

ORAL PRESENTATION

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# MicroRNA-mediated regulation of IL-10, IL-12 and TNF $\alpha$ gene expression in severely injured trauma patients

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From London Trauma Conference 2014  
London, UK. 9-12 December 2014

## Background

Severe trauma induces a blunted immune response associated with an enhanced susceptibility to nosocomial infections [1]. Within 2 hours of injury, expression of the prototypical anti-inflammatory cytokine, IL-10, increases whilst expression of the pro-inflammatory cytokines, TNF $\alpha$  and IL-12, decreases [1]. We hypothesise that microRNAs (miRs) may exacerbate this immunosuppressive gene expression pattern.

## Methods

Following ethical approval and consent, 30 ICU patients admitted following trauma and 16 healthy age and sex-matched controls were recruited. Blood samples were obtained within 2 hours of injury and at 24 hours. miRs were isolated using PAXGene (Qiagen). miRs were selected on the basis of their miRBase target prediction scores for the promoters of IL-10, IL-12 and TNF $\alpha$ . Six miRs selected for analysis were miR374b, -202 and 125a3p (IL-10), -410 and -21 (IL-12) and -454 (TNF $\alpha$ ). qPCR was used to quantify candidate miRs and the results were normalised relative to small nucleolar RNAs U6/RNU44. Infections were assessed using predefined criteria [2].

## Results

Twenty three patients (77%) developed an infection, 15 (50%) were shocked (base deficit  $\geq$  6 mEq/L) on admission and 6 (20%) died. Within 2 hours,

expressions of miR-202, -125a3p, -21 and -454 were reduced (all  $p < 0.03$ ) in patients compared to healthy controls. This reduction was maintained (all  $p < 0.01$ ) 24 hours after injury. At 24 hours, miR-202 was down-regulated (2.4-fold,  $p = 0.01$ ) in shocked compared to non-shocked patients. Decreased miR-374b expression on admission was associated with subsequent development of pneumonia ( $p = 0.009$ ).

## Conclusion

Expression of miRs complementary to cytokine promoters varies significantly following severe traumatic injury and is associated with clinical outcomes. Reduction in inhibitory miRs could partly explain increased IL-10 expression and provide a mechanistic link between severe trauma, the observed immunosuppressive phenotype and an increased incidence of nosocomial infections. In vitro studies are now needed to invoke causation.

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Published: 11 September 2015

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doi:10.1186/1757-7241-23-S2-O5

**Cite this article as:** Jones *et al.*: MicroRNA-mediated regulation of IL-10,  
IL-12 and TNF $\alpha$  gene expression in severely injured trauma patients.  
*Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine* 2015  
23(Suppl 2):O5.

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