Interleukin-1β is essential for blood-induced cartilage damage *in vitro*

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Introduction

Joint damage due to recurrent joint bleeds remains the most common complication in haemophilia. A joint bleed can also occur during major joint surgery or as a result of joint trauma. Exposure of the joint to blood ultimately leads to joint damage, both by direct effects of blood on cartilage and via synovial inflammation.

Cartilage destruction is considered to result from both cartilage matrix-degrading proteases as well as cartilage-destructive pro-inflammatory cytokines such as IL1β, TNFα and IL6.

To unravel the role of the individual cytokines in the pathogenesis of blood-induced cartilage damage, we investigated as a first step whether direct blocking of IL1β specifically prevents blood-induced cartilage damage *in vitro*.

Methods

Full thickness healthy human articular cartilage explants, obtained post-mortem, were cultured for 4 days in the presence or absence of 50% v/v whole blood.

A recombinant human IL1β monoclonal antibody (IL1βmAb) was added during blood exposure in a concentration of 0, 1, 3, 10, 30, or 100ng/mL. Cartilage matrix proteoglycan turnover was determined 12 days later to analyse long-term effects.

Moreover, to investigate the direct effects of IL1βmAb on cartilage, explants were cultured for 4 days in the presence of 10ng/mL IL1βmAb in the absence of blood. Cartilage matrix turnover was determined at day 16.

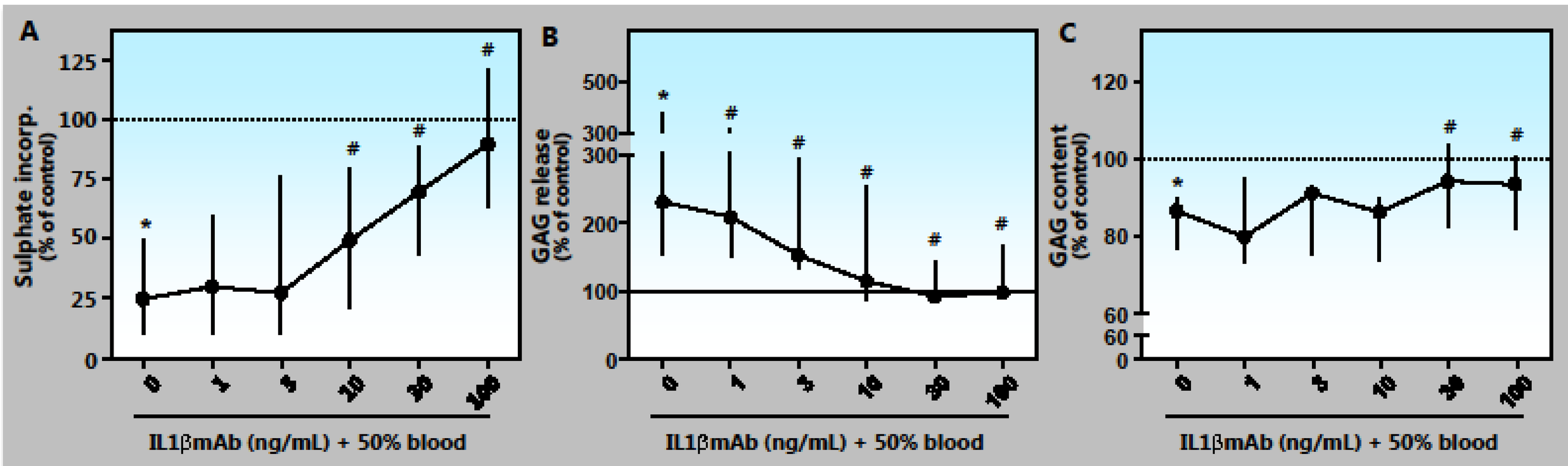

Figure 1 Dose-response effect of IL1βmAb on cartilage proteoglycan synthesis rate (A), -release (B), and –content (C). Median values ± IQR of 8 individual cartilage and blood donors are shown.

* indicates $p<0.05$ compared to control
\# indicates $p<0.05$ compared to blood

Results

- Exposure to blood decreased the proteoglycan-synthesis rate (-75%; **figure 1A**) and increased the proteoglycan release (+129%, **figure 1B**), resulting in a decreased proteoglycan content (-14%; **figure 1C**; all $p<0.05$).
- Adding IL1βmAb resulted in a dose-dependent increase of the proteoglycan synthesis rate leading to normalisation at higher concentrations (10ng/mL and above; **figure 1A**). Moreover, proteoglycan release was statistically significantly decreased already from a concentration of 1 ng/mL and above (**figure1B**). Similar, the proteoglycan content increased statistically significantly upon addition of the IL1βmAb (30 ng/mL and above; all $p<0.05$; **figure 1C**).
- In the absence of blood, IL1βmAb did not have direct effects on cartilage proteoglycan turnover (**figure 2**).

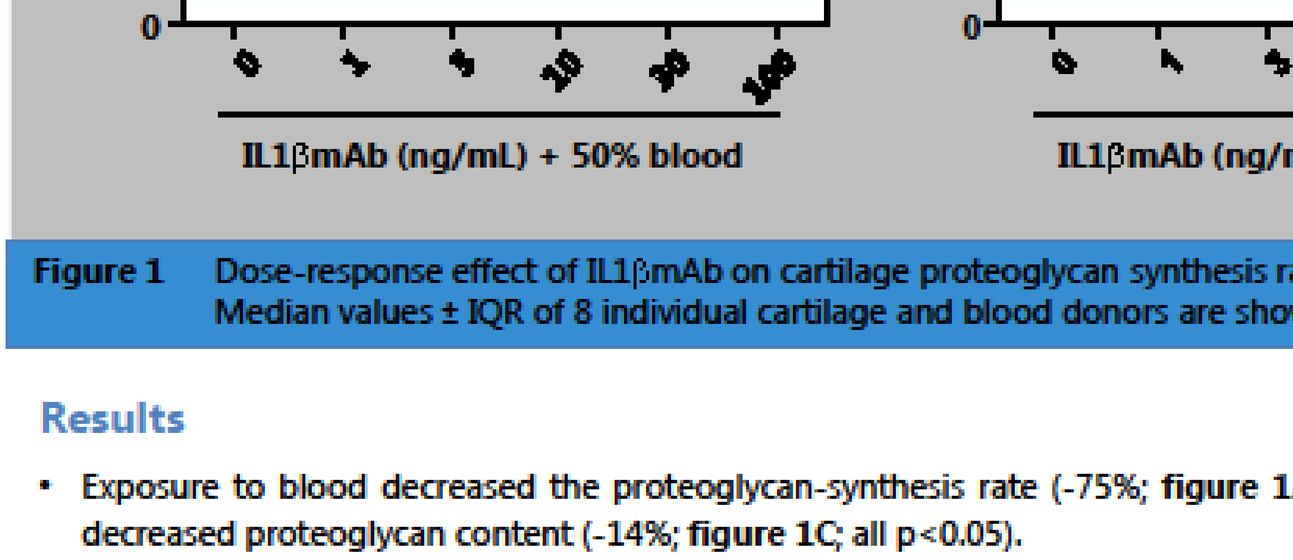

Figure 2 Blocking IL1β in the absence of blood has no effect on proteoglycan turnover. Median ± IQR of 7 individual cartilage donors are shown.

Conclusion

This study demonstrates that IL1β is a crucial factor in the development of blood-induced cartilage damage *in vitro*. Blocking this pro-inflammatory cytokine with a monoclonal antibody protects cartilage from the damaging effects of blood exposure.

Further research is warranted to investigate the *in vivo* capacity of IL1βmAb in prevention and its position as a treatment of haemophilic arthropathy or after a joint bleed in case of trauma or major joint surgery.

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