Identification of a Spectrum of Therapeutic Targets of a New Treatment for Osteoarthritis Composed by Curcuminoids Extract, Hydrolyzed Collagen and Green Tea Extract

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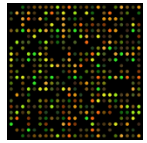
INTRODUCTION

Osteoarthritis (OA) is a chronic, painful and inflammatory condition. The goal of treatment in OA is to reduce pain and improve function. There is no cure for the disease, but some attempts to slow the progression. We have previously demonstrated that a mixture of curcuminoids extract, hydrolyzed collagen and green tea extract (COT) inhibited inflammatory and catabolic mediator's synthesis by osteoarthritic human chondrocytes in monolayer[a]. The objective of this study was to identify new targets of COT using genomic and proteomic approaches.

METHODS

Enzymatically isolated primary human chondrocytes were cultured in monolayer until confluence and then incubated for 24 or 48 hours in the absence or in the presence of human interleukin-1β (IL-1 β) (10^{-11} M) and with or without COT, each compound at the concentration of 4 µg/ml, microarray gene expression profiling between control (ctrl), COT, IL-1β and COT IL-1β conditions was performed. The biological relevance of regulated genes was determined with Ingenuity Pathway Analysis. Immunoassays (ELISA) wre used to confirm the identified genes that were differentially expressed.



OA key pathways

- Inflammation
- Cartilage metabolism
- Angiogenesis

Figure 1. Differential gene expression between ctrl, COT, IL-1β and COT IL-1β conditions obtained by Human HT-12 BeadChip Array (Illumina). 2549 genes were differentially expressed between ctrl and IL-1β conditions, 2280 genes were differentially expressed between IL-1β and COT IL-1β conditions and 1907 genes were differntially expressed between ctrl and COT conditions. The key regulated pathways were related to inflammation, cartilage metabolism and angiogenesis.

OA key pathways	Genes
Inflammation	IL-8, IL-6, CXCL6, CCL20, CXCL1, NOS2A, CCL8, CXCL2, CCL5, PTGS2, TNFAIP6, PTGES, CXCL5, CXCL10, CCL2
Cartilage metabolism	MMP-13, MMP-1, BMP-2, BMP-6, ADAMTS5, ADAMTS9, ADAMTS1
Angiogenesis	ECGF1, SERPIN E1, SERPIN C1, STC1, AQP9, HBEGF, RCAN1

Figure 2. Main genes regulated in OA key pathways.

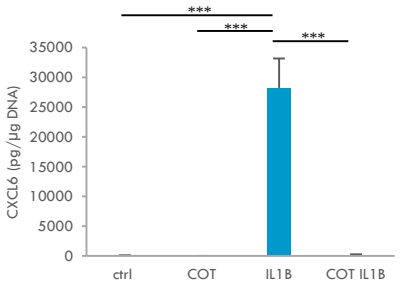


Figure 3. CXCL6 production by human chondrocytes in ctrl, COT, IL-1β and COT IL-1β conditions. Results were expressed as mean ± SEM of 12 independent experiments performed with chondrocytes isolated from 12 different patients. ***p<0.001 IL-1β stimulated CXCL6 gene expression and protein production were strongly down-regulated by COT.

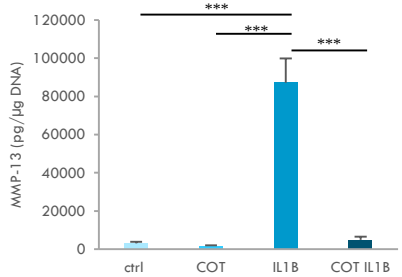


Figure 4. MMP-13 production by human chondrocytes in ctrl, COT, IL-1β and COT IL-1β conditions. Results were expressed as mean ± SEM of 12 independent experiments performed with chondrocytes isolated from 12 different patients. ***p<0.001 IL-1β stimulated MMP-13 gene expression and protein production were strongly down-regulated by COT.

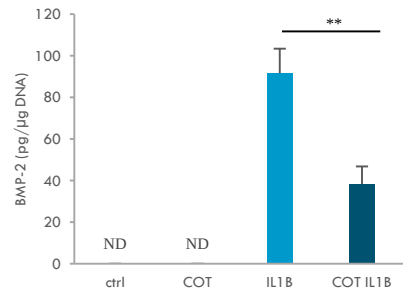


Figure 5. BMP-2 production by human chondrocytes in ctrl, COT, IL-1β and COT IL-1β conditions. Results were expressed as mean ± SEM of 12 independent experiments performed with chondrocytes isolated from 12 different patients. **p<0.01 IL-1β stimulated BMP-2 gene expression and protein production were strongly down-regulated by COT.

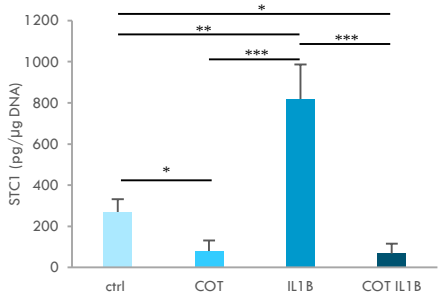


Figure 6. STC1 production by human chondrocytes in ctrl, COT, IL-1β and COT IL-1β conditions. Results were expressed as mean ± SEM of 12 independent experiments performed with chondrocytes isolated from 12 different patients. *p<0,05 **p<0,01 ***p<0.001 IL-1β stimulated STC1 gene expression and protein production were strongly down-regulated by COT. Moreover, COT significantly decreased STC1 production in basal condition.

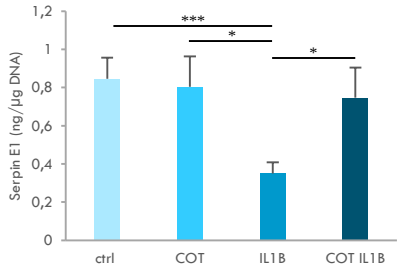


Figure 7. Serpin E1 production by human chondrocytes in ctrl, COT, IL-1β and COT IL-1β conditions. Results were expressed as mean ± SEM of 12 independent experiments performed with chondrocytes isolated from 12 different patients. *p<0,05 ***p<0.001 Serpin E1 gene expression and protein production were down-regulated by IL-1β. COT reversed the inhibitory effect of IL-1β.

CONCLUSION

The mixture COT has beneficial effect on OA physiopathology by regulating the synthesis of key catabolic, inflammatory and angiogenesis factors. These findings give a scientific rationale for the use of these natural ingredients in the management of OA.

[a]Reference Comblain F, Serisier S, Barthelemy N, Balligand M, Henrotin Y: **Review of dietary supplements for the management of osteoarthritis in dogs in studies from 2004 to 2014.** *J Vet Pharmacol Ther* 2015.

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