]Chang Gung University, Taiwan

長庚醫療財團法人
Chang Gung Medical Foundation

Introduction

- Acute kidney injury is a common and complex complication that has high morality and the risk for chronic kidney disease among survivors.
- The accuracy of current AKI biomarkers can be affected by water retention and diuretics.
- We aimed to identify a non-recovery marker of acute kidney injury in patients with acute decompensated heart failure.

Method and Materials

- Patients with acute decompensated heart failure admitted to the intensive care unit were enrolled between Dec 2016 and Jan 2020.
- AKI was defined as that occurring within 7 d after admission according to the KDIGO criteria. Non-recovery AKI was defined as serum creatinine more than 1.5 times the baseline after 2 weeks.
- A high-resolution chemical labeling proteomic platform , Isobaric Tag for Relative and Absolute Quantification technology(iTRAQ), was used to identify a relevant urine marker protein.
- A network analysis of differentially expressed proteins identified in each clinical set was performed using the MetaCore analytical suite.

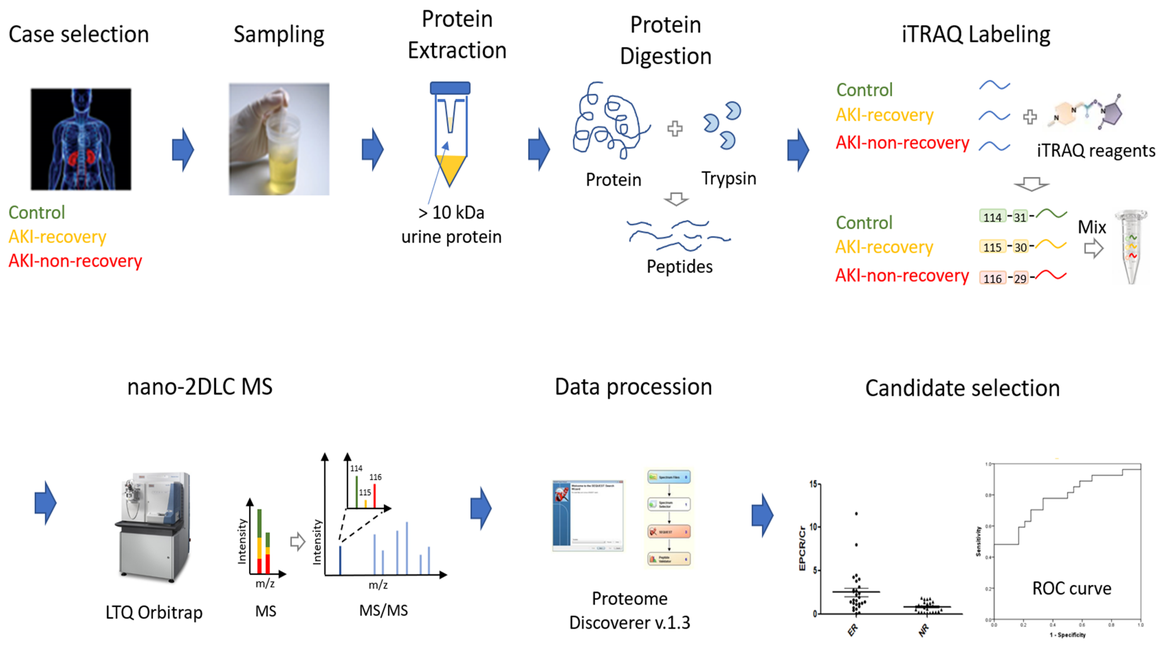

Figure 1. Work flow of this study

Results

- A total of 2384 urine proteins were identified in the iTRAQ experiment, 2308 of which yielded at least one quantifiable peptide. We identified 189 increased and 109 decreased proteins in two AKI groups.
- A total of 51 patients with AKI who were not part of the discovery group were enrolled and divided into recovery and non-recovery groups, and ELISA was used to test the ability of endothelial cell protein C receptor (EPCR) to distinguish between these groups. The AUROC of urine EPCR/creatinine was 0 .776±0.065 (95%CI: 0.648-0.905).
- Our MetaCore analysis identified two potentially important pathways of EPCR: protein folding and Immune response via the alternative complement pathway and lectin-induced pathway.

Table 1. Study cohort

iTRAQ tags	Diagnosis	Patient size	Average age	iTRAQ labeling tag
114	Control	*15*	73.4 ± 7.4	114
115	AKI with recovery	*9*	74.4 ± 8.5	115
116	AKI with Non-recovery	*6*	71.8 ± 3.8	116

Table 2. Urine proteome analysis

		With 1 Unique Peptide	
	With Quantative Results	2384	2308
	Without Quantative Results		76
Protein (Peptide) of False Discovery Rate		0.01	
Both ratios of 115/114 and 116/114 tags > 2		189	
AKI > control		589	
Both ratios of 115/114 and 116/114 tags > 2		189	
Ether one ratio of 115/114 or 116/114 tags > 2		400	
AKI < control		**537**	
Both ratios of 115/114 and 116/114 tags > 2		109	
Ether one ratio of 115/114 or 116/114 tags < 2		428	
No significant changes in concentrations		177	
Loss of identification in one ratio; and not consistence in two ratios		5	

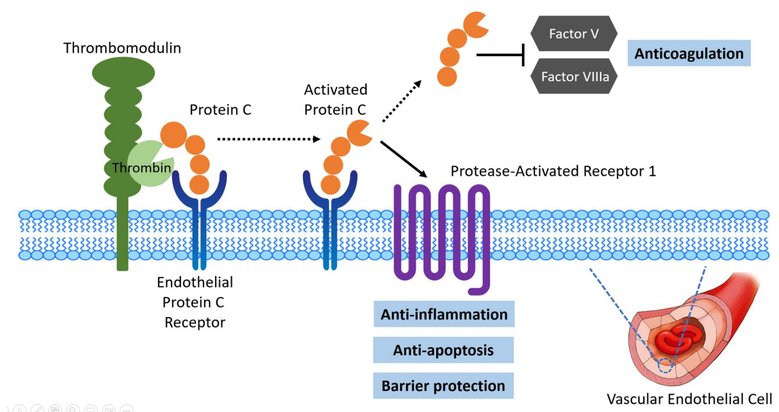

Figure 2. Role of endothelial protein C receptor (EPCR)

Conclusions

We found that the EPCR was an outstanding marker for non-recovery acute kidney injury in patients with decompensated heart failure. Further validation is needed.