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The Functional Role of Arginase 1 and Neutrophil Proteomics in Predicting Ischemic Stroke Outcome

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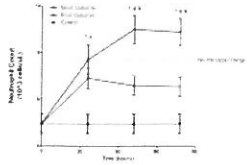
Introduction: Peripheral neutrophil (PMN) count is elevated within the first few hours of acute ischemic stroke (AIS), and neutrophilia is associated with greater AIS severity, larger infarct volume, and poor functional outcome. In animal models, PMN inhibition results in decreased infarct volume and improved functional outcome; however, this strategy has not been successfully translated in clinical trials. We hypothesize that PMNs are a heterogeneous population, consisting of both "beneficial" and "detrimental" subtypes, depending on their functional protein expression, and one PMN protein, arginase 1 (ARG1), may be a key contributor to detrimental PMN function post-AIS. We have previously described a distinct temporal pattern of PMN expression following AIS between favorable and poor outcome AIS patients. Thus, the purpose of this study was to expand upon this examine the function relationship between ARG1, as well as other PMN proteins, and outcome following AIS.

Hypothesis: We hypothesized that PMNs isolated from AIS patients with poor outcome will have higher ARG1 expression compared to neutrophils in the favorable outcome group. Further, we hypothesize that PMNs isolated from AIS patients with poor outcome will have a distinct functional proteome, giving rise to altered or more aggressive function that leads to a poor outcome following AIS.

Methods: We quantified PMN ARG1 expression in a subset of 24 AIS patients – n=12 favorable and n=12 poor outcome. PMN ARG1 protein expression was determined by flow cytometry by co-staining for the surface marker for PMNs, CD66b, and intracellular ARG1. Further, in a subset of these patients – n=3 favorable and n=3 poor outcome, we performed a proteomic analysis on isolated PMNs.

Results: ARG1 protein expression was significantly higher in PMNs isolated from AIS patients with a poor outcome (mean ARG1 = 665 + 117) compared to AIS patients with a favorable outcome (mean ARG1 = 453+108) (p=0.008). Further, in the samples sent for proteomics, we observed several differences in the PMN proteome between the AIS outcome groups. Specifically, the PMN proteins - ARG1, defensins 1 and 4, and protein s100a9 – were increased in the poor outcome compared to the favorable outcome group.

Conclusion: In conclusion, targeting specific PMN proteins, such as ARG1, rather inhibiting PMNs as a whole, may represent a more targeted and successful approach to modulating PMNs post-AIS to improve outcome.



Neutrophil counts at 0-24, 24-48, and 48-72 hours post-AIS. Dashed line denotes upper value of normal neutrophil count.

* Represents sig. difference between control and favorable outcome, # represents sig. difference between control and poor outcome, + represents sig. difference between favorable and poor outcome.

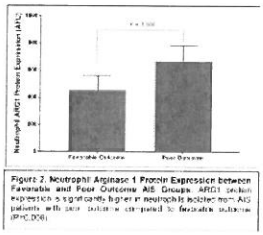


Figure 2. Neutrophil Arginase 1 Protein Expression between Favorable and Poor Outcome AIS Groups. ARG1 protein expression is significantly higher in neutrophils isolated from AIS patients with poor outcome compared to favorable outcome (P=0.008)