Expression of specific pathways in the inflamed synovial membrane of OA patient

Identification of new potential key intermediates

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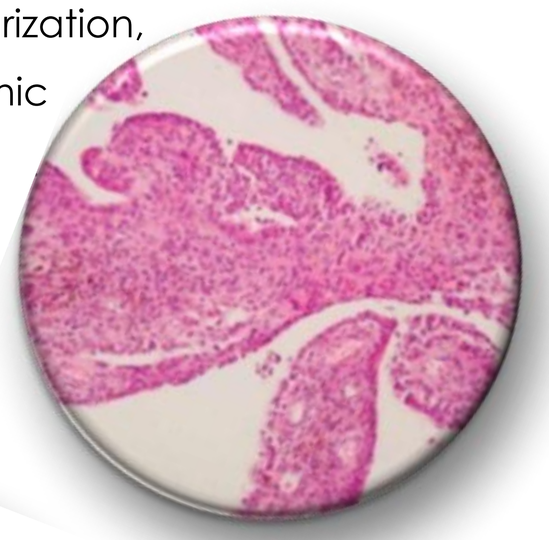
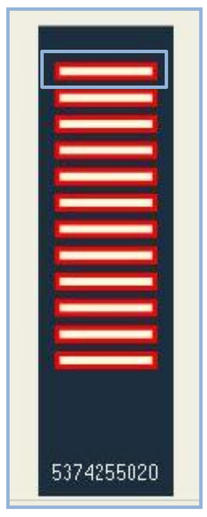
P U R P O S E . Synovial membrane plays a key role in osteoarthritis (OA) pathophysiology, contributing to both patient symptoms and disease progression. Using an original methodology comparing normal/reactive (NR) and inflammatory (I) synovial membrane areas from the same OA patient, we analyzed the gene expression pattern of synovial cells from these different areas and identified differentially regulated pathways. ■

M E T H O D S . Synovial cells (SC) were isolated from OA synovial specimens obtained from 12 patients undergoing knee replacement. The inflammatory status of the synovial membrane was characterized by the surgeon according the macroscopic criteria including the synovial vascularization, the villi formation and the hypertrophic aspect of the tissue. At the surgery time, the synovial membrane was dissected and the biopsies from NR and I areas cultured separately for a period of 7 days. ■





➡ ***OA key pathways***

- ➢ Inflammation
- ➢ Cartilage metabolism
- ➢ Angiogenesis
- ➢ Wnt signaling

Fig.1

Differential gene expression between NR and I synovial biospies obtained by Human HT-12 BeadChip Array (Illumina). 896 differentially expressed genes between NR and I zones were identified. Among them, 576 genes were up-regulated (I/NR > 1.5) and 320 down-regulated (I/NR < 0.75). A significant number of the top ranking differentially expressed genes were identified as inflammatory, cartilage metabolism, Wnt or angiogenic pathways.

Category	Differentially expressed genes (Fold change)	
	Up-regulated	Down-regulated
Anabolism	HAS1 (2.16); COLL22A1 (2.05)	COL1A2 (0.76) ; VIM (0.76); MATN2 (0.74); HABP4 (0.72); HAPLN1 (0.66); HAS3 (0.65); COL16A1 (0.64); CILP (0.63); COL6A3 (0.63); GPC4 (0.58); HAPLN1 (0.58); ACAN (0.42)
Catabolism	MMP9 (3.53); MMP3 (2.82); CTSH (2.02); ADAMDEC1 (1.76); CTSS (1.52); BMP6 (2.48)	

Table 1

Differential expression of key intermediates of anabolism and catabolism between NR and I synovial biopsies

Category	Up-regulated genes (Fold change)
Cytokines	IL-8 (4.45); IL-6 (3.43); TNFRSF21 (1.99); IFI30 (1.91); TNFAIP6 (1.62); IRF8 (1.61)
Chemokines	CXCL5 (4.38); CXCL6 (3.89); CXCL16 (2.8); CXCL2 (2.62); CXCL1 (2.52)
Enzymes	ALOX5AP (3.35); PLD1 (2.64); ALOX5 (2.32); PTGES (2.04); PLCB1 (1.87); SOD2 (1.79); TBXAS1 (1.75); PI3 (1.71); PLA2G4A (1.58)
Other	TREM1 (3.45); S100A9 (2.68); OSM (1.57); PPARG (1.49)

Table 2

Up-regulated expression of key inflammatory intermediates between NR and I synovial biopsies

Category	Differentially expressed genes (Fold change)	
	Up-regulated	Down-regulated
Angiogenesis	STC1 (5.83); PF4V1 (2.97); EDNRB (2.64); AQP9 (2.58); HBEGF (2.51); BDKRB1 (2.4); RCAN1 (2.31); ECGF1 (1.97); DNER (1.85); RCAN1 (1.84); BDKRB2 (1.7); PECAM1 (1.65)	PDGFC (0.71); RNH1 (0.69)

Table 3

Differential expression of key intermediates of angiogenesis between NR and I synovial biopsies

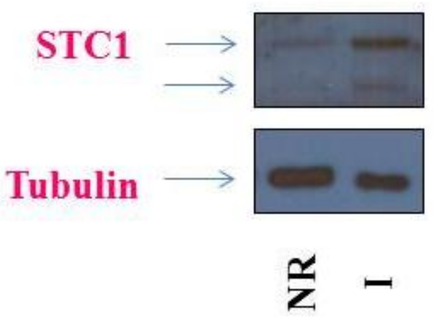
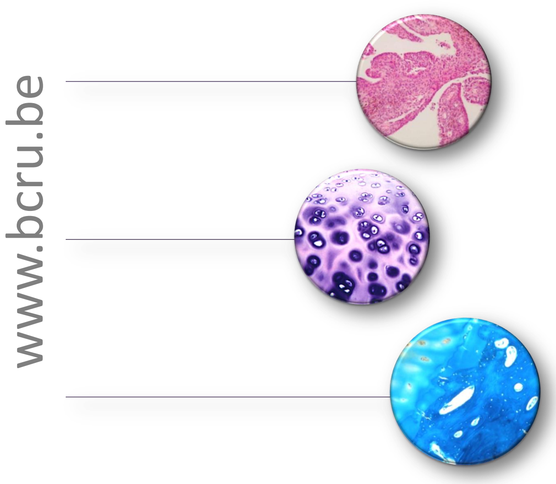


Fig. 2

STC1 expression in NR and I synovial biopsies. Total protein extracts from NR or I areas were analyzed by Western blotting with anti-STC1 and anti-α tubulin (control) antibodies.

C O N C L U S I O N . Using a unique culture system, this study is the first to identify different expression pattern between two areas of the synovial membrane in the same OA patient. These differences concern several key pathways involved in OA pathogenesis. This analysis also provided interesting information regarding new potent intermediates as S100A9 and STC-1. ■



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