SYNOVIUM ANGIOGENESIS IN OSTEOARTHRITIS: A NEW THERAPY TARGET FOR CHONDROITIN SULFATE

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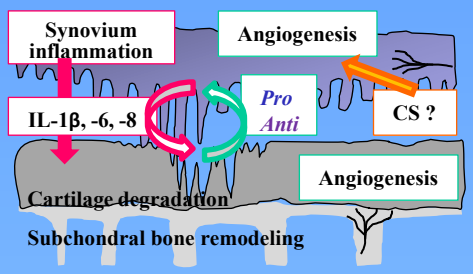

PURPOSE

Angiogenesis and inflammation are closely integrated process. Chondroitin sulfate (CS) is a symptomatic slow acting drug for OA. The mechanisms underlying these effects remain poorly understood. This work aimed to study

- the *pro* inflammatory and *pro/anti* angiogenic status of synovium
- the effect of CS on angiogenic factors expression by synovial cells (SC)

METHODS

- OA synovial specimen (n=6): Macroscopic Ayral score to distinguish Inflamed (I) or Non inflamed (NI) area.
- Five days culture of primary SC coming from either NI or I area : (SCNI or SCI).
- Production of interleukin (IL)-6, 8, ***pro*** angiogenic factor Vascular Endothelial Growth Factor (VEGF) and ***anti*** angiogenic factor thrombospondine (TSP)-1 (ELISA)

SC culture (3 to 5 synovial specimen), P4, 5 or 24 h incubation

- Without IL-1β (basal) + CS (0, 10, 50, 200 µg/ml)
- With IL-1β (1ng/ml) + CS (0, 10, 50, 200 µg/ml)

- ***Pro*** angiogenic genes expression (RT PCR): VEGF, basic Fibroblast Growth Factor (bFGF), Nerve Growth Factor (NGF), Matrix Metalloproteinase (MMP)-2, angiopoietin (ang)-1
- ***Anti*** angiogenic genes expression (RT PCR): TSP-1 and -2, Vascular Endothelial Growth Inhibitor (VEGI)

RESULTS

1. An increase of pro inflammatory and pro angiogenic status is observed in SCI

Inflam-mation	***Pro***	IL-6	419 ± 109	↑***
		IL-8	730 ± 309	↑***
Angio-genesis	***Pro***	VEGF	134±16	↑***
	Anti	TSP-1	66±15	↓***

Table 1: Production of IL-6, 8, VEGF and TSP-1 of SCNI and SCI. Results are expressed as % of production of SCNI (means ± SEM).

2. IL-1β stimulates *pro* angiogenic genes expression

3. * IL-1β stimulates *anti* angiogenic genes expression after 5 h
*** IL-1β inhibits *anti* angiogenic genes expression after 24 h**

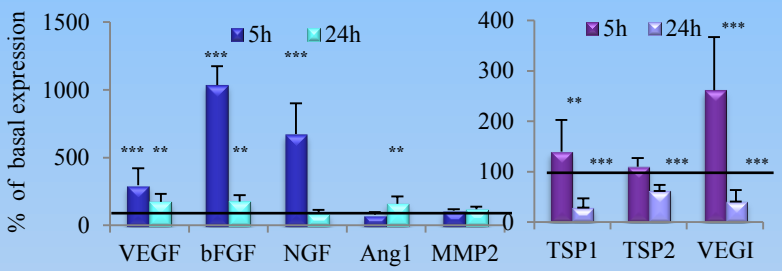

Fig.1: Effect of IL-1β on pro and anti angiogenic genes expression. Results are expressed as % of basal expression (means ± SD).

4. The inhibiting effect of IL-1β (24 h) on *anti* angiogenic factors expression (TSP-1 and VEGI) was counteracted by CS

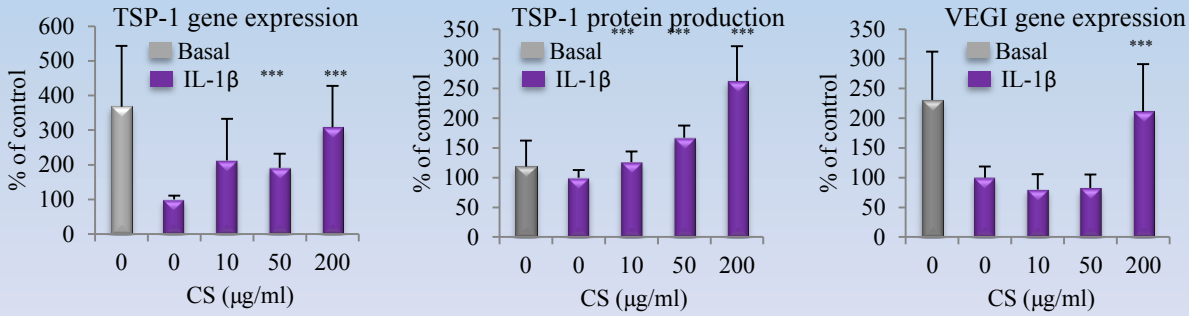

Fig.2: Effect of CS on anti angiogenic factors expression after 24 h of treatment. Results are expressed as % of expression obtained in the absence of CS (means ± SD).

CONCLUSIONS

- **Synovium inflammation is associated with an imbalance between *pro* and *anti* angiogenic factors production.**
- **IL-1β is a key inflammatory mediator capable of inducing this *pro* angiogenic imbalance.**
- **The basal expression of *pro and anti* angiogenic genes expression and the IL-1β stimulated *pro* angiogenic genes expression are not affected by CS**
- **CS trends to normalize the IL-1β-induced angiogenic response in OA SC. This could constitute a new mechanism of action of this drug, modulating the molecular mechanisms underlying the synovium angiogenesis in OA. These results also contribute to understand the molecular mechanism of angiogenesis in OA.**