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EVENT ABSTRACT

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Human macrophages release higher IL-1ra over IL-1beta when stimulated by block acetylated chitosan microparticles and not by random acetylated chitosans or water-soluble oligomers

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Introduction: Human macrophages were previously shown to release excess IL-1ra over IL-1β when stimulated by chitosan microparticles (140 kDa, 80% glucosamine and 20% block N-acetyl glucosamine, 80% degree of deacetylation (DDA))[1]. These data suggest the potential of using chitosan to treat knee joint inflammation by guiding the in situ release of immunomodulatory cytokines. The purpose of this study was to identify the minimal chitosan motif required to induce higher IL-1ra release, using a U937 human macrophage model and a novel chitosan library with distinct DDA, acetylation patterns, and array of 5 different number-average molecular weights (M_n).

Materials and Methods: 15 chitosans with different M_n, DDA, and block (B) or random (R) acetylation pattern were generated, including acid-soluble ≥ 140 kDa and 10 kDa chitosans, and water-soluble 1, 3, 5 kDa oligomers (Table 1). B-acetylated (80% DDA, M_n=190 kDa) or fully deacetylated (98% DDA, M_n=140 kDa) chitosans were nitrous acid depolymerized. 98% DDA chitosans were reacetylated to 60% or 80% DDA to obtain R-acetylated chitosans. Chitosan M_n and polydispersity were determined by size exclusion chromatography and DDA by H^1 NMR. Phorbol ester-differentiated U937 macrophages were stimulated for 24 hours with 5, 50 or 150 µg/mL chitosans that form particles in culture medium at an M_n ≥ 10 kDa , or with LPS and IL-4 as controls. Cell culture medium was analyzed for cytokine release by ELISA (N=3). Cell cytotoxicity was determined by lactate dehydrogenase release.

Chitosan	DDA (%)	Acetylation Pattern	Number average Mw (kDa)
80-190K-B	82	Block	188
80-10K-B	83	Block	11
80-5K-B	81	Block	5
80-3K-B	83	Block	3
80-1K-B	80	Block	1
80-140K-R	80	Random	144
80-10K-R	80	Random	11
80-5K-R	81	Random	5
80-3K-R	81	Random	3
80-1K-R	81	Random	1
60-140K-R	65	Random	152
60-10K-R	62	Random	16
60-5K-R	53	Random	4
60-3K-R	59	Random	3
60-1K-R	61	Random	1

Table 1: Chitosans generated and analyzed in this study

Results: Macrophages with no stimulation released high levels of IL-1ra (5364±1720 pg/mL) and negligible levels of IL-1β (56±6 pg/mL). Amongst all chitosans, only the B-acetylated 80% DDA 190 kDa chitosan (80-190K-B) stimulated a reproducible 2 to 3-fold increase in IL-1ra release at selected doses (Fig. 1A). The B-acetylated 80% DDA 10 and 190 kDa chitosans stimulated a 2 to 5-fold increase in IL-1β release (Fig. 1B). In contrast, R-acetylated 80% DDA 140 kDa (80-140K-R) chitosan induced a modest 2-fold increase in IL-1β without further enhancing IL-1ra release (Fig. 1). All other chitosans had no effects on cytokine release at any dose. Cell viability remained over 80% under all conditions.

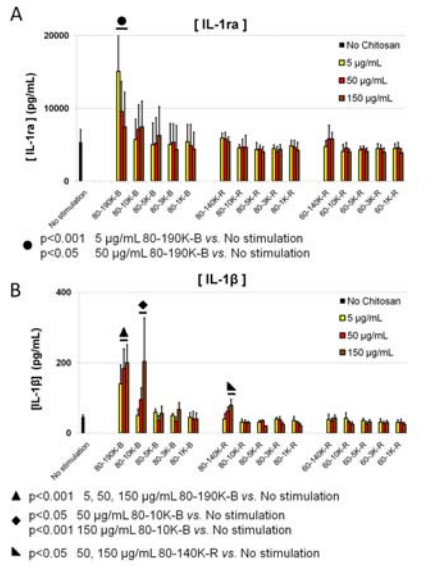

Figure 1: Release of (A) IL-1ra and (B) IL-1β by U937 macrophages in response to the chitosan library. Macrophages stimulated with LPS released 126±18 ng/mL IL-1ra and 560±213 pg/mL IL-1β while macrophages stimulated with IL-4 released 102±13 ng/mL IL-1ra and 13±0.2 pg/mL IL-1β. Data show mean ± standard deviation. N=3

Discussion: The failure of the 1 to 5 kDa B-acetylated chitosans to induce any cytokine release indicates that there is a minimal M_n required for chitosan to stimulate IL-1β in macrophages and suggests full cytocompatibility of chitosan oligomers at 150 µg/mL. At 80% DDA and above 10 kDa M_n, the B-acetylation pattern contributes to stimulating IL-1β release. These data are consistent with previous report suggesting that chitosan microparticle formation is necessary to activate the inflammasome and stimulate IL-1β liberation from macrophages[2]. The ability of the 80-190K-B, and not the 80-140K-R, to enhance IL-1ra release indicates that the B-acetylation pattern is necessary to shift macrophages towards a more anabolic phenotype.

Conclusion: A novel, comprehensive chitosan library was successfully generated to evaluate the impact of chitosan M_n, DDA and acetylation pattern on cytokine release in human macrophages. Water-soluble chitosan oligomers had no influence on IL-1ra and IL-1β release. Above 100 kDa, 80% DDA B-acetylated but not R-acetylated chitosans stimulated more IL-1ra, suggesting that B-acetylated chitosans are more useful for inducing the release of anti-inflammatory factors that preserve joint health.

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