Neutrophil neprilysin expression correlates with inflammatory activation in chronic HFrEF patients

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Background: Inhibition of neprilysin by the angiotensin receptor-neprilysin inhibitor has shown remarkable success in the treatment of heart failure with reduced ejection fraction (HFrEF). However, the exact mechanism of action is still a matter of debate. Neprilysin (NEP) is a ubiquitous transmembrane endopeptidase markedly expressed on the cell surface of neutrophils, in this context also known as CD10. Originally, CD10 has been identified as a cell surface marker to discriminate mature from immature neutrophils. Other inflammatory neutrophil surface markers such as CD11b, CD64 and CD66b are commonly used to determine the activation status of neutrophils. In our previous explorative study, NEP expression on neutrophils correlated inversely with HF severity and mortality. This study aimed to explore the relationship between NEP expression and typical neutrophil activation markers and to confirm its relation to HF severity reflected by NT-proBNP and NYHA class in a bigger cohort of HFrEF patients.

Methods: We prospectively enrolled 208 consecutive patients with stable HFrEF. Mean fluorescence intensity (MFI) of CD10 expression on peripheral blood neutrophils was determined by flow cytometry of whole blood samples. In addition, for a subset of 117 patients the expression of CD11b, CD64 and CD66b was measured. EDTA anticoagulated blood (100 μl) was stained using a combination of six antibodies with fluorescence minus one sample as control [CD10 (#332777), CD45 (#560178), CD16 (#335035), CD11b (#555388), CD64 (#561191), CD66b (#562254); BD Biosciences, San Jose, CA, USA].

Results: Median age was 64 years (IQR 54–72), 57 (27%) patients were female. Median NT-proBNP values were 1819 pg/ml (IQR 740–4264). Approximately half of the study population with 115 (55.3%) patients had a non-ischemic etiology of HF. Median MFI of NEP (CD10) on neutrophils was 5542 (IQR 4168–6903). Neutrophil NEP expression decreased with HF severity reflected by NYHA stage (p=0.006) and tertiles of NT-proBNP (p=0.003). Interestingly, non-ischemic HFrEF was characterized by higher neutrophil NEP expression compared to ischemic HFrEF [5703 (IQR 4548–7235) vs 4994 (IQR 3844–6718), p=0.018]. Neutrophil NEP expression correlated highly significant with CD11b expression (r=0.61, p<0.001) but not with CD64 and CD66b [p=ns] (Figure 1).

Conclusion: These data support the evidence for an inverse correlation of neutrophil NEP expression with HF severity in stable HFrEF patients and for NEP upregulation on neutrophils in patients with non-ischemic cardiomyopathy. There was a strong relationship between neutrophil NEP regulation and the activation marker CD11b, proposing a link between the neutrophil NEP compartment and systemic inflammatory response.

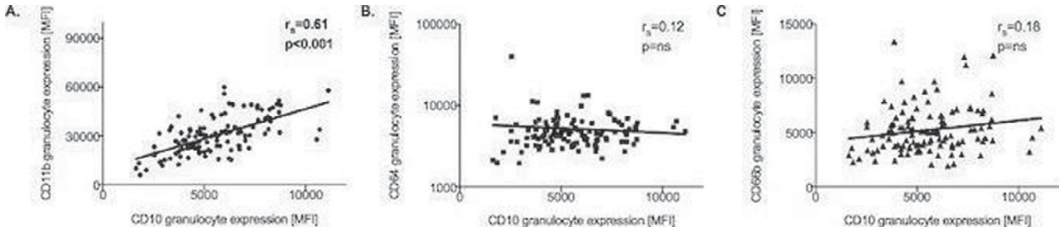

Figure 1

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