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Reumatologia
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Città della Salute
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di Torino

AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

LIRAGLUTIDE NELLA TERAPIE PER OA

Simone Parisi

AOU Città della Salute e della Scienza di Torino - SC Reumatologia

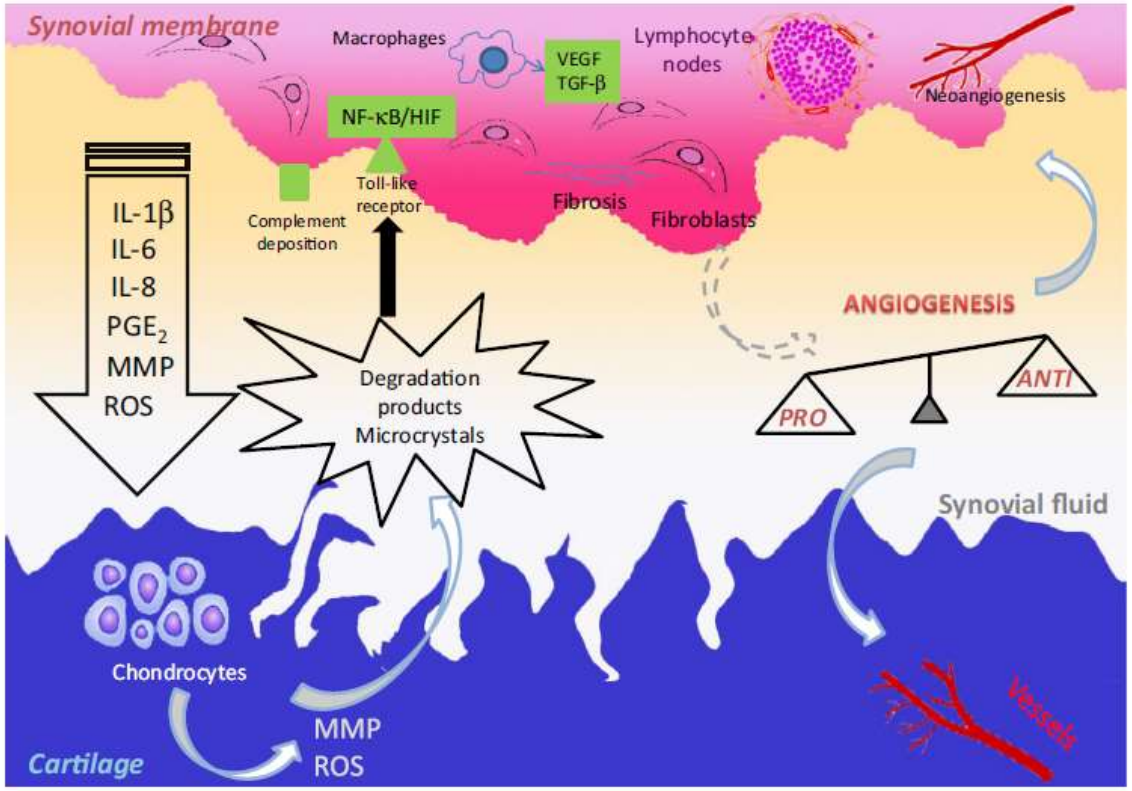
Approcci interdisciplinari in reumatologia - 7ª edizione

MALATTIE REUMATICHE E DISORDINI ENDOCRINO-METABOLICI

Webinar
16-17 ottobre 2020

ABBVIE, AMGEN, BALDACCI, BIOGEN, BMS, CELGENE, CHIESI, GRUNENTHAL, JANSSEN, NOVARTIS, PFIZER, LILLY, SANOFI, UCB

IMMUNOPATOGENESI



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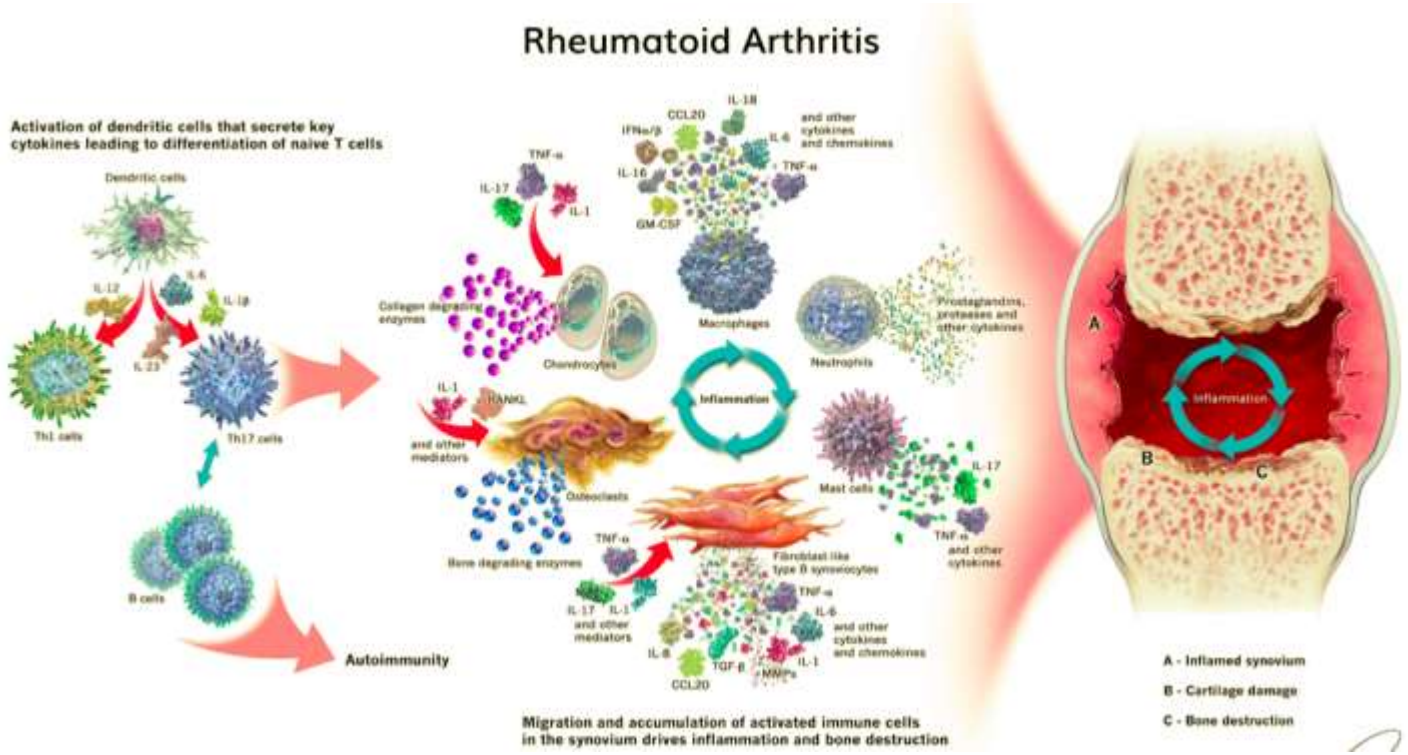

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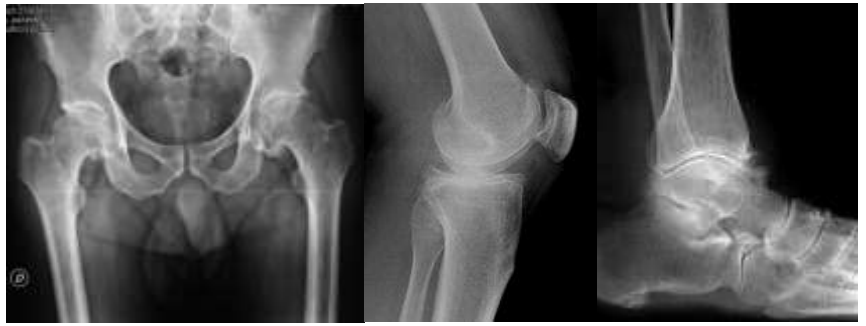
OBIETTIVI DEL TRATTAMENTO

- RIDUZIONE DEL DOLORE
- MANTENIMENTO DEL FUNZIONALITA' ARTICOLARE
- CONTENIMENTO DELLA DISABILITA'
- RALLENTAMENTO/BLOCCO DELLA PROGRESSIONE DI MALATTIA

- PREVENZIONE
- TERAPIA MEDICA
- TERAPIA FISICA
- TERAPIA CHIRURGICA



TERAPIA INTRA-ARTICOLARE

- STEROIDI
- ACIDO IALURONICO
- EMOCOMPONENTI A USO NON TRASFUSIONALE
- NUOVI TRATTAMENTI

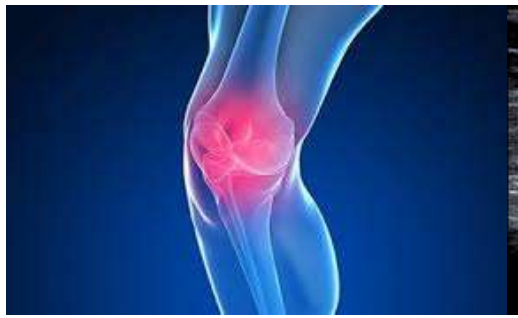
Online version at http://www.minervamedica.it

Minerva Medica 2019 mese;110(0):000–000
DOI: 10.23736/S0026-4806.19.06190-1

ORIGINAL ARTICLE

Ultrasound-guided intra-articular injection: efficacy of hyaluronic acid compared to glucocorticoid in the treatment of knee osteoarthritis

Simone PARISI *, Maria C. DITTO, Marta PRIORA, Richard BORRELLI, Angela LAGANÀ, Clara L. PERONI, Enrico FUSARO



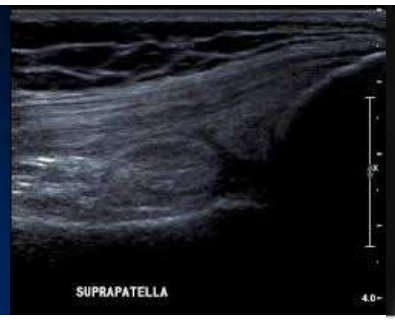


Figure 1

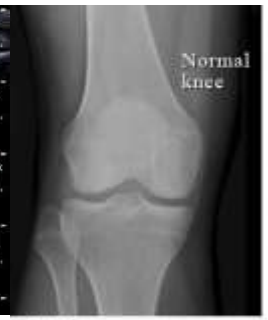
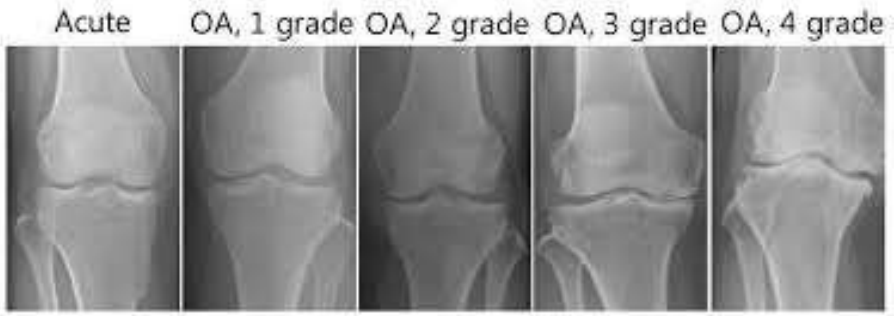
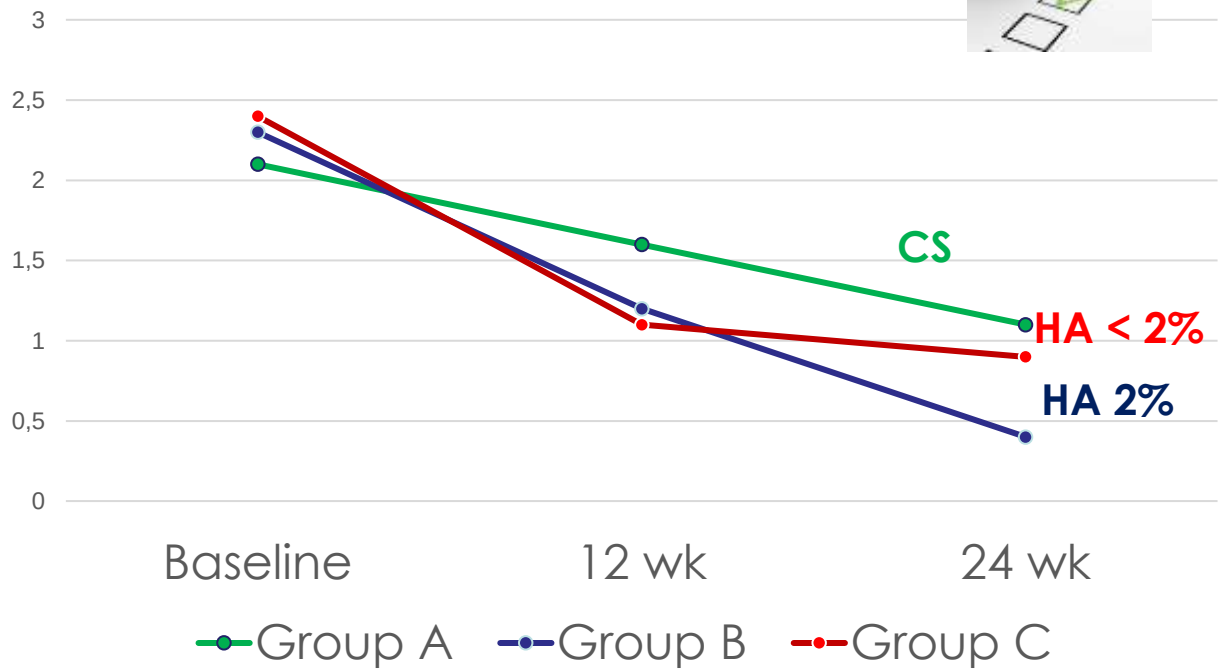


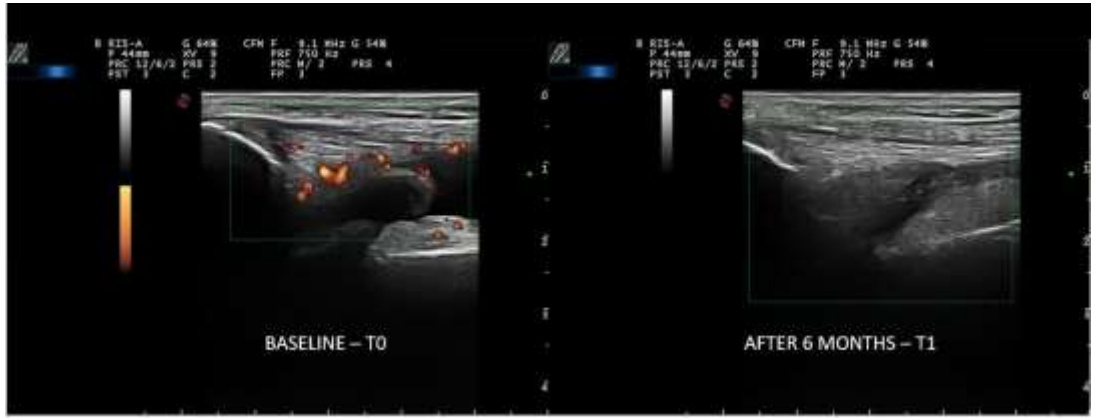
Figure 2

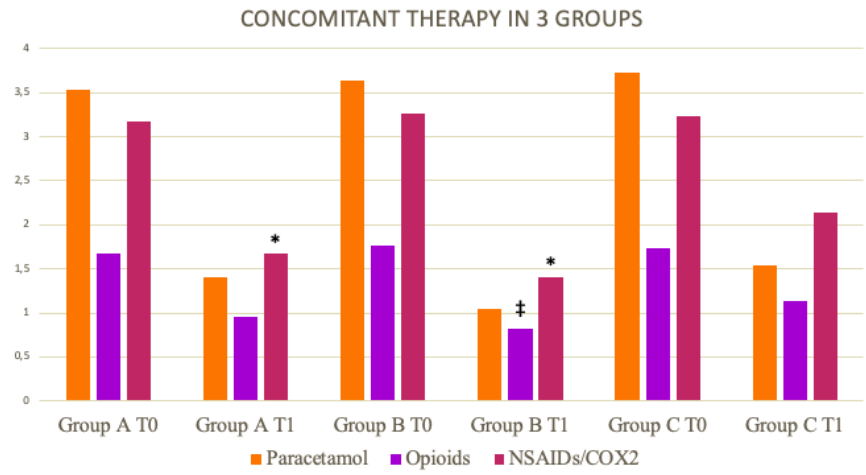
RESULTS



US PWD







PWD signal got better in group B (p-value 0.001) and C (p-value 0.011) 3 months after the treatment. Furthermore, in group B the PWD signal proved to be statistically significantly decreased after 6 months as well (p= 0.035)

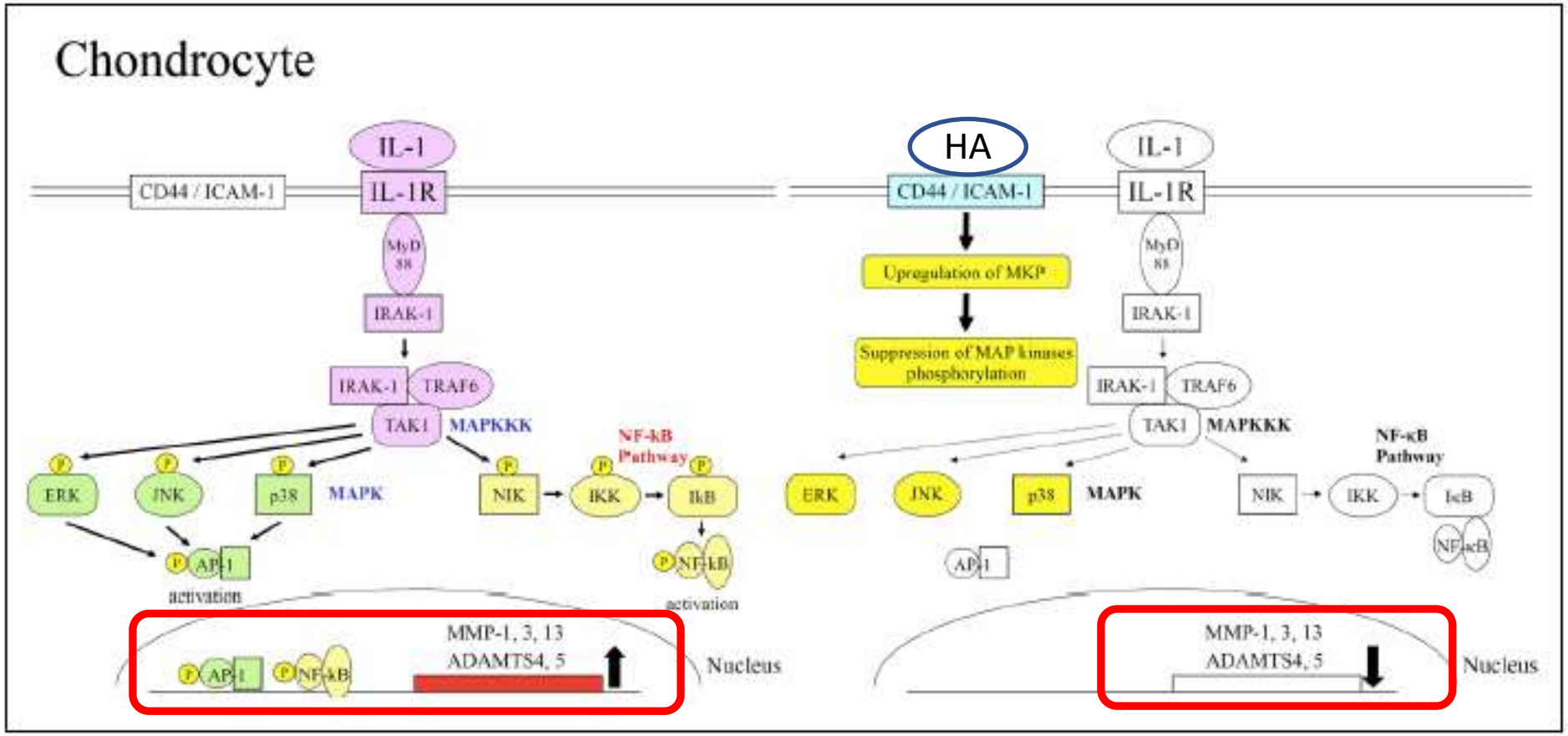
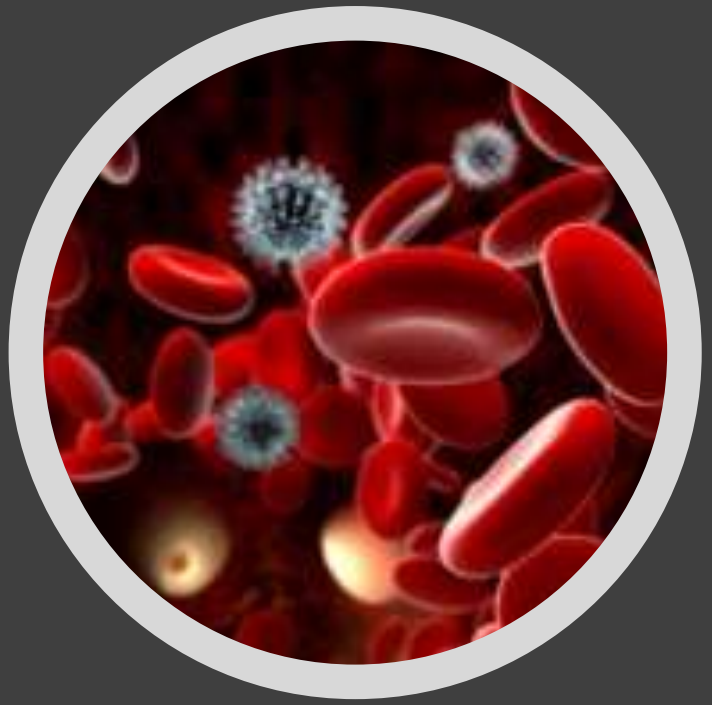


Figure 3. Upregulation of MMP and ADAMTS gene expressions by IL-1 and the molecular mechanism of its downregulation by Supartz FX in chondrocytes. As in synoviocytes, the binding of IL-1 to its receptor activates MAP kinase and NF-κB signal transductions in chondrocytes. These signal transductions induce activation of AP-1 and NF-κB transcription factors, and MMP and ADAMTS gene expressions are upregulated by these transcription factors. The binding of Supartz FX to CD44 or ICAM-1 suppresses phosphorylation of MAP kinases. These molecular changes inactivate AP-1, and MMP and ADAMTS gene expressions are downregulated.

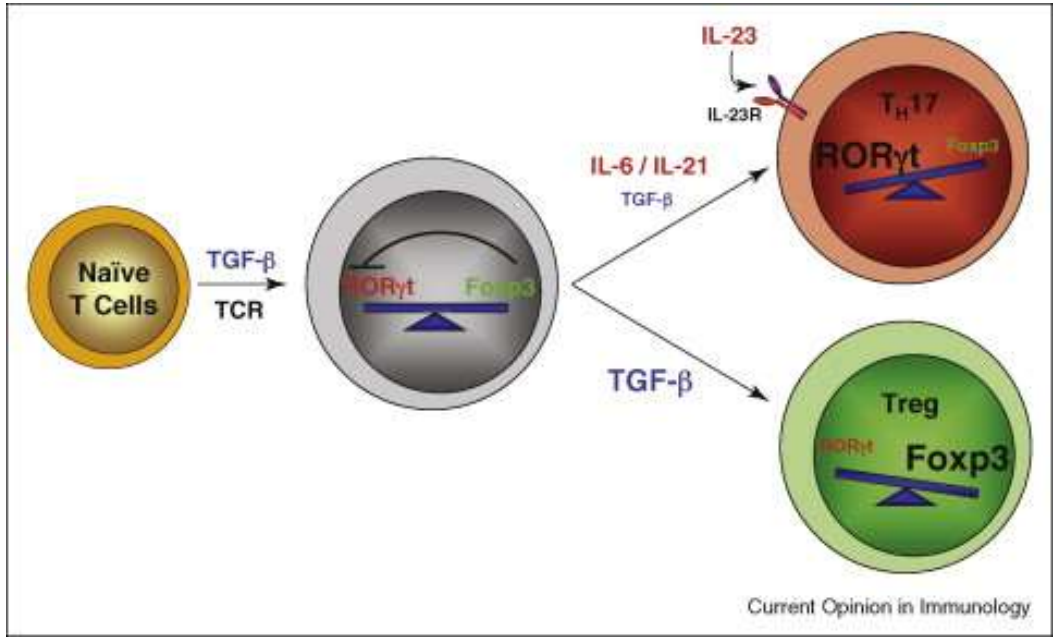


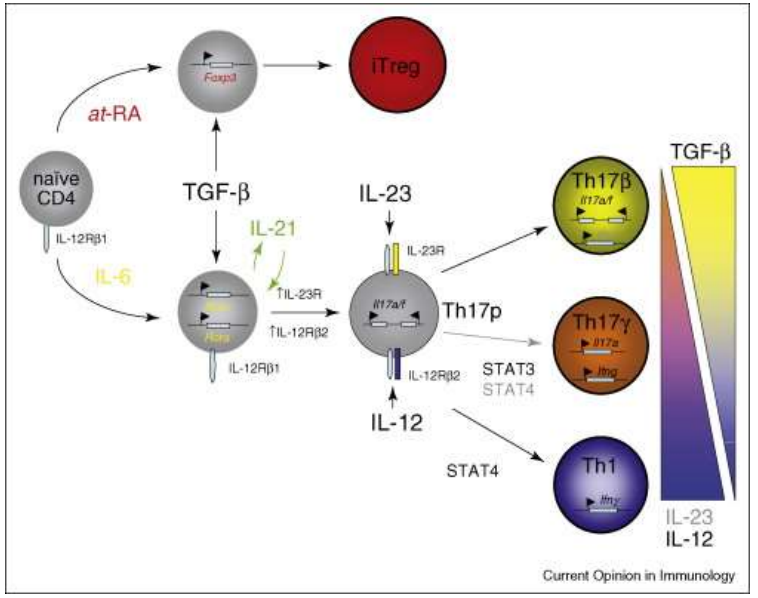
PRP

RAZIONALE

I principi attivi del PRP sono il TGF-beta ed i fattori di crescita quali IGF, il PDGF

Il TGF-beta a concentrazioni adeguate inibisce la risposta immune mediata da cellule Th17, contrastandone il priming e convertendo i Tcell naive in T Reg soppressori (Zhou et al, 2008; Crome et al, 2010); il TGFb ha anche la capacità di inibire altre cellule dell'infiammazione, quali altri fenotipi linfocitari e macrofagi, mentre i fattori di crescita piastrinici, per contro, stimolano i tenociti a produrre collagene riparando le lesioni tendinee già in essere (Everts et al, 2006).





www.aging-us.com AGING 2018, Vol. 10, No. 12

Research Paper

Mechanistic insight into hyaluronic acid and platelet-rich plasma-mediated anti-inflammatory and anti-apoptotic activities in osteoarthritic mice

Chi-Sheng Chiou[1,2], Chi-Ming Wu [3], Navneet Kumar Dubey[4,5], Wen-Cheng Lo[6,7], Feng-Chou Tsai[8], Tran Dang Xuan Tung[1,9], Wei-Ching Hung[10], Wei-Che Hsu[10], Wei-Hong Chen[10], Win-Ping Deng[1,10,11]

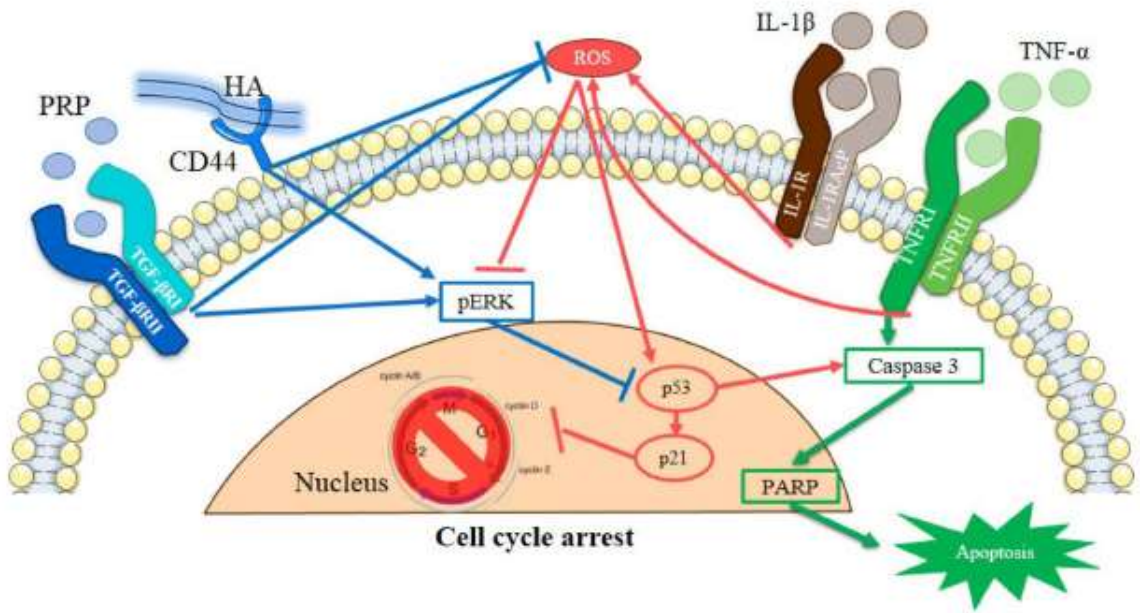


Figure 7. Schematic representation of HA and PRP-mediated cellular apoptosis in osteoarthritic chondrocytes.

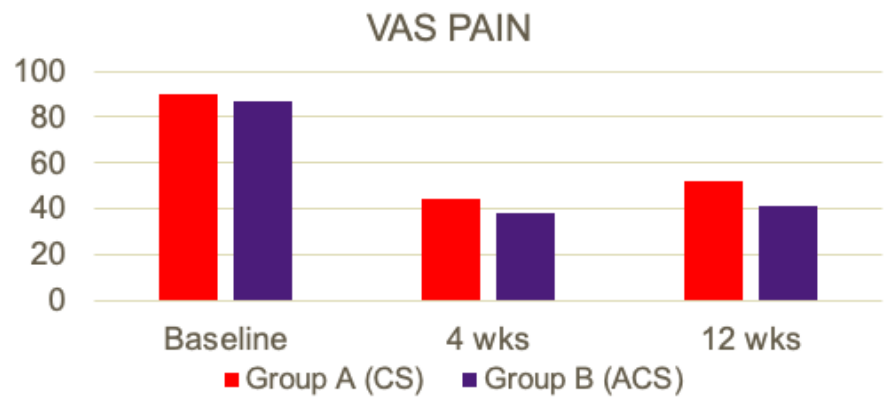
EFFICACY OF AUTOLOGOUS CONDITIONED SERUM IN THE TREATMENT OF KNEE OSTEOARTHRITIS SECONDARY TO RHEUMATOID ARTHRITIS

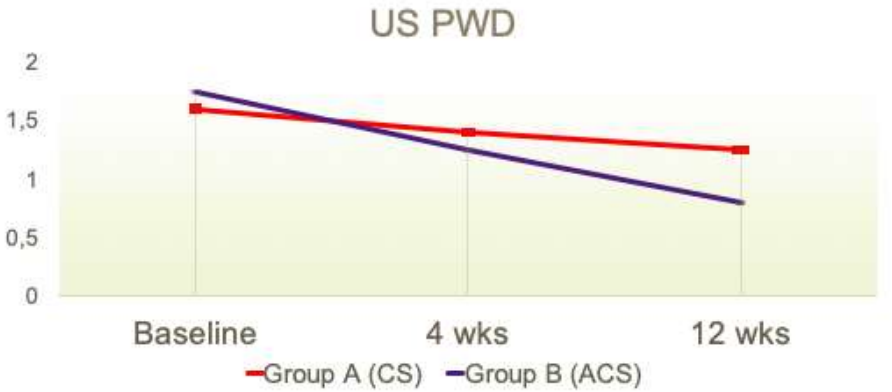
S.C. Reumatologia AO Città della Salute e della Scienza di Torino

Simone Parisi, Maria Chiara Ditto, Angela Laganà, Clara Lisa Peroni, Sergio D'Antico, Enrico Fusaro
S.C. Reumatologia Azienda Ospedaliero Universitaria Città della Salute e della Scienza di Torino, Turin, Italy

SIERO AUTOLOGO CONDIZIONATO

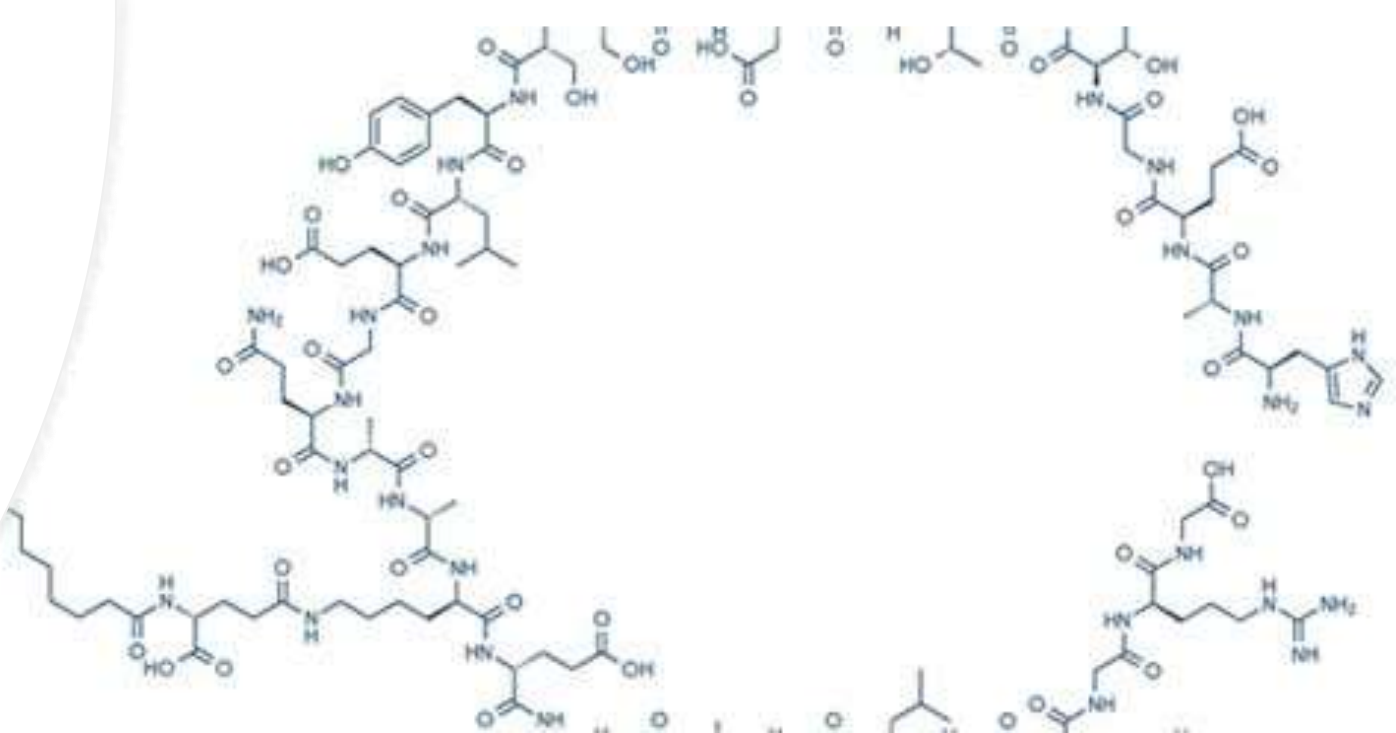
ACS therapy improved joint function and **reduced** knee **pain** more effective than triamcinolone; combined with its favorable **safety profile**, ACS appears to be a more effective treatment than glucocorticoids and could enhance the quality of life in patients with knee OA in RA. ACS has the potential to offer an alternative, **chondroprotective**, natural, molecular approach to treating pain and functionality in patients with symptomatic knee OA in particular related to RA.





LIRAGLUTIDE

- La liraglutide è un **principio incretino-mimetico** (analogo del peptide-1 simil-glucagone **GLP-1**, ormone endogeno incretinico che potenzia la secrezione di insulina glucosio-dipendente dalle cellule beta del pancreas) utilizzato nel trattamento del diabete mellito di tipo 2 e nel trattamento dell'obesità e del sovrappeso.



Que et al. Journal of Inflammation (2019) 16:13
https://doi.org/10.1186/s12950-019-0218-y

Journal of Inflammation

RESEARCH Open Access

The GLP-1 agonist, liraglutide, ameliorates inflammation through the activation of the PKA/CREB pathway in a rat model of knee osteoarthritis

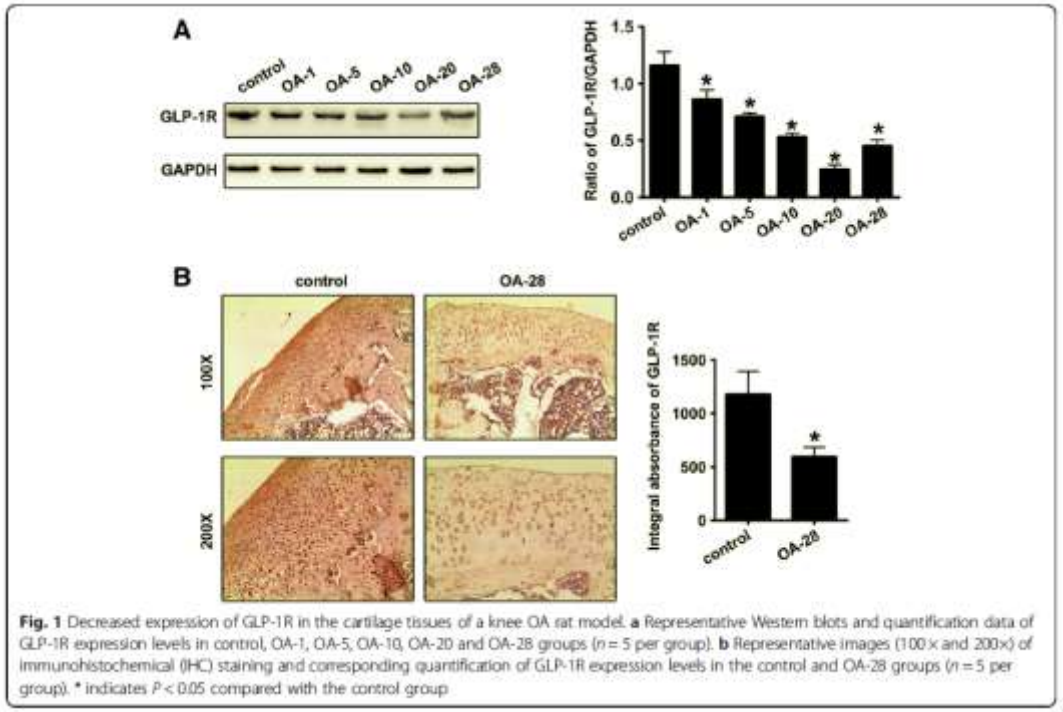


Fig. 1 Decreased expression of GLP-1R in the cartilage tissues of a knee OA rat model. **a** Representative Western blots and quantification data of GLP-1R expression levels in control, OA-1, OA-5, OA-10, OA-20 and OA-28 groups ($n = 5$ per group). **b** Representative images (100 × and 200×) of immunohistochemical (IHC) staining and corresponding quantification of GLP-1R expression levels in the control and OA-28 groups ($n = 5$ per group). * indicates $P < 0.05$ compared with the control group

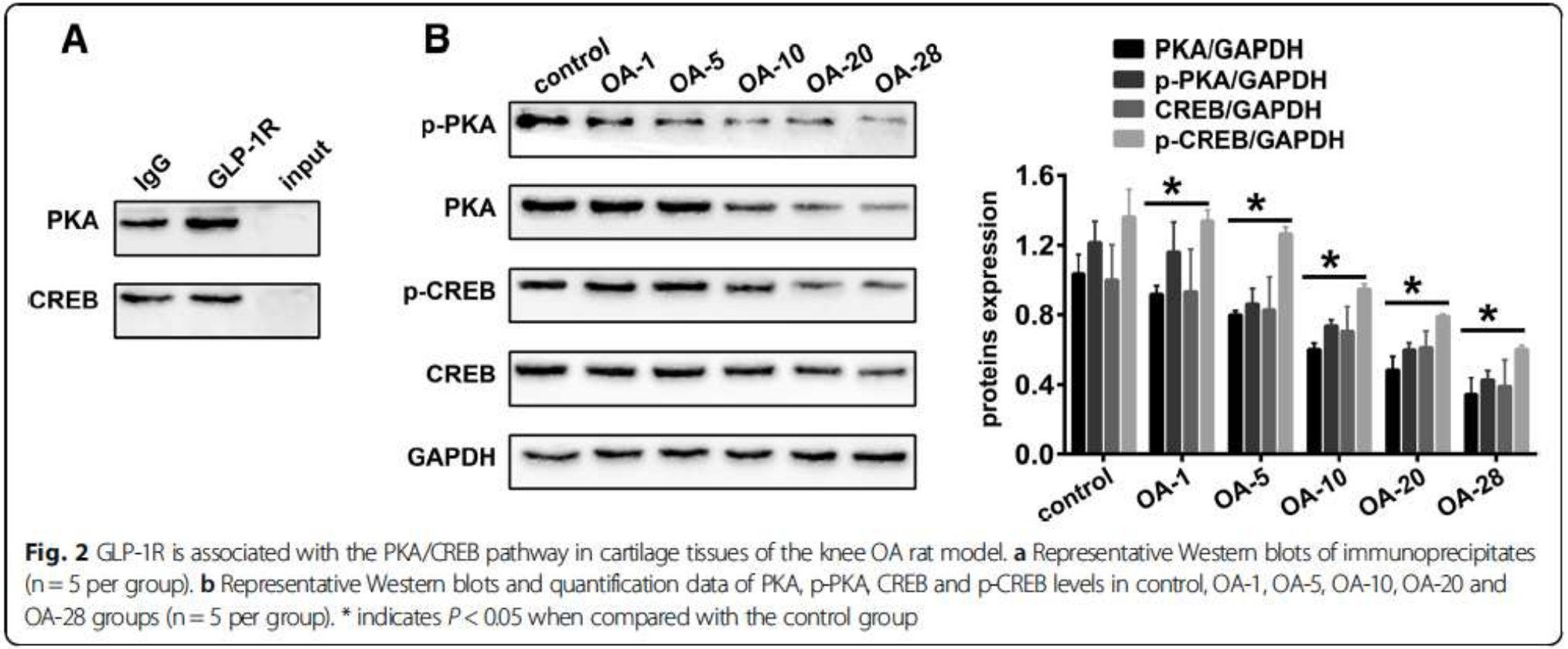


Fig. 2 GLP-1R is associated with the PKA/CREB pathway in cartilage tissues of the knee OA rat model. **a** Representative Western blots of immunoprecipitates (n = 5 per group). **b** Representative Western blots and quantification data of PKA, p-PKA, CREB and p-CREB levels in control, OA-1, OA-5, OA-10, OA-20 and OA-28 groups (n = 5 per group). * indicates $P < 0.05$ when compared with the control group

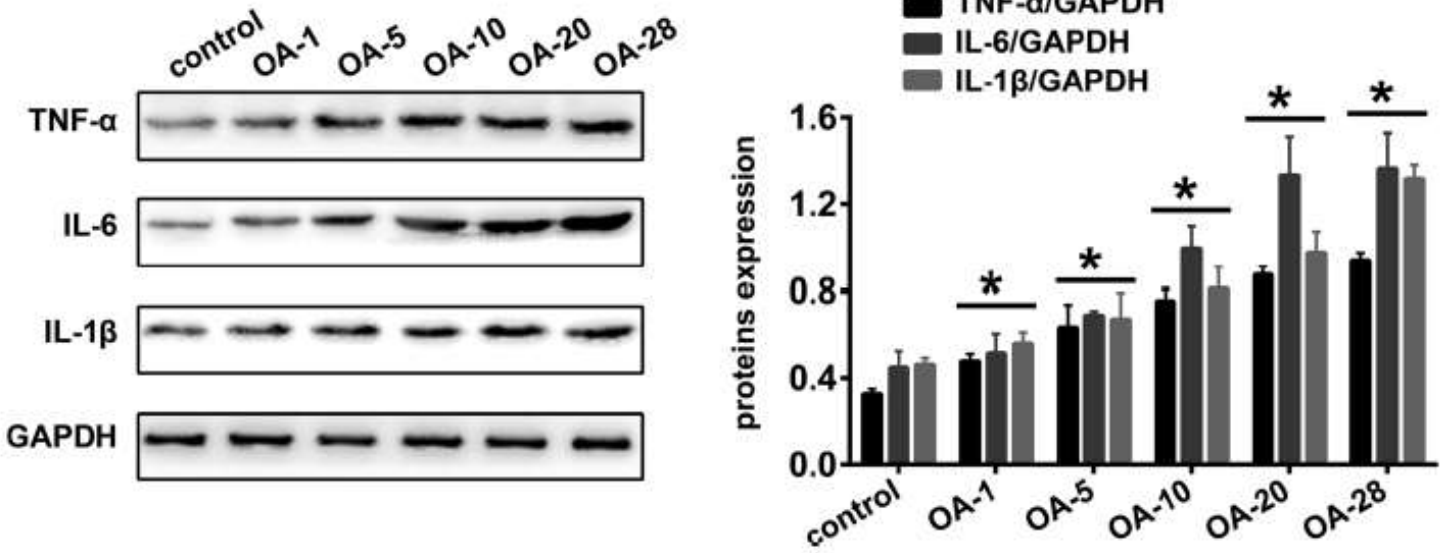


Fig. 3 Induction of knee OA is accompanied by inflammation. Representative Western blots and quantification data for TNF-α, IL-6,and IL-1β expression levels in control, OA-1, OA-5, OA-10, OA-20 and OA-28 groups (n = 5 per group). * indicates $P < 0.05$ compared with the control group

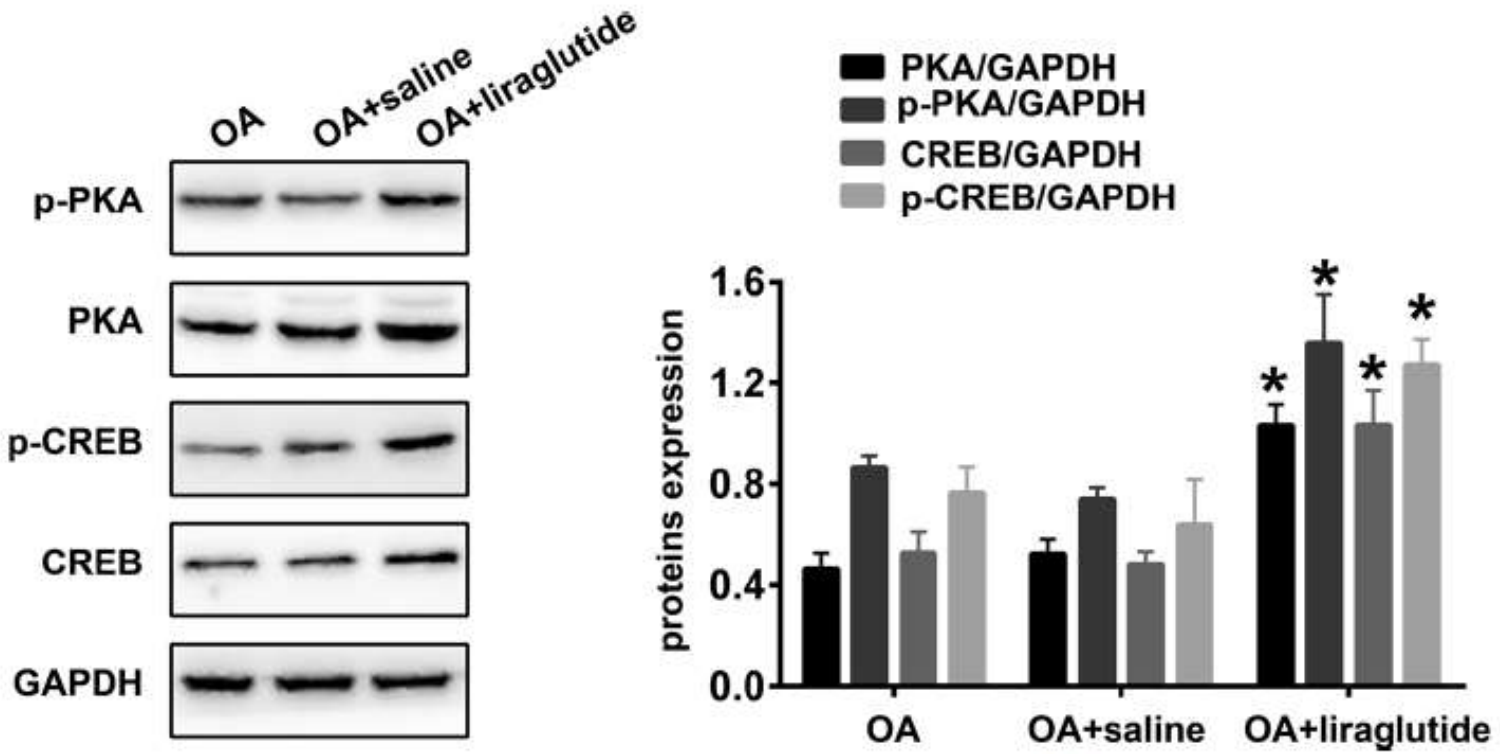


Fig. 5 Liraglutide activates the PKA/CREB pathway in cartilage tissues of the knee OA rat model. Representative Western blots and quantification data of PKA, p-PKA, CREB and p-CREB in the "OA", "OA + saline" and "OA + liraglutide" groups (n = 5 per group). * Indicates $P < 0.05$ compared with the "OA + saline" group

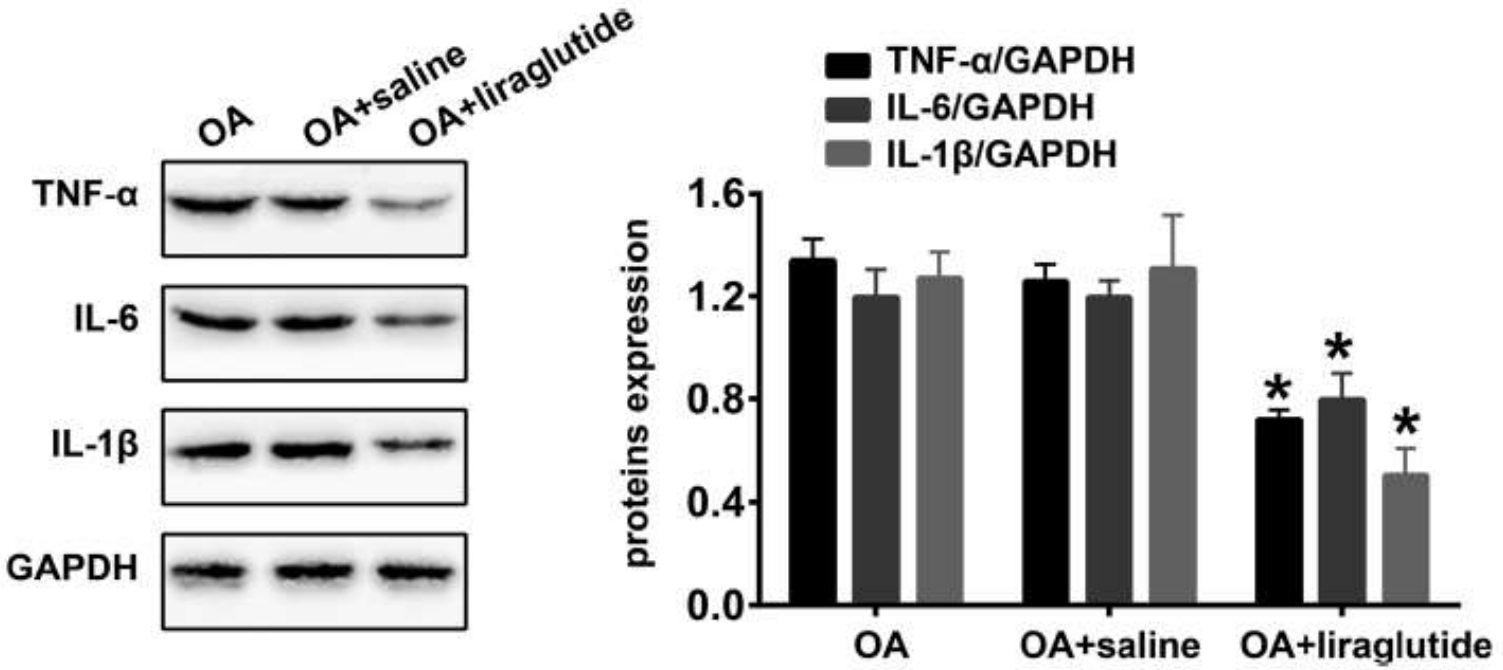


Fig. 6 Liraglutide ameliorates inflammation in the knee OA rat model. Representative Western blots and quantification data for TNF-α, IL-6 and IL-1β in the "OA", "OA + saline" and "OA + liraglutide" groups (n = 5 per group). * indicates $P < 0.05$ compared with the "OA + saline" group

Liraglutide e attivazione della via PKA / CREB e inibizione dell'infiammazione

Dopo il legame del GLP-1 al GLP-1R, questo complesso potrebbe **sovraregolare cAMP** attivando così la **pathway PKA / CREB** . CREB si lega alla proteina legante CREB (CBP), un membro della famiglia delle Istone acetiltransferasi (HATs) e **catalizza così l'acetilazione dell'istone determinando lo switch della cromatina** da stato chiuso ad **aperto**.

Questa modifica promuove il legame della RNA polimerasi II e l'inizio della trascrizione, coinvolgendo **citochine anti-nfiammatorie**, come come **IL-10** e fosfatasi 1 a doppia specificità (**DUSP1**).

Questi dati suggeriscono che l'attivazione dei segnali CREB gioca un ruolo importante nella risposta antinfiammatoria, con il coinvolgimento di GLP-1R in questo processo.

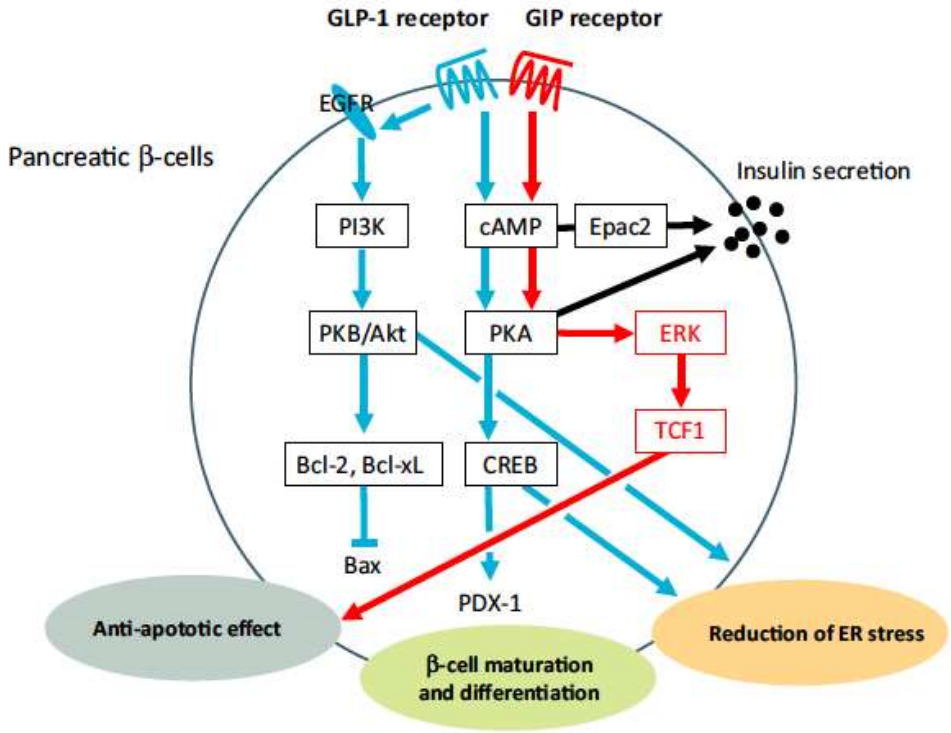


Fig. 1 Molecular mechanism of GIP- and GLP-1-induced insulin secretion and β-cell survival. GIP and GLP-1 potentiate glucose-dependent insulin secretion through PKA and Epac2 (*black arrows*). GLP-1 is well known to be associated with β-cell survival (as it exerts an antiapototic effect), reduction of ER stress, and β-cell maturation and differentiation (*blue arrows*). Campbell et al. have shown a new pathway for GIP-induced β-cell survival (*red arrows*)

Un'azione chiave di IL-10 è trasformare i macrofagi di un fenotipo "infiammatorio" M1 che produce livelli elevati di citochine proinfiammatorie e bassi livelli di citochine antinfiammatorie, a un fenotipo "regolatorio" M2 che producono bassi livelli di citochine pro-infiammatorie e alti livelli di molecole antinfiammatorie

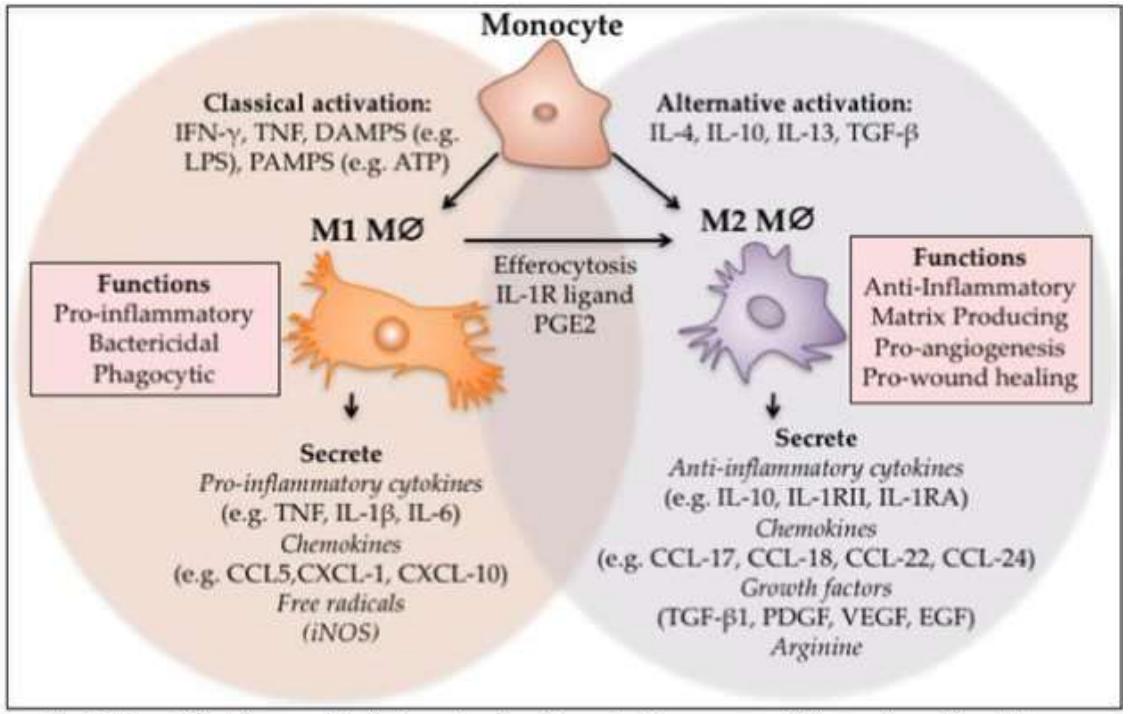


Fig. 1: Fenotipi dei macrofagi e loro funzioni durante il processo di riparazione tissutale. (Da: Hesketh M, Sahin KB, West ZE e Murray RZ: Macrophage phenotypes regulate scar formation and chronic wound healing. Int J Mol Sci 2017; 18: 1545-55

Sorg H, et al. Eur Surg Res 2017; 58: 81-94.

DUSP1 limita l'attivazione della pathway MyD88 attraverso la defosforilazione e l'inattivazione di p38 MAPK e chinasi N-terminali c-Jun (JNK), e può essere indotta da glucocorticoidi.

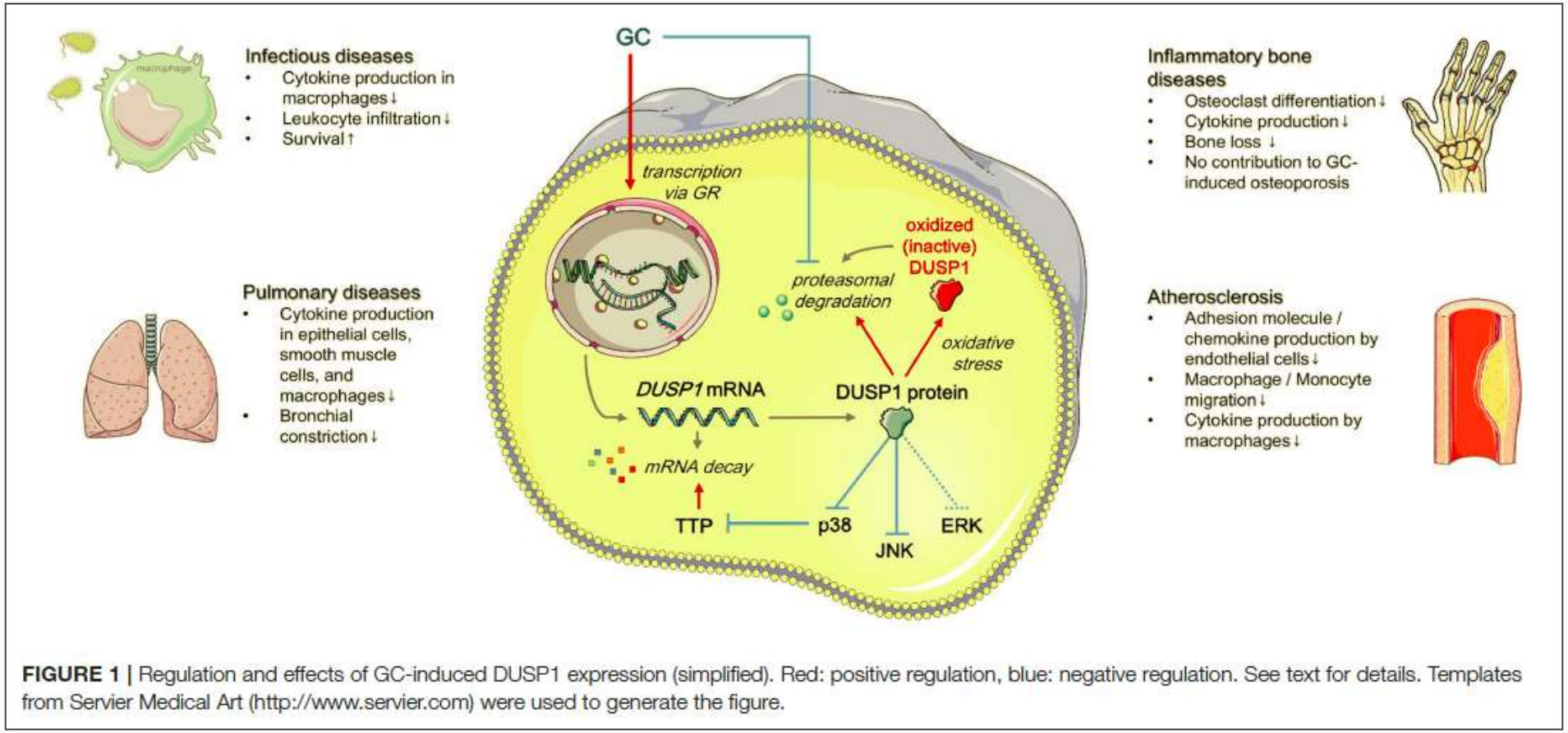


FIGURE 1 | Regulation and effects of GC-induced DUSP1 expression (simplified). Red: positive regulation, blue: negative regulation. See text for details. Templates from Servier Medical Art (http://www.servier.com) were used to generate the figure.

Hoppstädter J and Ammit AJ (2019)Front. Immunol. 10:1446.

Osteoarthritis and Cartilage

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Review

The PI3K/AKT/mTOR signaling pathway in osteoarthritis: a narrative review

K. Sun †, J. Luo ‡, J. Guo †, X. Yao †, X. Jing †, F. Guo † *

† Department of Orthopedics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, 430030, China
‡ The Center for Biomedical Research, The Tongji Hospital Research Building, Tongji Hospital, Tongji Medical College, Huazhong University of Science & Technology, Wuhan, 430030, China

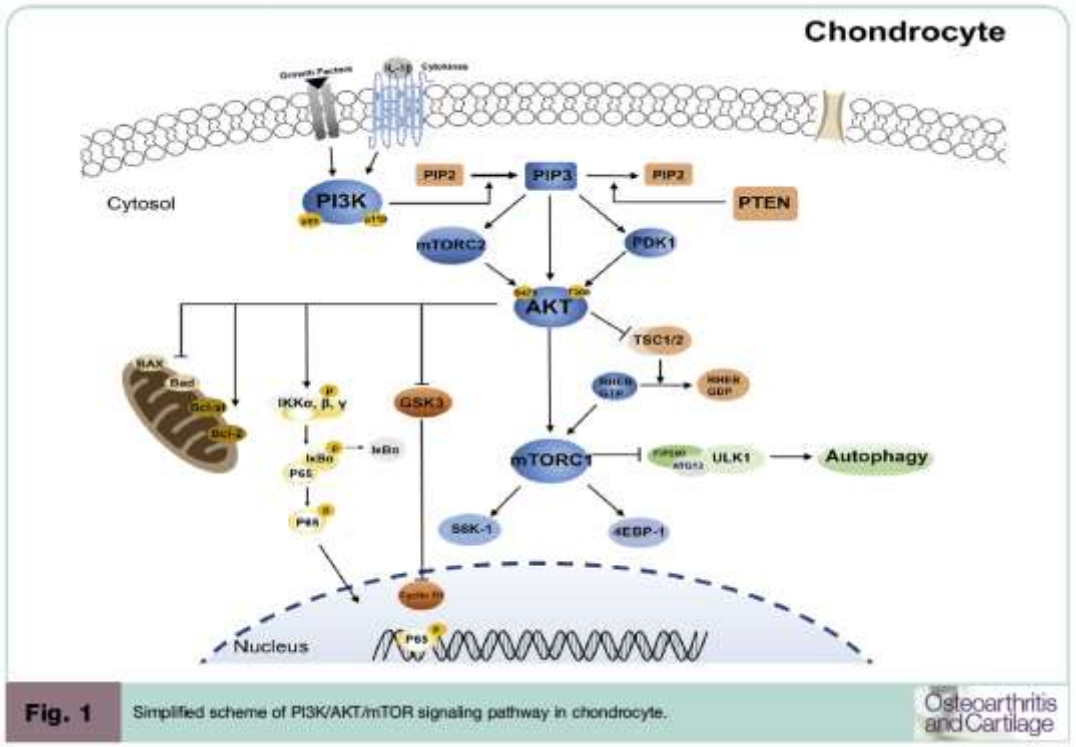
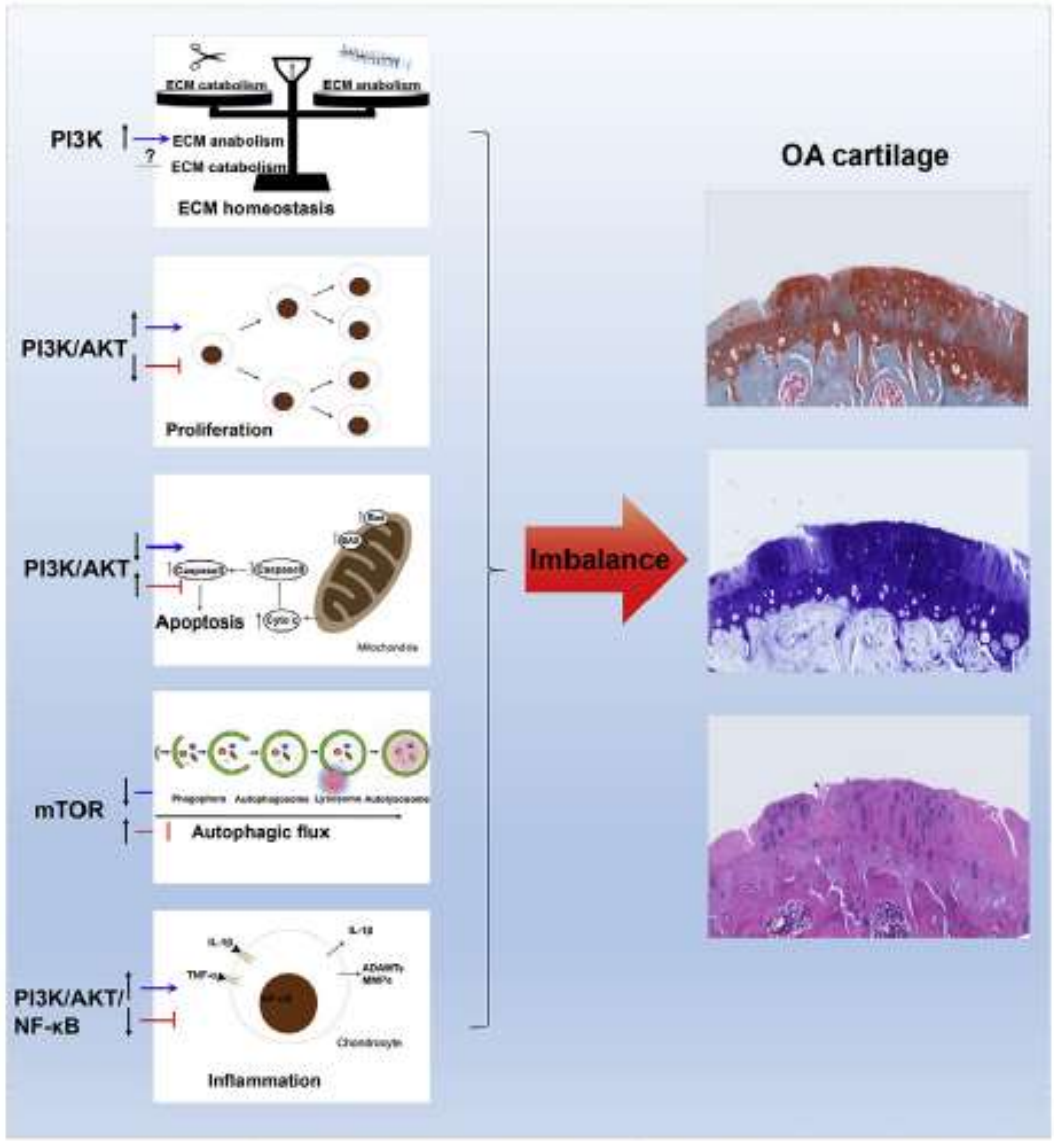
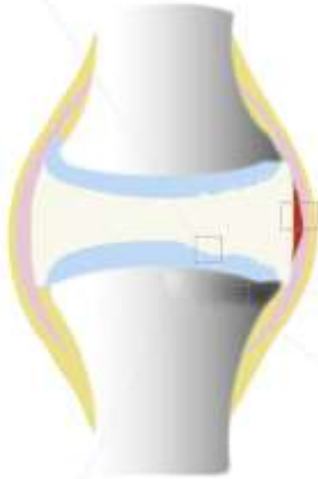


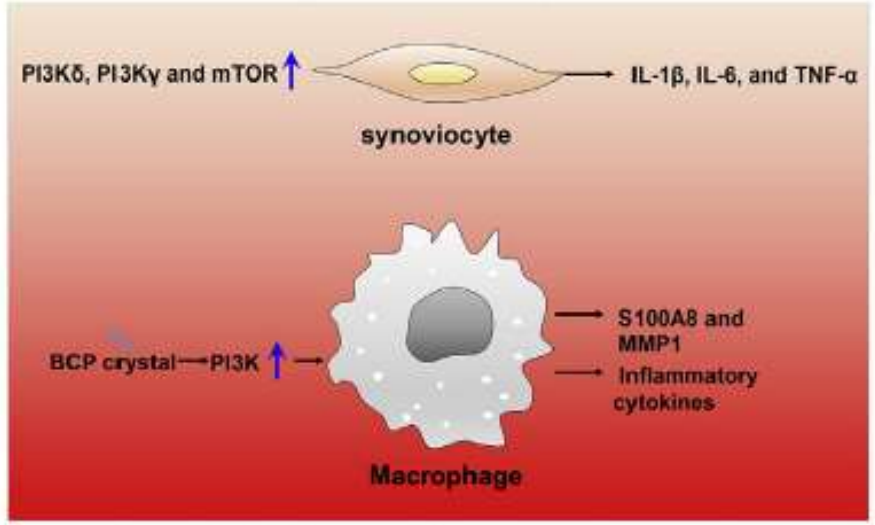
Fig. 1 Simplified scheme of PI3K/AKT/mTOR signaling pathway in chondrocyte.

Osteoarthritis and Cartilage



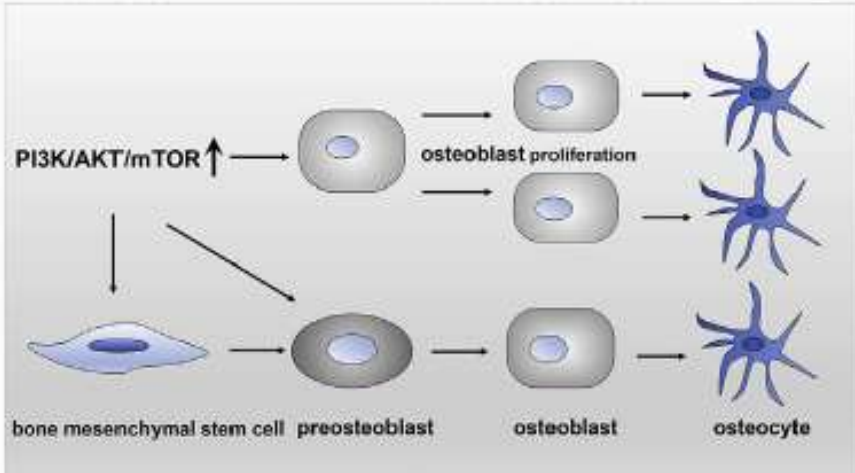
Cartilage degeneration





Synovial inflammation

Subchondral bone sclerosis



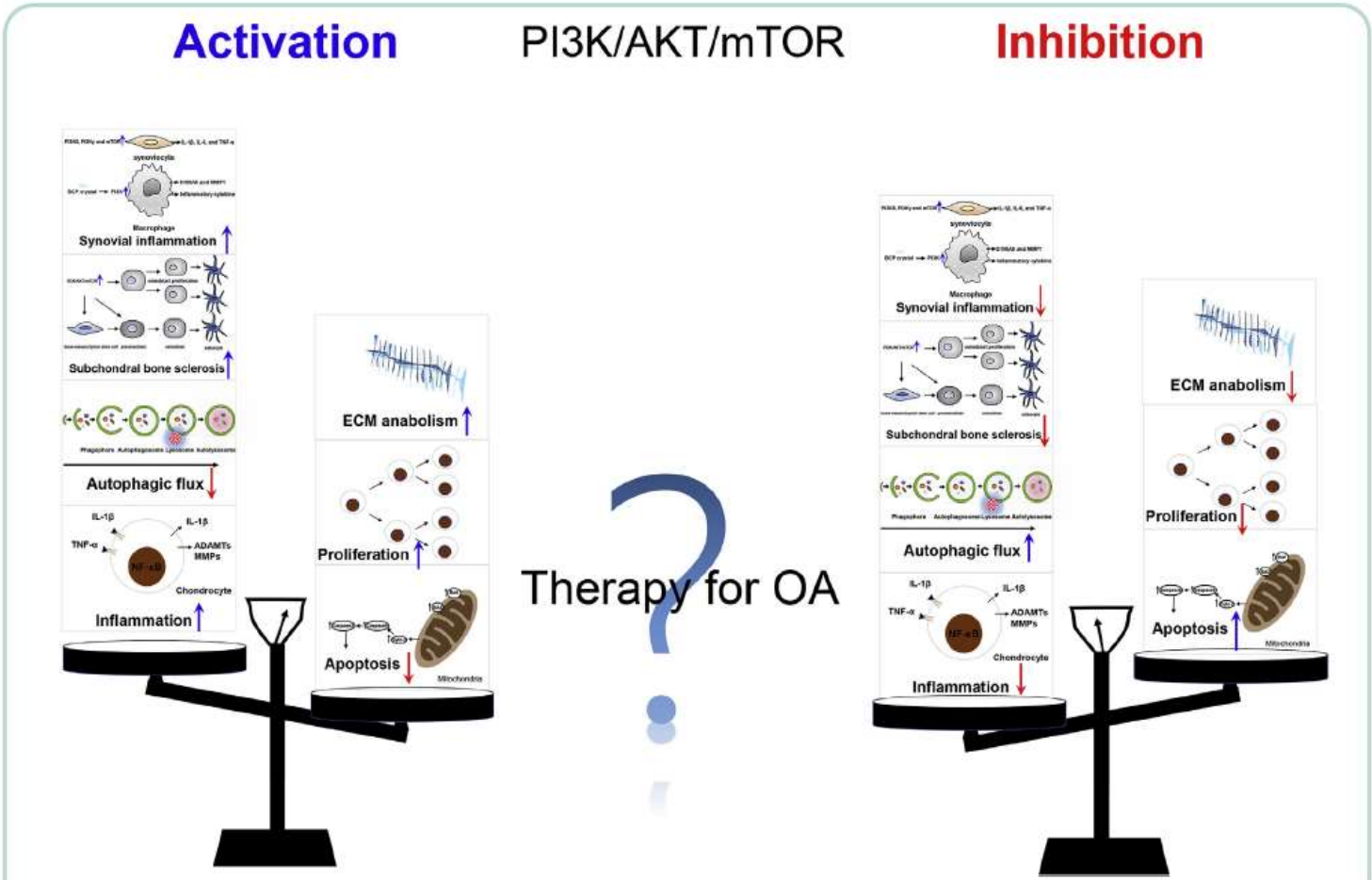


Fig. 3

Challenges of the PI3K/AKT/mTOR-based treatment for OA. The PI3K/AKT/mTOR signaling mediated synovial inflammation, subchondral bone sclerosis, ECM homeostasis, chondrocyte proliferation, apoptosis, autophagy, and inflammation greatly affect cell fate and OA pathophysiology. There will be an imbalance among these cell processes if simply activating or inhibiting PI3K/AKT/mTOR signaling. Thus, how this axis interacts with other signaling pathways, and how to target its function in OA without disrupting important physiological axis-regulated processes need to be clarfied.

Osteoarthritis and Cartilage

Chen et al. Cell Death and Disease (2018)9:212
DOI 10.1038/s41419-017-0217-y

Cell Death & Disease

ARTICLE Open Access

Glucagon-like peptide-1 receptor regulates endoplasmic reticulum stress-induced apoptosis and the associated inflammatory response in chondrocytes and the progression of osteoarthritis in rat

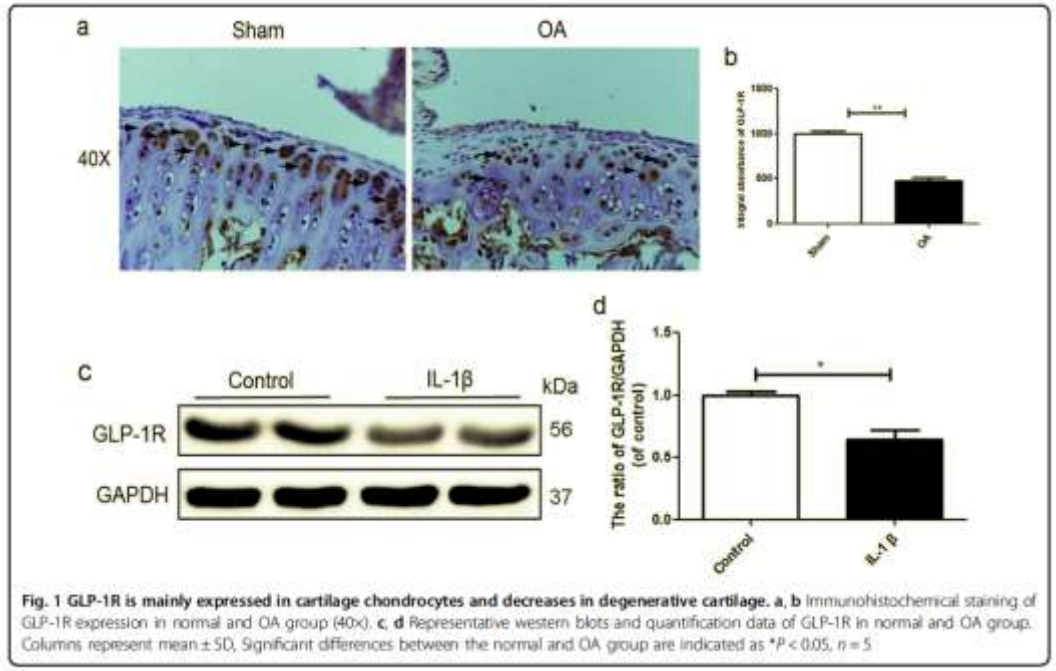


Fig. 1 GLP-1R is mainly expressed in cartilage chondrocytes and decreases in degenerative cartilage. a, b Immunohistochemical staining of GLP-1R expression in normal and OA group (40×). **c, d** Representative western blots and quantification data of GLP-1R in normal and OA group. Columns represent mean ± SD, Significant differences between the normal and OA group are indicated as $^{*}P < 0.05$, $n = 5$

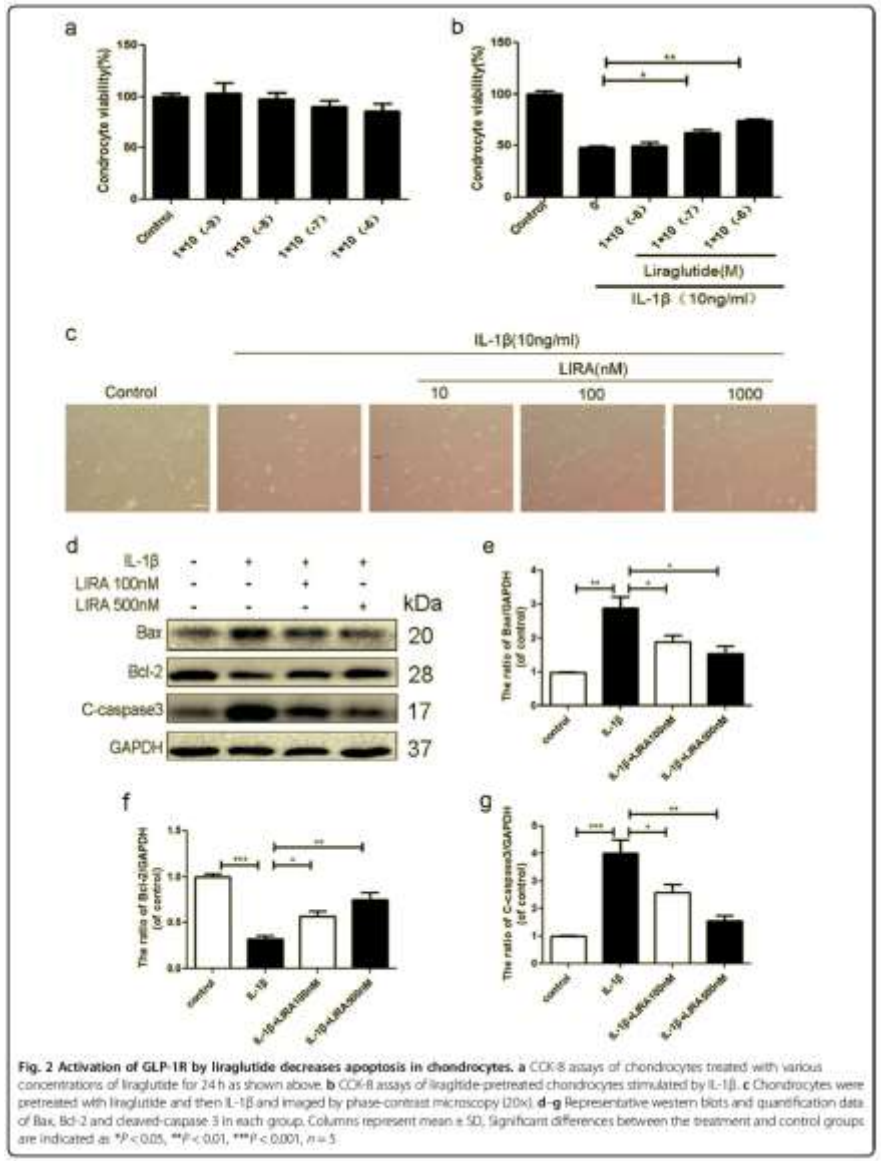


Fig. 2 Activation of GLP-1R by liraglutide decreases apoptosis in chondrocytes. a CCK-8 assays of chondrocytes treated with various concentrations of liraglutide for 24 h as shown above. **b** CCK-8 assays of liraglitide-pretreated chondrocytes stimulated by IL-1β. **c** Chondrocytes were pretreated with liraglutide and then IL-1β and imaged by phase-contrast microscopy (20×). **d**–**g** Representative western blots and quantification data of Bax, Bcl-2 and cleaved-caspase 3 in each group. Columns represent mean ± SD. Significant differences between the treatment and control groups are indicated as $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $n = 5$

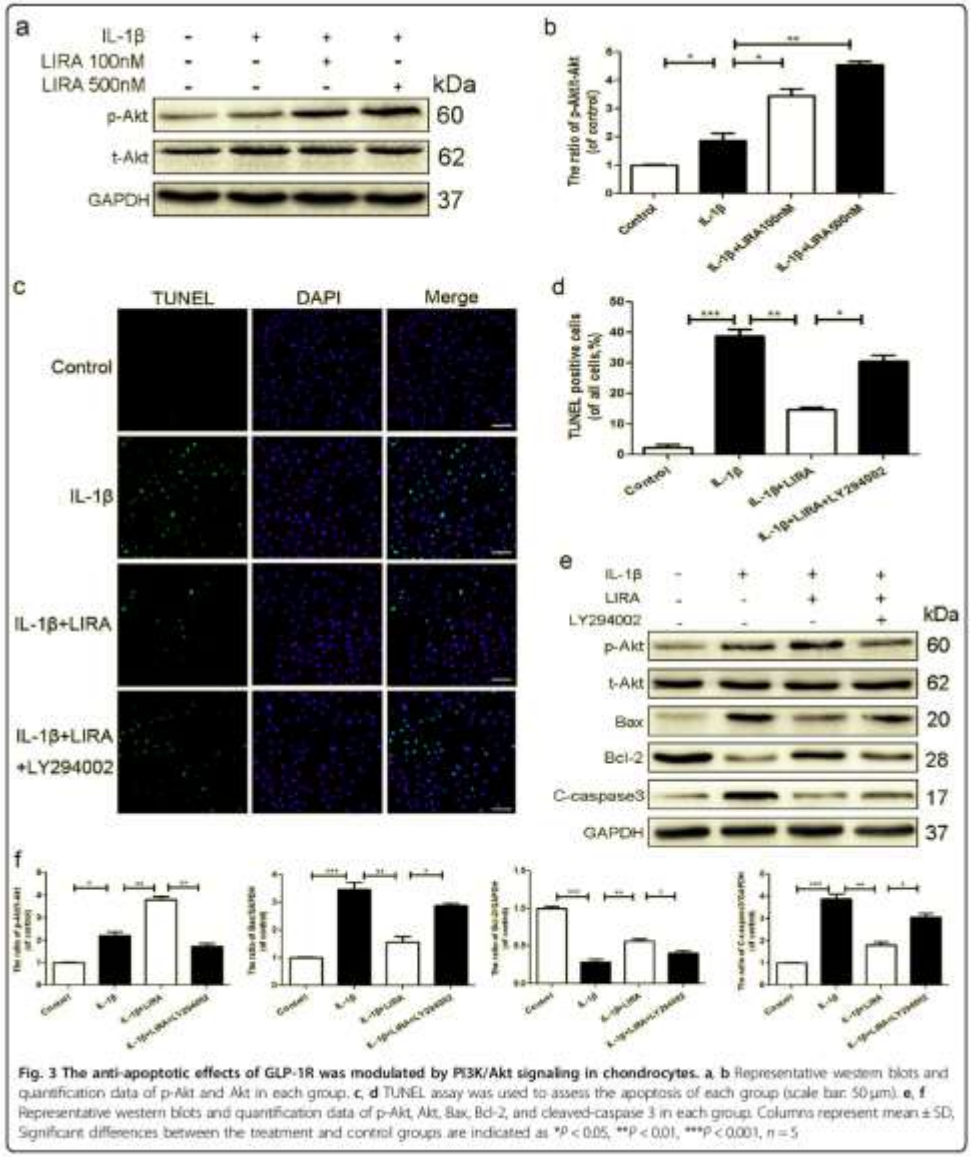


Fig. 3 The anti-apoptotic effects of GLP-1R was modulated by PI3K/Akt signaling in chondrocytes. a, **b** Representative western blots and quantification data of p-Akt and Akt in each group. **c**, **d** TUNEL assay was used to assess the apoptosis of each group (scale bar: 50 μm). **e**, **f** Representative western blots and quantification data of p-Akt, Akt, Bax, Bcl-2, and cleaved-caspase 3 in each group. Columns represent mean ± SD. Significant differences between the treatment and control groups are indicated as $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $n = 5$

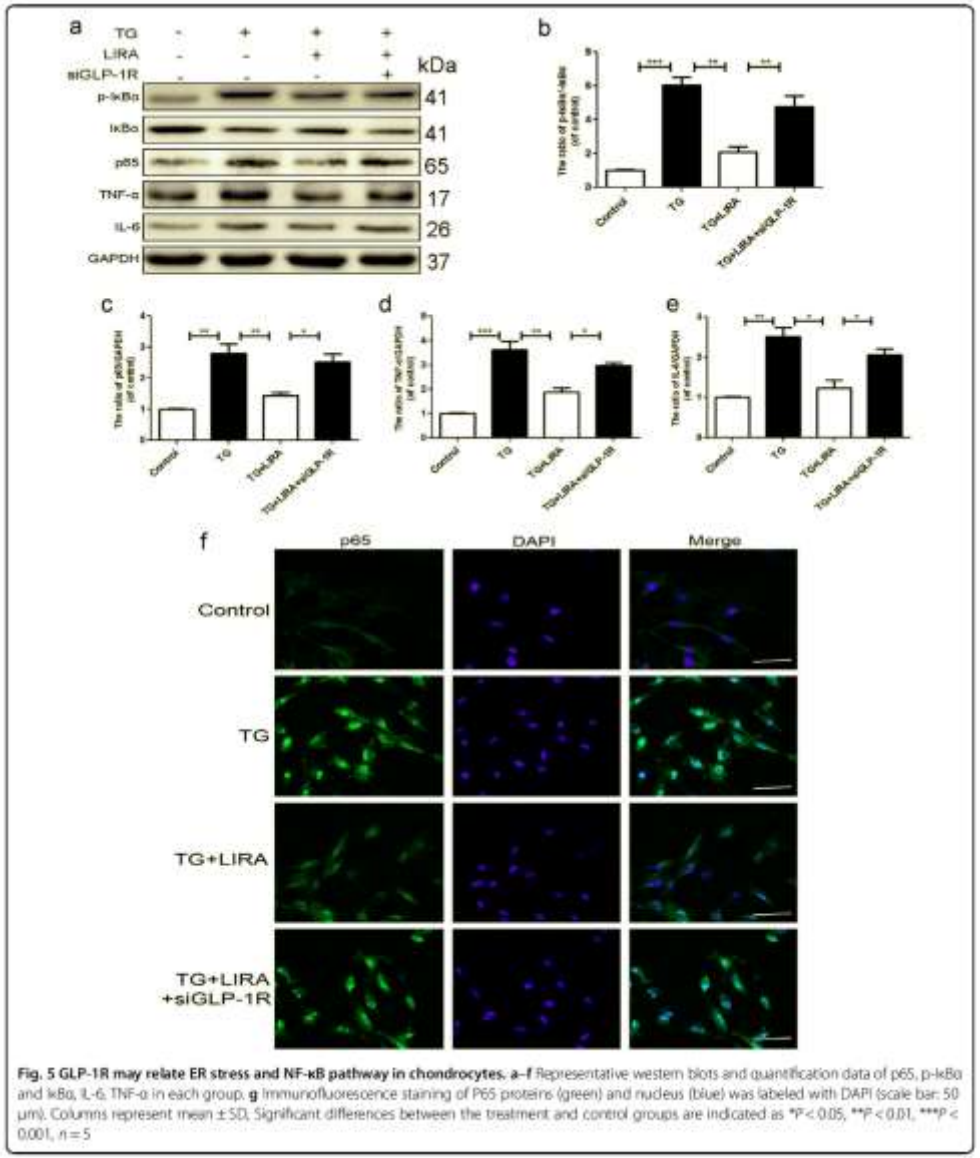


Fig. 5 GLP-1R may relate ER stress and NF-κB pathway in chondrocytes. a–f Representative western blots and quantification data of p65, p-IκBα and IκBα, IL-6, TNF-α in each group. **g** Immunofluorescence staining of P65 proteins (green) and nucleus (blue) was labeled with DAPI (scale bar: 50 μm). Columns represent mean ± SD. Significant differences between the treatment and control groups are indicated as $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $n = 5$

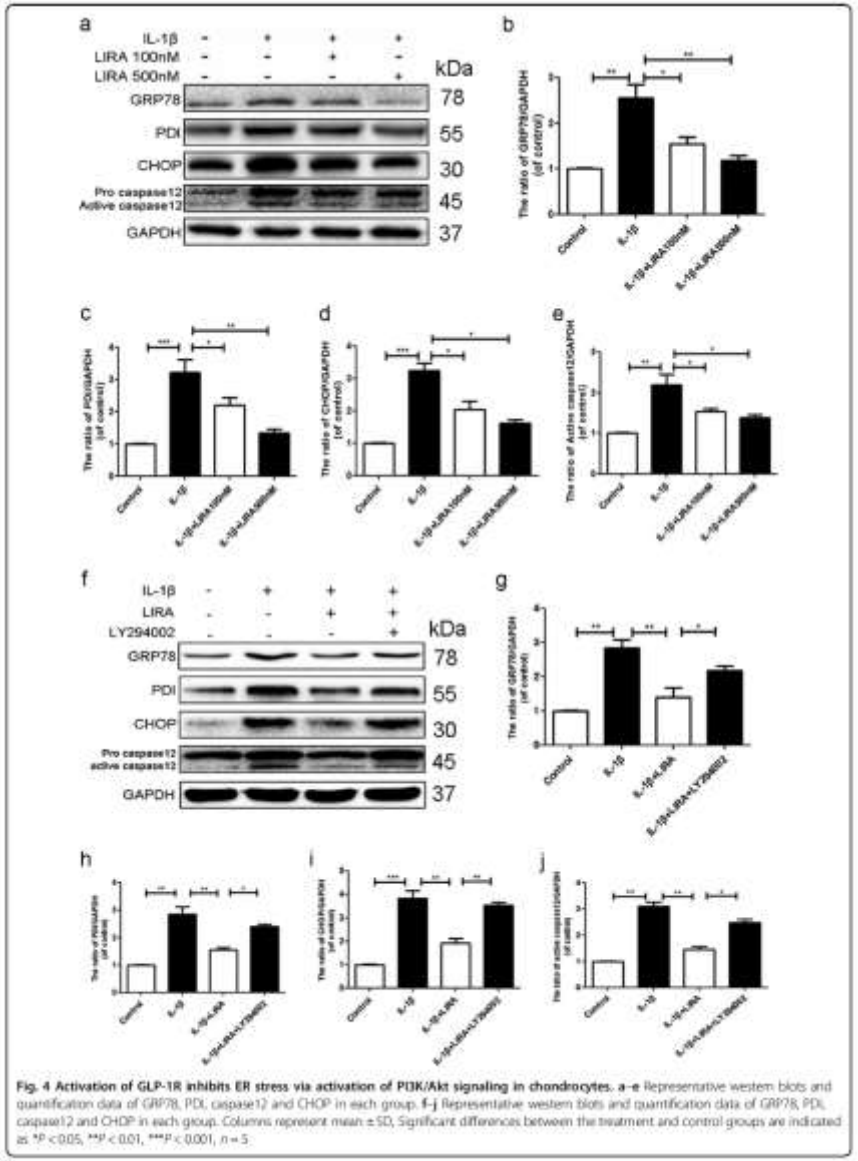


Fig. 4 Activation of GLP-1R inhibits ER stress via activation of PI3K/Akt signaling in chondrocytes. a–e Representative western blots and quantification data of GRP78, PDI, caspase12 and CHOP in each group. **f–j** Representative western blots and quantification data of GRP78, PDI, caspase12 and CHOP in each group. Columns represent mean ± SD. Significant differences between the treatment and control groups are indicated as $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $n = 5$

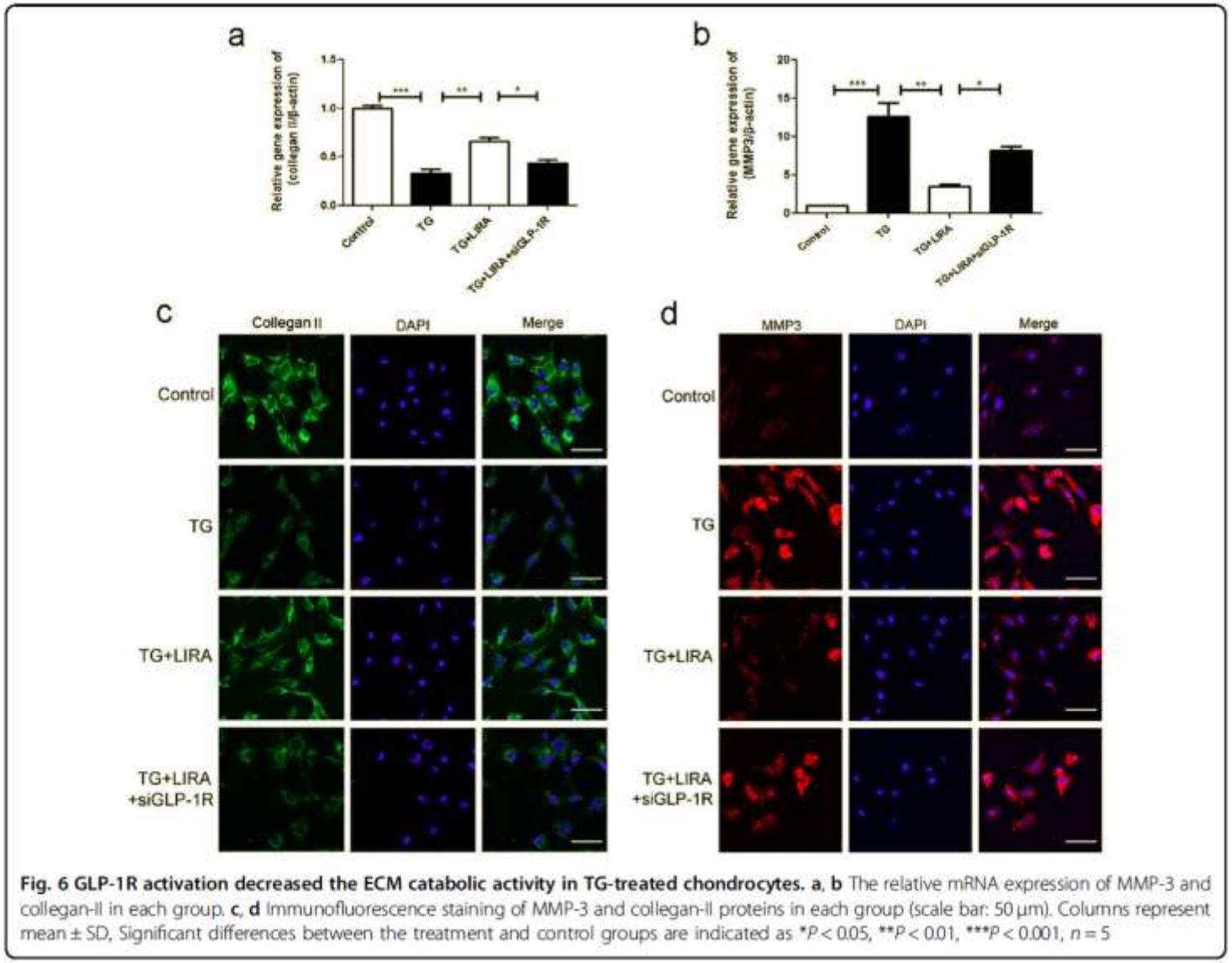


Fig. 6 GLP-1R activation decreased the ECM catabolic activity in TG-treated chondrocytes. a, b The relative mRNA expression of MMP-3 and collegan-II in each group. **c, d** Immunofluorescence staining of MMP-3 and collegan-II proteins in each group (scale bar: 50 μm). Columns represent mean ± SD, Significant differences between the treatment and control groups are indicated as $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $n = 5$

L'Infiammazione svolge un ruolo fondamentale nei processi metabolici della ECM e prove crescenti suggeriscono che **l'infiammazione** mediata dalla **sovraespressione** delle **MMP** si traduce in un **processo catabolico della matrice**

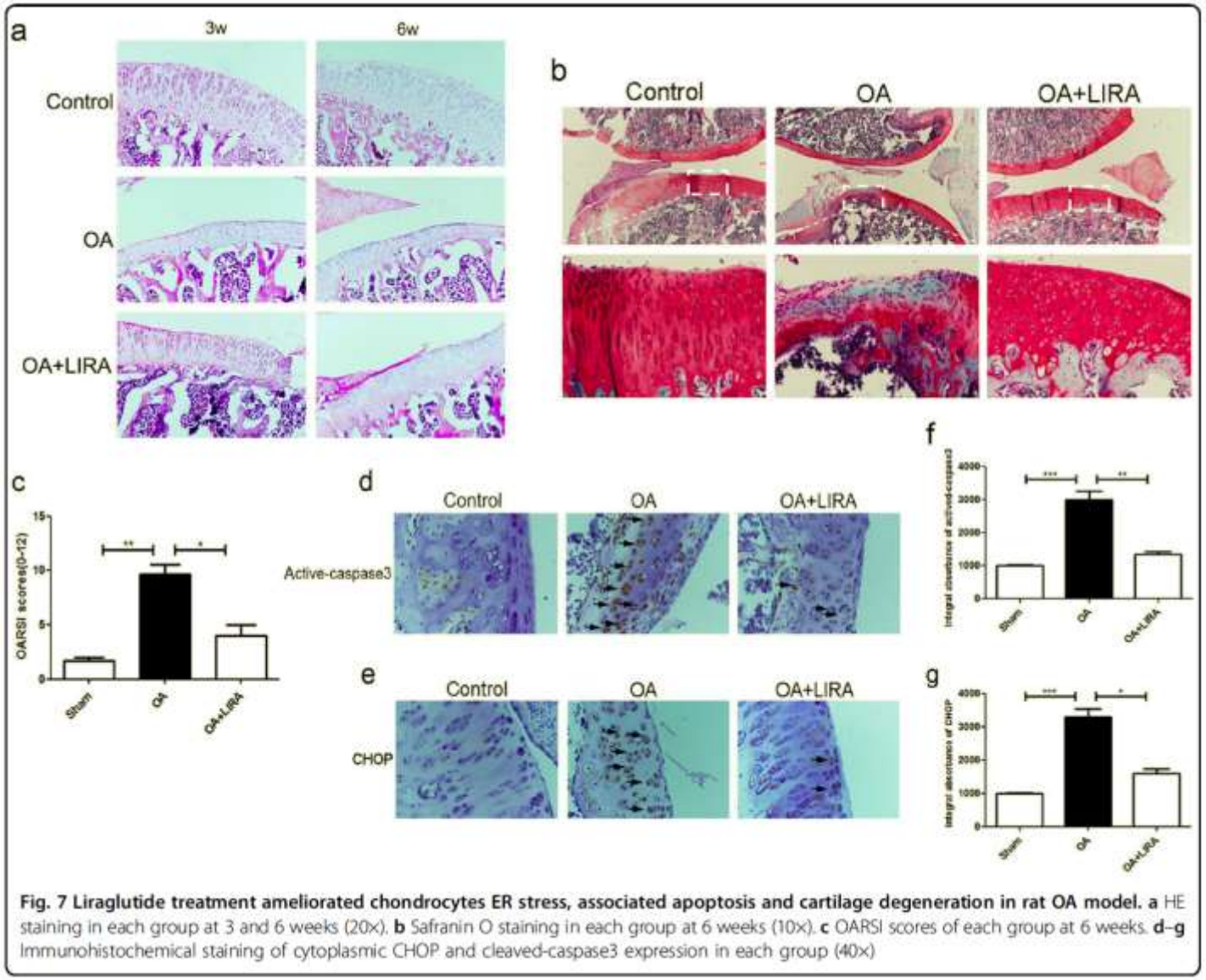


Fig. 7 Liraglutide treatment ameliorated chondrocytes ER stress, associated apoptosis and cartilage degeneration in rat OA model. a HE staining in each group at 3 and 6 weeks (20×). **b** Safranin O staining in each group at 6 weeks (10×). **c** OARSI scores of each group at 6 weeks. **d–g** Immunohistochemical staining of cytoplasmic CHOP and cleaved-caspase3 expression in each group (40×)

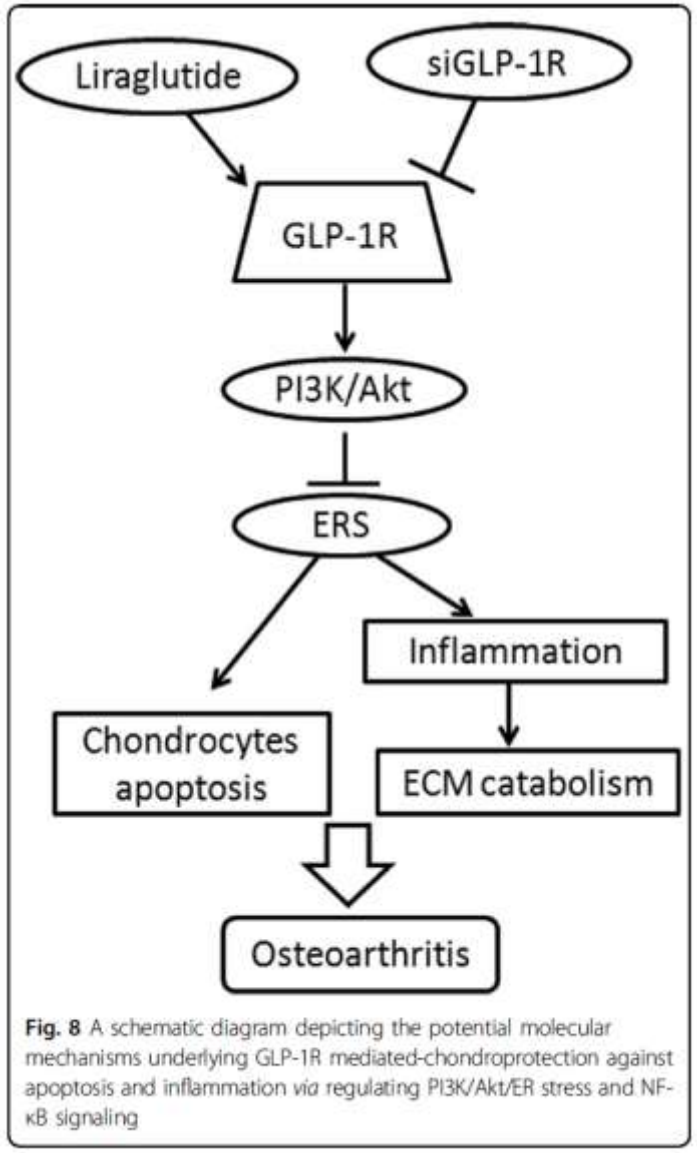


Fig. 8 A schematic diagram depicting the potential molecular mechanisms underlying GLP-1R mediated-chondroprotection against apoptosis and inflammation *via* regulating PI3K/Akt/ER stress and NF-κB signaling

Gli effetti protettivi del GLP-1R potrebbero essere mediati dalla pathway **PI3K / Akt** che **inattiva** anche **pro-caspase-9** e provoca la defosforilazione di **caspase9**, **diminuendo** il livello di **apoptosi**.

L' Attivazione di **GLP-1R riduce** i livelli di **Bax pro-apoptotico** e di cleaved-caspase3, e **aumenta** i livelli di **Bcl-2 anti-apoptotico** nei condrociti trattati con IL-1β per OA, indicando che GLP-1R può essere un potenziale bersaglio per il trattamento dell'OA.

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Original Article

Liraglutide suppresses TNF-α-induced degradation of extracellular matrix in human chondrocytes: a therapeutic implication in osteoarthritis

Jing Mei[1*], Jie Sun[3*], Jin Wu[1*], Xiannian Zheng[2]

La **liraglutide attenua** in modo significativo la **sovrapproduzione di ROS e NOX-4** innescata da TNF-a. Suggerendo una potente e potenziale capacità antiossidante.

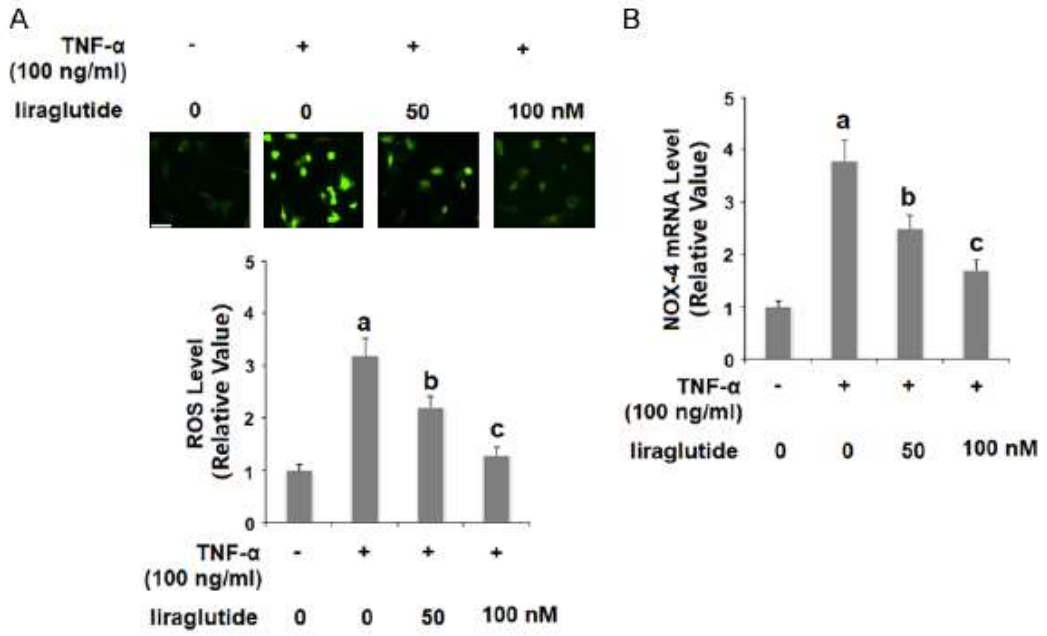

Figure 1. Liraglutide attenuates TNF-α-induced oxidative stress in human primary chondrocytes. Human primary chondrocytes were incubated with 100 ng/ml TNF-α in the presence or absence of liraglutide (50 and 100 nM) for 24 h. A. The level of intracellular reactive oxygen species (ROS) was determined by DCFH-DA; Scale bars, 100 μm; B. Expression of NOX-4 at the mRNA level was determined by real time PCR analysis (a, b, c, $P<0.01$ vs. previous column group, n=5-6).

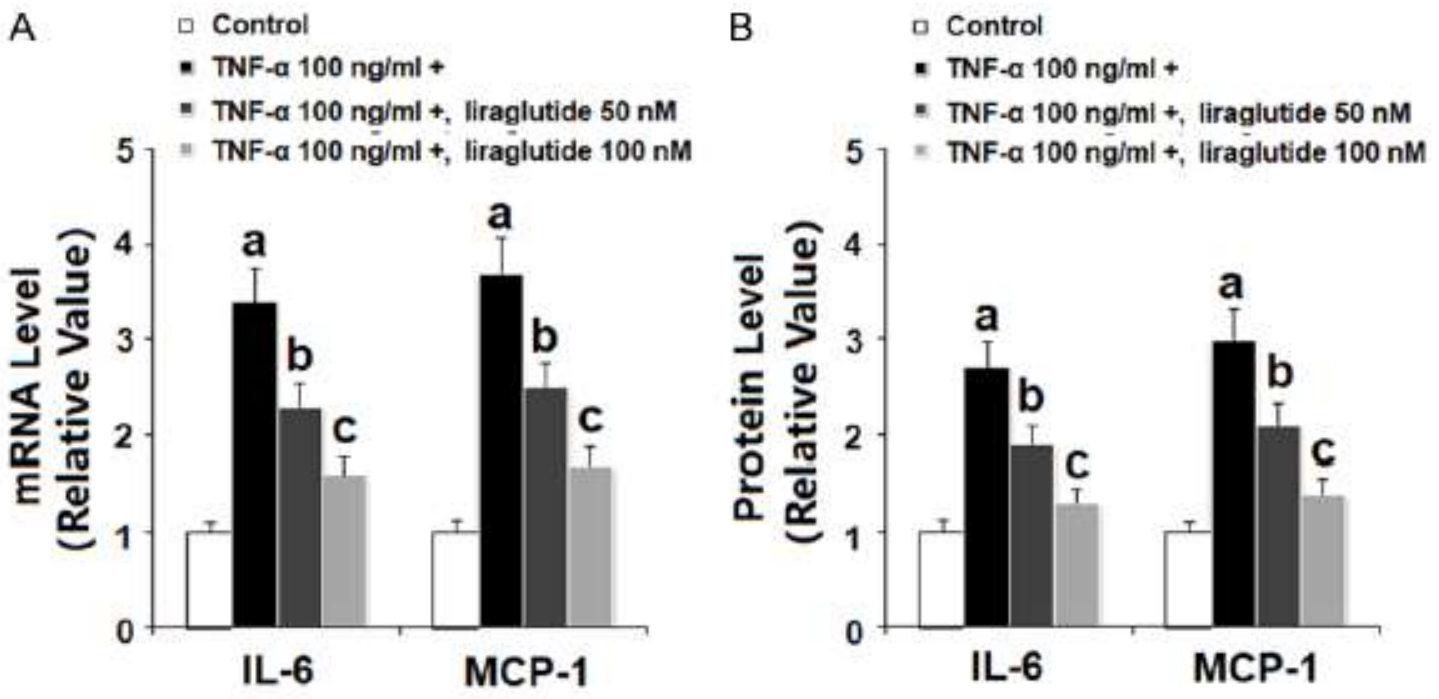

Figure 2. Liraglutide reduces TNF-α-induced expression and secretion of pro-inflammatory cytokines in human primary chondrocytes. Human primary chondrocytes were incubated with 100 ng/ml TNF-α in the presence or absence of liraglutide (50 and 100 nM) for 24 h. A. Expression of IL-6 and MCP-1 at the mRNA level was determined by real time PCR analysis; B. Expression of IL-6 and MCP-1 at the protein level was determined by ELISA analysis (a, b, c, $P < 0.01$ vs. previous column group, n=5-6).

La Liraglutide **inibisce** fortemente l'espressione di **IL-6 indotta da TNF-α**.
La Liraglutide ha avuto un **effetto inibitorio** altrettanto potente sull'espressione di **MCP-1**, chemochina che induce la degradazione della cartilagine nell'OA.

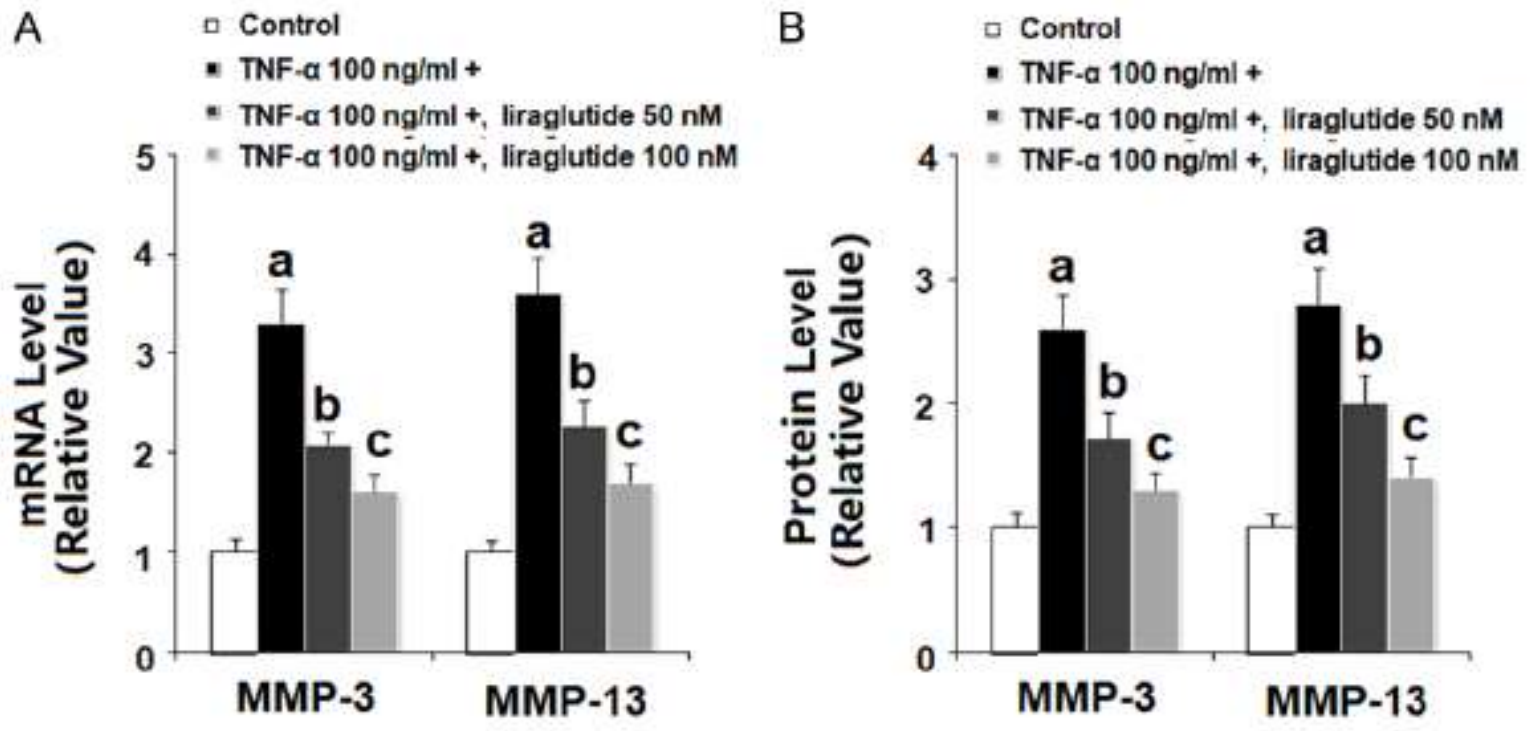

Figure 3. Liraglutide mitigates TNF-α-induced expression of MMP-3 and MMP-13 in human primary chondrocytes. Human primary chondrocytes were incubated with 100 ng/ml TNF-α in the presence or absence of liraglutide (50 and 100 nM) for 24 h. A. Expression of MMP-3 and MMP-13 at the mRNA level was determined by real time PCR analysis; B. Expression of MMP-3 and MMP-13 at the protein level was determined by ELISA analysis (a, b, c, $P < 0.01$ vs. previous column group, n=5-6).

Effetti di Liraglutide sulla degradazione del collagene di tipo II e dell'aggrecano rispettivamente da parte di MMP e ADAMTS

Effetto **inibitorio di liraglutide** contro l'espressione indotta da TNF-a di **MMP-3 e MMP-13** e, notevole effetto preventivo contro la degradazione del collagene di tipo II

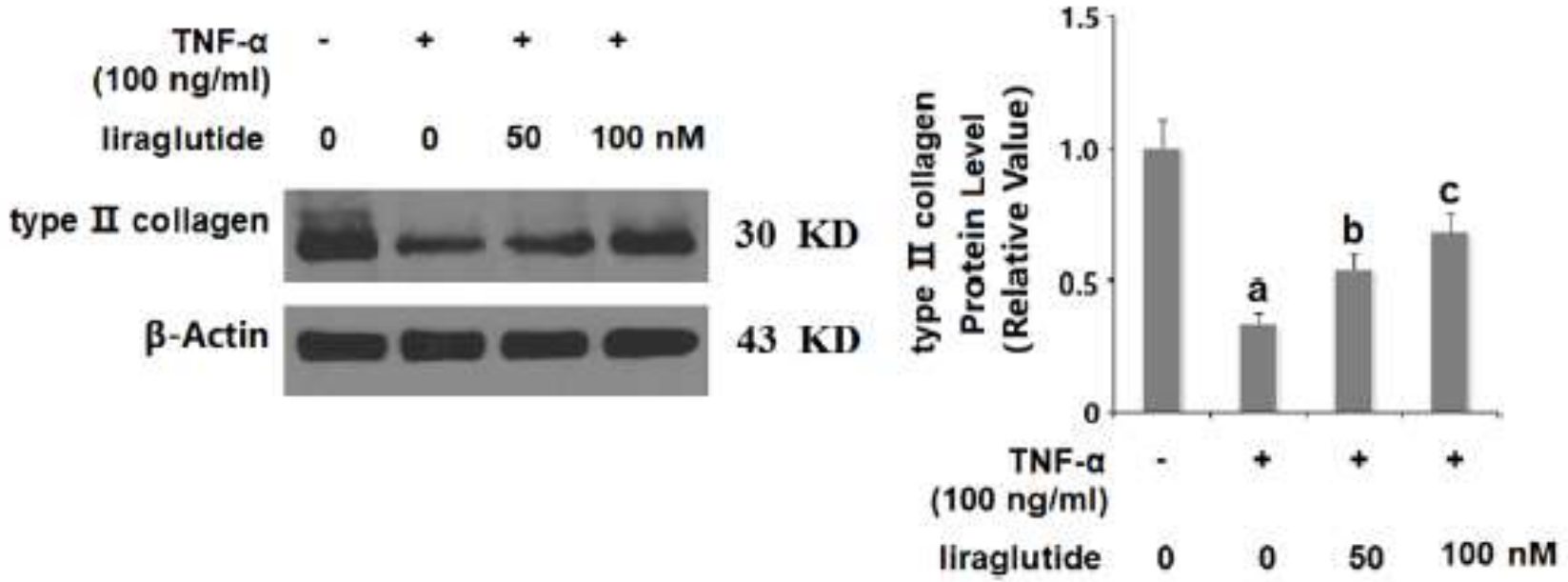

Figure 4. Liraglutide mitigates TNF-α-induced degradation of type II collagen in human primary chondrocytes. Human primary chondrocytes were incubated with 100 ng/ml TNF-α in the presence or absence of liraglutide (50 and 100 nM) for 24 h. Expression of type II collagen was determined by western blot analysis (a, b, c, $P < 0.01$ vs. previous column group, n=5-6).

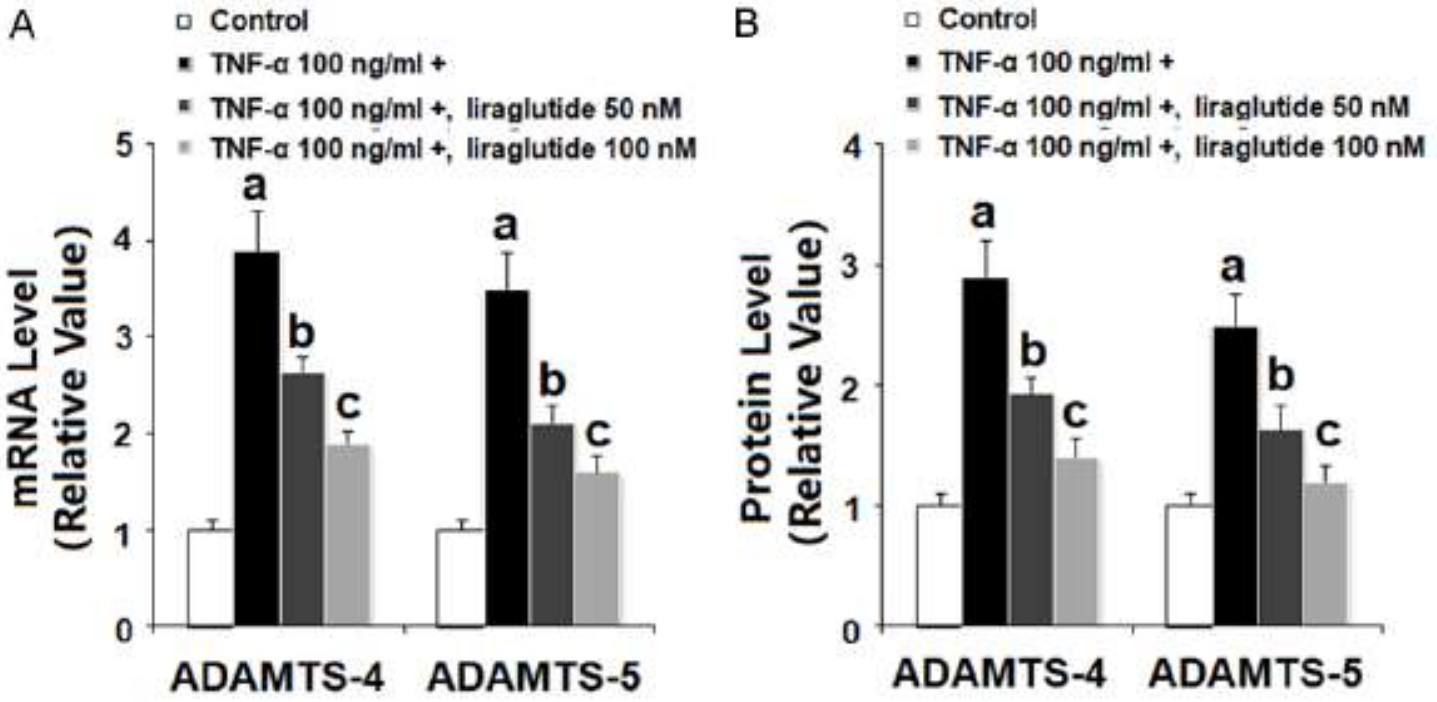

Figure 5. Liraglutide mitigates TNF-α-induced expression of and ADAMTS-4 and ADAMTS-5 in human primary chondrocytes. Human primary chondrocytes were incubated with 100 ng/ml TNF-α in the presence or absence of liraglutide (50 and 100 nM) for 24 h. A. Expression of ADAMTS-4 and ADAMTS-5 at the mRNA level was determined by real time PCR analysis; B. Expression of ADAMTS-4 and ADAMTS-5 at the protein level was determined by ELISA analysis (a, b, c, $P < 0.01$ vs. previous column group, n=5-6).

Effetto **inibitorio** di Liraglutide contro l'espressione indotta da TNF-a di **ADAMTS-4 e ADAMTS-5** e la successiva degradazione di aggrecano, dimostrando così un nuovo ruolo potenziale di liraglutide nel preservare la cartilagine prevenendo la degradazione di entrambi i tipi II collagene e aggrecano indotti da TNF-a.

Avendo un ruolo essenziale nella degradazione della cartilagine nell'OA, **la via di segnalazione NF-κB** regola un'ampia gamma di **risposte pro-infiammatorie** così come l'espressione di MMP e ADAMTS nei condrociti.

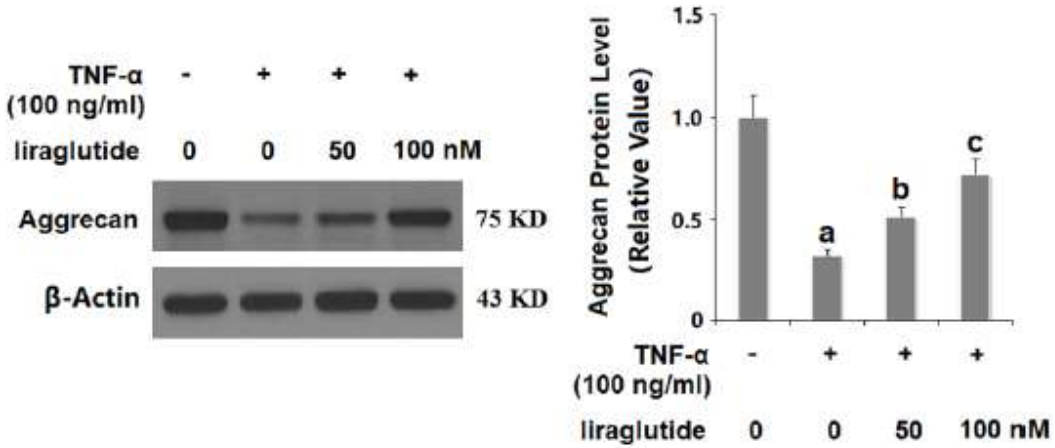

Figure 6. Liraglutide abrogates TNF-α-induced degradation of aggrecan in human primary chondrocytes. Human primary chondrocytes were incubated with 100 ng/ml TNF-α in the presence or absence of liraglutide (50 and 100 nM) for 24 h. Expression of aggrecan was determined by western blot analysis (a, b, c, $P < 0.01$ vs. previous column group, n=5).

L'agonismo del GLP-1R da parte di liraglutide ha **fortemente inibito l'attivazione di NF-κB.**

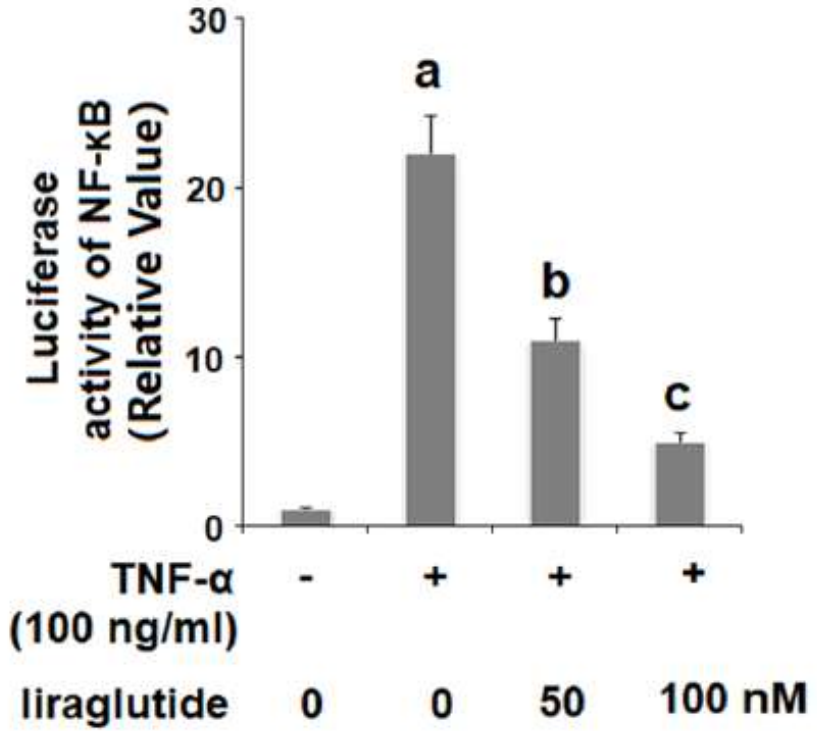

Figure 7. Liraglutide mitigates TNF-α-induced activation of NF-κB. Human primary chondrocytes were incubated with 100 ng/ml TNF-α in the presence or absence of liraglutide (50 and 100 nM) for 24 h. Luciferase activity of NF-κB was determined (a, b, c, $P < 0.01$ vs. previous column group, n=5-6).

Protective Effects Of Intra-Articular Formulated Liraglutide In Osteoarthritis: Preclinical Studies

Francis Berenbaum[1], Coralie Meurot[2], Margot Vieubled[2], Laure Sudre[3], Carole Bougault[3*], Revital Rattenbach[2], Céline Martin[2], Claire Jacques[3]

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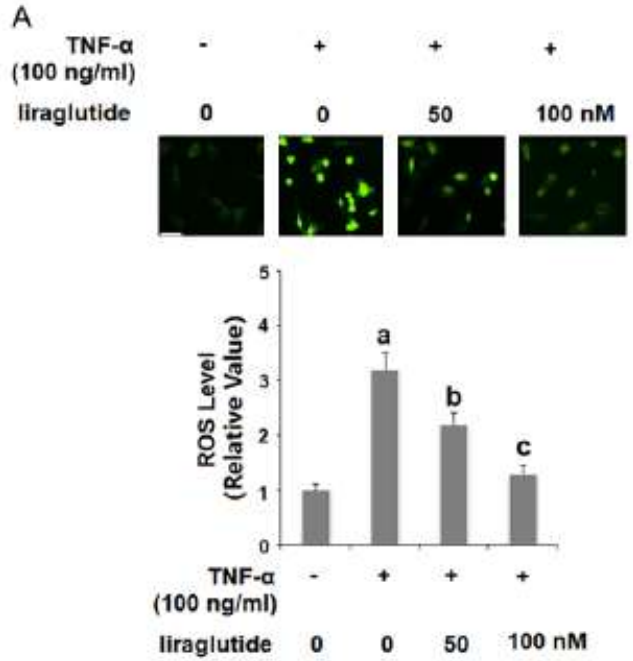
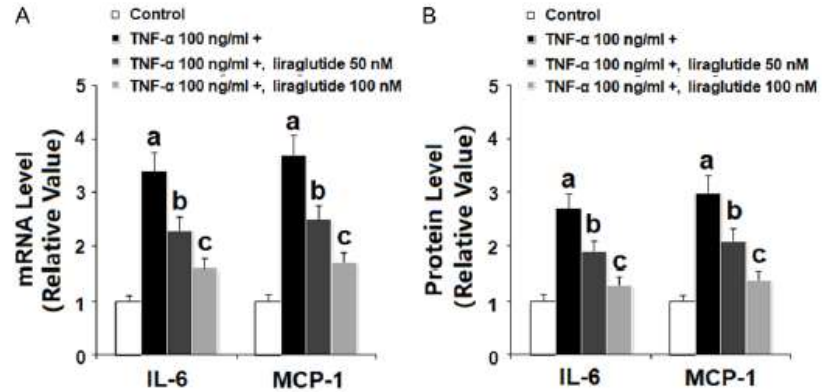
Original Article

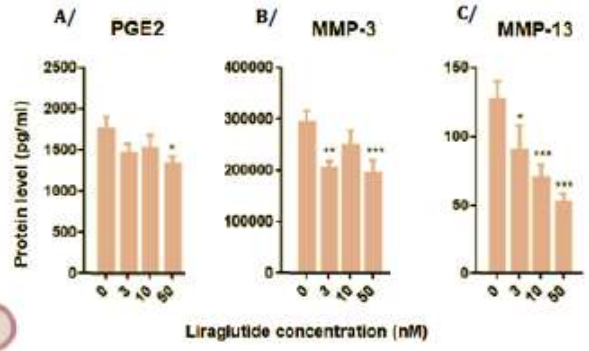
Liraglutide suppresses TNF-α-induced degradation of extracellular matrix in human chondrocytes: a therapeutic implication in osteoarthritis

Jing Mei[1*], Jie Sun[3*], Jin Wu[1*], Xiannian Zheng[2]

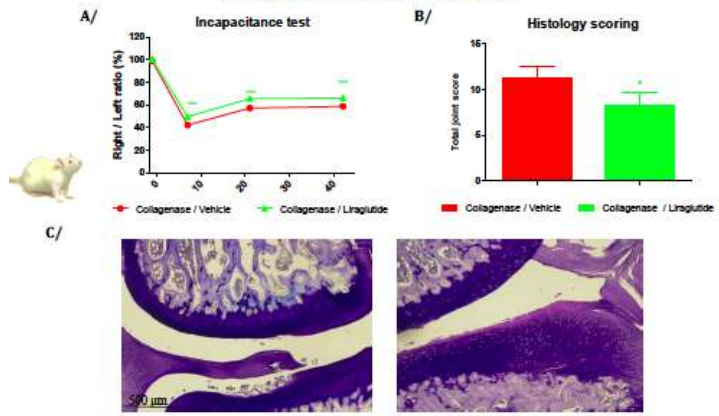




(1) Liraglutide decreases inflammatory and catabolic mediators production in IL1-β-stimulated mouse chondrocytes



(3) Liraglutide has analgesic properties and cartilage protection effects in collagenase-induced model in rats



- **Anti-Inflammatory**
- **Analgesic**
- **Cartilage Protection**

1. Liraglutide treatment in *in vitro* OA model has shown significant decrease in the release of OA inflammatory and catabolic markers.
2. Intra-articular administration of formulated Liraglutide decreases pain in two animal models of OA.
3. Intra-articular administration of formulated Liraglutide protects the joint from OA-related cartilage degradation.

Open access Protocol

BMJ Open

Effect of liraglutide on body weight and pain in patients with overweight and knee osteoarthritis: protocol for a randomised, double-blind, placebo-controlled, parallel-group, single-centre trial

Henrik Gudbergsen,[1] Marius Henriksen,[1,2] Eva Ejlersen Wæhrens,[1] Anders Overgaard,[1] Henning Bliddal,[1] Robin Christensen,[1,3] Mikael Ploug Boesen,[1,4] Filip Krag Knop,[5,6] Arne Astrup,[7] Marianne Uggen Rasmussen,[1] Cecilie Bartholdy,[1] Cecilie Daugaard,[1] Else Marie Bartels,[1] Karen Ellegaard,[1] Berit Lilienthal Heitmann,[8,9] Lars Erik Kristensen[1]

Strengths and limitations of this study

- This will be the first randomised controlled trial examining the efficacy and safety of daily liraglutide 3 mg/day in patients with overweight and knee osteoarthritis (OA).
- Participants will be randomised to receive either liraglutide 3 mg/day or liraglutide placebo 3 mg/day for 52 weeks as an add-on to dietetic guidance.
- The selected primary and secondary outcomes are aligned with outcome measures in rheumatology recommendations.
- This trial has a strict focus on an adult population with clinical knee OA who can successfully go through an intensive dietary programme (the target being to lose at least 5% of their initial body weight).
- The trial has implication for the large number of patients impacted by overweight and knee OA.

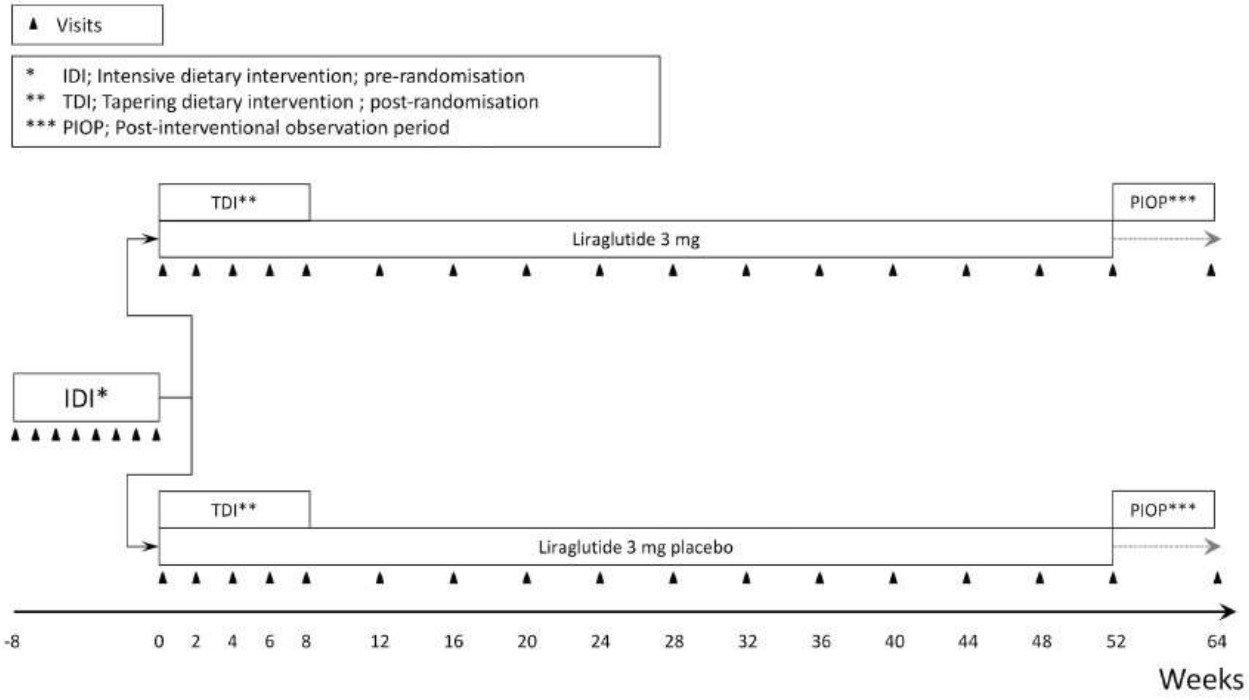
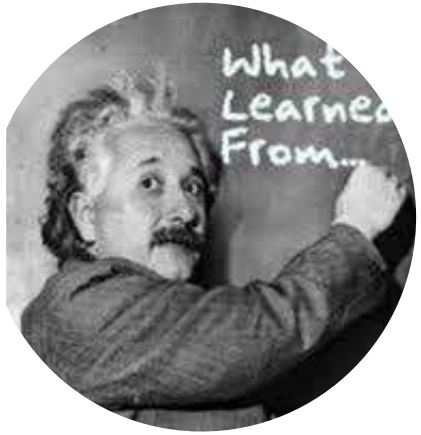


Figure 1 Trial design.

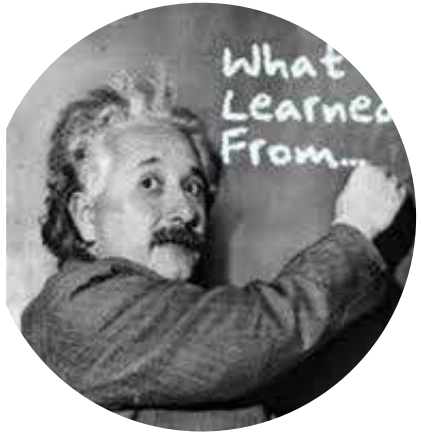


CONCLUSIONI

- I livelli di GLP-1R sono diminuiti significativamente nei modelli murini di OA.

- GLP-1R interagisce con la pathway PKA / CREB e la liraglutide sembra attivare i segnali PKA / CREB, inibendo l'espressione di proteine legate all'infiammazione. TNF-α, IL-6 e IL-1β.

- La liraglutide sembra esercitare un prezioso effetto protettivo contro lo stress ossidativo, l'infiammazione, la degradazione della cartilagine e l'attivazione di NF-κB indotta dal TNF-α nei condrociti umani.



CONCLUSIONI

•La patway PI3K / Akt / ER e la sua regolazione è strettamente coinvolta negli effetti protettivi anti-apoptotici e antinfiammatori in cui la liraglutide sembra avere un ruolo favorevole.

•Questi risultati dimostrano che GLP-1R può essere un nuovo target per il trattamento dell'OA, in particolare in pazienti con diabete mellito.

APPROCCI INTERDISCIPLINARI IN REUMATOLOGIA

8a edizione

REUMATOLOGIA E RIABILITAZIONE

Torino, 15 e 16 ottobre 2021

Responsabili scientifici

Enrico Fusaro

Giuseppe Massazza

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