SKRIPSI

PENGARUH FAKTOR PERTUMBUHAN PLATELET TERHADAP KADAR ALPHA-SMA PADA TIKUS PUTIH MODEL OSTEOARTHRITIS

SARAH

04011182025020

PROGRAM STUDI PENDIDIKAN DOKTER

FAKULTAS KEDOKTERAN

UNIVERSITAS SRIWIJAYA

2023

SKRIPSI

PENGARUH FAKTOR PERTUMBUHAN PLATELET TERHADAP KADAR ALPHA-SMA PADA TIKUS PUTIH MODEL OSTEOARTHRITIS

Diajukan untuk memenuhi salah satu syarat memperoleh gelar

Sarjana Kedokteran (S. Ked)

SARAH

04011182025020

PROGRAM STUDI PENDIDIKAN DOKTER

FAKULTAS KEDOKTERAN

UNIVERSITAS SRIWIJAYA

2023

HALAMAN PENGESAHAN

PENGARUH *ACTIVATED GROWTH FACTOR* (AGF) DARI PLATELET TERHADAP KADAR ALPHA-SMA PADA TIKUS PUTIH MODEL OSTEOARTHRITIS

LAPORAN AKHIR SKRIPSI

Diajukan untuk memenuhi salah satu syarat memperoleh gelar Sarjana Kedokteran (S.Ked)

Oleh:
Sarah
04011182025020

Palembang, 11 Desember 2023
Fakultas Kedokteran Universitas Sriwijaya

Pembimbing I
dr. Rachmat Hidayat, M.Sc
NIP. 198705212012121002 .....

Pembimbing II
Septi Purnamasari, S.ST, M.Bmd
NIP. 198909152019032022 .....

Penguji I
dr. Ziske Maritska, M.Si.Med
NIP. 198403262010122004 .....

Penguji II
Rara Inggarsih, S.ST., M.Kes
NIP. 198908052019032017 .....

Mengetahui
Wakil Dekan I

Prof. Dr. dr. Irfannuddin, Sp.KO., M.Pd.Ked
NIP. 197306131999031001

Koordinator Program Studi
Pendidikan Dokter

dr. Susilawati, M.Kes
NIP. 197802272010122001

HALAMAN PERSETUJUAN

Karya Tulis Ilimah berupa Laporan Akhir Skripsi ini dengan Judul "Pengaruh *Activated Growth Factor* (AGF) dari Platelet Terhadap Kadar Alpha-SMA pada Tikus Putih Model Osteoarthritis" telah dipertahankan di hadapan Tim Penguji Karya Tulis Ilmiah Program Studi Pendidikan Dokter Fakultas Kedokteran Universitas Sriwijaya pada 11 Desember 2022

Palembang, 11 Desember 2023

Tim Penguji Karya Tulis Ilmiah berupa Laporan Akhir Skripsi

Pembimbing I
dr. Rachmat Hidayat, M.Sc
NIP. 198705212012121002 .....

Pembimbing II
Septi Puruamasari, S.ST, M.Biod
NIP. 198909152019032022 .....

Penguji I
dr. Ziske Maritska, M.Si.Med
NIP. 198403262010122004 .....

Penguji II
Rara Inggerith, S.ST., M.Kes
NIP. 198908052019032017 .....

Mengetahui
Wakil Dekan I

Prof. Dr. dr. Irfannuddin, Sp.KO., M.Pd.Ked
NIP. 197306131999031001

Koordinator Program Studi
Pendidikan Dokter

dr. Susilawati, M.Kes
NIP. 197802272010122001

HALAMAN PERNYATAAN INTEGRITAS

Yang bertanda tangan di bawah ini:

Nama	: Sarah
NIM	: 04011182025020
Judul	: Pengaruh *Activated Growth Factor* (AGF) dari Platelet Terhadap Kadar Alpha-SMA pada Tikus Putih Model Osteoarthritis

Menyatakan bahwa Skripsi saya merupakan hasil karya sendiri didampingi tim pembimbing dan bukan hasil penjiplakan/plagiat. Apabila ditemukan unsur penjiplakan/plagiat dalam Skripsi ini, maka saya bersedia menerima sanksi akademik dari Universitas Sriwijaya sesuai aturan yang berlaku.

Demikian, pernyataan ini saya buat dalam keadaan sadar dan tanpa ada paksaan dari siapapun.

Palembang, 11 Desember 2023

Sarah

ABSTRAK

PENGARUH FAKTOR PERTUMBUHAN PLATELET TERHADAP KADAR ALPHA-SMA PADA TIKUS PUTIH MODEL OSTEOARTHRITIS

(Sarah, Desember 2023)

Fakultas Kedokteran Universitas Sriwijaya

Latar Belakang: Osteoarthritis (OA) adalah gangguan sendi yang paling umum dan merupakan penyebab utama disabilitas dengan dampak sosial ekonomi yang besar dan terjadi akibat ketidakseimbangan mediator proinflamasi dan antiinflamasi atau aktivitas anabolik dan katabolik. Penelitian ini bertujuan untuk mengetahui pengaruh Faktor Pertumbuhan Platelet (FPP) terhadap kadar Alpha-SMA.
Metode: Penelitian ini merupakan studi eksperimental *in vivo post-test only control group* di *Eureka Research Laboratory*. Tiga puluh ekor tikus putih wistar Jantan dibagi ke dalam lima kelompok perlakuan berupa kelompok kontrol normal, kelompok kontrol negatif, kelompok FPP I (TGF-β 100 pg/mL), kelompok FPP II (TGF-β 1000 pg/mL), dan kelompok FPP III (TGF-β 10000 pg/mL). FPP didapatkan dari darah intravena tikus dan disentrifugasi dengan kecepatan yang sudah ditentukan. Aktivasi GF dilakukan dengan menambahkan 10% CaCl2 lalu diukur kadarnya. Pada seluruh kelompok tikus dilakukan aklimatisasi selama 7 hari dan setelahnya dilakukan induksi osteoarthritis dengan injeksi monoiodoasetat (MIA) intraartikular 4,8 mg/60µL pada seluruh kelompok tikus kecuali pada kelompok kontrol normal. Selanjutnya, tikus diberikan perlakuan sesuai kelompok selama 21 hari. Pada hari ke-21, dilakukan euthanasia pada tikus dan kadar Alpha-SMA pada tikus dengan menggunakan ELISA kit metode *sandwich*.
Hasil: Secara berurutan, rerata kadar Alpha-SMA tiap kelompok dalam pg/mL adalah: 91,495 ± 2,36; 10,682 ± 1,09; 30,502 ± 2,00; 52,892 ± 1,29; dan 76,180 ± 2,65. Pada kelompok FPP, terjadi peningkatan Alpha-SMA yang berbanding lurus dengan dosis TGF-β yang diinjeksikan.
Kesimpulan: FPP berpengaruh dalam meningkatkan kadar Alpha-SMA sendi tikus putih model osteoarthritis.

Kata Kunci: *Faktor Pertumbuhan Platelet, Osteoarthritis, Alpha-SMA, TGF-β.*

ABSTRACT

THE EFFECT OF ACTIVATED GROWTH FACTOR (AGF) FROM PLATELETS ON ALPHA-SMA LEVELS IN OSTEOARTHRITIS-INDUCED OSTEOARTHRITIS ALBINO RAT

(Sarah, December 2023)
Faculty of Medicine Sriwijaya University

Background: Osteoarthritis (OA) is the most common joint disorder and a major cause of disability, resulting in a significant socio-economic impact. It occurs due to an imbalance of pro-inflammatory and anti-inflammatory mediators, influencing anabolic and catabolic activities. This study aims to determine the effect of activated growth factor (AGF) on Alpha-SMA levels.

Method: This research is an in vivo post-test-only control group experimental study conducted at the Eureka Research Laboratory. Thirty male Wistar white rats were divided into five treatment groups: normal control group, negative control group, AGF I group (TGF-β 100 pg/mL), AGF II group (TGF-β 1000 pg/mL), and AGF III group (TGF-β 10,000 pg/mL). Growth factor activation was performed by adding 10% CaCl2, and then TGF-β levels were measured. All groups of mice were acclimatized for 7 days. After that, osteoarthritis was induced with intra-articular injection of monoiodoacetate (MIA) 4.8 mg/60μL in all groups of mice except the normal control group. Next, mice were given treatment according to the group for 21 days. On the 21st day, mice were euthanized, and Alpha-SMA levels were measured using the sandwich method ELISA kit.

Results: Sequentially, the mean Alpha-SMA levels for each group in pg/mL were: 91.495 ± 2.36; 10.682 ± 1.09; 30.502 ± 2.00; 52.892 ± 1.29; and 76.180 ± 2.65. In the AGF group, there was an increase in Alpha-SMA levels directly proportional to the dose of TGF-β injected.

Conclusion: AGF has an effect on increasing Alpha-SMA levels in the joints of white mice with a model of osteoarthritis.

Keywords: *Activated Growth Factor, Osteoarthritis, Alpha-SMA, TGF-β.*

Mengetahui,

Pembimbing I	Pembimbing II
dr. Rachmat Hidayat, M.Sc	**Septi Purnamasari, S.ST, M.Bmd**
NIP. 198705212012121002	NIP. 198909152019032022

RINGKASAN

PENGARUH FAKTOR PERTUMBUHAN PLATELET TERHADAP KADAR ALPHA-SMA PADA TIKUS PUTIH MODEL OSTEOARTHRITIS

Karya tulis ilmiah berupa Skripsi, 11 Desember 2023

Sarah; Dibimbing oleh dr. Rachmat Hidayat, M.Sc. dan Septi Purnamasari, S.ST, M.Bmd

Program Studi Pendidikan Dokter, Fakultas Kedokteran, Universitas Sriwijaya
xix + 109 halaman, 14 tabel, 24 gambar, 6 lampiran.

Osteoarthritis (OA) adalah gangguan sendi yang paling umum dan merupakan penyebab utama disabilitas dengan dampak sosial ekonomi yang besar dan terjadi akibat ketidakseimbangan mediator proinflamasi dan antiinflamasi atau aktivitas anabolik dan katabolik. Penelitian ini bertujuan untuk mengetahui pengaruh Faktor Pertumbuhan Platelet terhadap kadar Alpha-SMA.
Penelitian ini merupakan studi eksperimental *in vivo post-test only control group* di *Eureka Research Laboratory*. Tiga puluh ekor tikus putih wistar Jantan dibagi ke dalam lima kelompok perlakuan berupa kelompok kontrol normal, kelompok kontrol negatif, kelompok Faktor Pertumbuhan Platelet (FPP) I (TGF-β 100 pg/mL), kelompok FPP II (TGF-β 1000 pg/mL), dan kelompok FPP III (TGF-β 10000 pg/mL). FPP didapatkan dari darah intravena tikus dan disentrifugasi dengan kecepatan yang sudah ditentukan. Aktivasi GF dilakukan dengan menambahkan 10% CaCl2 lalu kadar TGF-β dihitung dalam satuan pg/mL. Sebelum perlakuan, dilakukan aklimatisasi pada seluruh kelompok tikus selama 7 hari dan setelahnya dilakukan induksi osteoarthritis dengan injeksi monoiodoasetat (MIA) intraartikular 4,8 mg/60µL pada seluruh kelompok tikus kecuali pada kelompok kontrol normal. Selanjutnya, tikus diberikan perlakuan sesuai kelompok perlakuan selama 21 hari. Pada hari ke-21, dilakukan euthanasia pada tikus dan kadar Alpha-SMA pada tikus diukur dengan menggunakan ELISA kit metode *sandwich*.

Pada penelitian ini, didapatkan hasil rerata kadar Alpha-SMA tiap kelompok dalam pg/mL adalah: 91,495 ± 2,36 untuk kelompok normal; 10,682 ± 1,09 untuk kelompok negatif; 30,502 ± 2,00 untuk kelompok FPP I (konsentrasi TGF-β 100 pg/mL); 52,892 ± 1,29 untuk kelompok FPP II (konsentrasi TGF-β 1000 pg/mL); dan 76,180 ± 2,65 untuk kelompok FPP III (konsentrasi TGF-β 10000 pg/mL).

Kata Kunci: *Faktor Pertumbuhan Platelet, Osteoarthritis, Alpha-SMA, TGF-β.*

SUMMARY

THE EFFECT OF ACTIVATED GROWTH FACTOR (AGF) FROM PLATELETS ON ALPHA-SMA LEVELS IN OSTEOARTHRITIS-INDUCED OSTEOARTHRITIS ALBINO RAT

Scientific Paper in the form of Skripsi, December 11, 2023

Sarah; Supervised by dr. Rachmat Hidayat, M.Sc. and Septi Purnamasari, S.ST, M.Bmd

Medical Science Department, Faculty of Medicine, Sriwijaya University
xix+ 109 pages, 14 tables, 24 pictures, 6 attachments

Osteoarthritis (OA), the prevailing joint pathology, stands as a prominent contributor to disability, wielding substantial socio-economic ramifications. This condition arises from an intricate dysregulation of pro-inflammatory and anti-inflammatory mediators, ultimately impacting anabolic and catabolic processes. This study seeks to discern the modulatory influence of activated growth factor (AGF) on Alpha-SMA levels, thereby advancing our comprehension of the molecular intricacies underlying osteoarthritic pathogenesis.

This investigation adopts an in vivo post-test-only control group experimental design, conducted at the Eureka Research Laboratory. Thirty male Wistar white rats are categorized into five distinct treatment cohorts: the normal control group, negative control group, AGF I group (TGF-β 100 pg/mL), AGF II group (TGF-β 1000 pg/mL), and AGF III group (TGF-β 10,000 pg/mL). AGF is procured from rat blood via intravenous extraction and subsequent centrifugation at a predetermined velocity. Growth factor activation ensues with the introduction of 10% CaCl2, culminating in the quantification of TGF-β levels. Following a 7-day acclimatization period, osteoarthritis is induced via intra-articular injection of monoiodoacetate (MIA) at 4.8 mg/60µL across all experimental groups, excluding the normal control group. Subsequently, a 21-day treatment regimen tailored to each group is implemented. After the 21st day, mice are ethically euthanized, and Alpha-SMA levels are meticulously assayed utilizing the sandwich method ELISA kit.

Sequentially, the mean Alpha-SMA levels across the experimental cohorts in pg/mL are discerned as follows: 91.495 ± 2.36; 10.682 ± 1.09; 30.502 ± 2.00; 52.892 ± 1.29; and 76.180 ± 2.65. Within the AGF group, a discernible elevation in Alpha-SMA levels is observed, exhibiting a direct proportionality to the administered dose of TGF-β.

The results highlight that AGF has a noticeable effect on increasing Alpha-SMA levels in the joints of white mice. This gives us a better understanding of its potential as a therapy for osteoarthritis.

Keywords: *Activated Growth Factor, Osteoarthritis, Alpha-SMA, TGF-β.*

KATA PENGANTAR

Puji syukur penulis panjatkan kehadirat Allah SWT atas berkah, rahmat, dan karunia-Nya sehingga saya dapat menyelesaikan proposal skripsi yang berjudul **"Pengaruh Faktor Pertumbuhan Platelet Terhadap Kadar Alpha-SMA pada Tikus Putih Model Osteoarthritis."** Karya tulis ini dibuat sebagai salah satu syarat untuk memperoleh gelar sarjana kedokteran (S.Ked) pada Program Studi Pendidikan Dokter Umum, Fakultas Kedokteran Universitas Sriwijaya. Dalam pengerjaan proposal skripsi ini tak jauh dari bimbingan, dukungan, motivasi serta segala bentuk bantuan lain yang ditujukan kepada saya. Dengan itu, saya mengucapkan terima kasih yang mendalam dan sebesar-besarnya kepada:

1. Dosen pembimbing saya, selaku pembimbing I dr. Rachmat Hidayat, M.Sc dan selaku pembimbing II Septi Purnamasari, S.ST, M.Bmd yang senantiasa membimbing dan mengarahkan saya dalam proses penelitian dan pembuatan laporan akhir ini.
2. dr. Ziske Maritska, M.Si.Med selaku Penguji I dan Bu Rara Inggarsih, S.ST., M.Kes selaku penguji II yang telah memberikan masukan dan kritik membangun agar karya tulis ini menjadi lebih baik.
3. Orang tua saya (Bunda dan Ayah), kakak saya, adik saya, serta kerabat yang selalu memberikan doa dan dukungan penuh kepada saya.
4. Sahabat seperjuangan saya dalam penelitian ini (Rizky dan Najla) serta teman-teman lainnya yang tidak bisa saya sebutkan namanya satu per satu yang sedari awal menyemangati dan membantu saya dalam menyusun usulan penelitian ini.

Palembang, 11 Desember 2023

Sarah

DAFTAR ISI

DAFTAR TABEL

DAFTAR GAMBAR

DAFTAR LAMPIRAN

DAFTAR SINGKATAN

ACLT	: *Anterior Cruciate Ligament Transection*
ADAMTs	: *A Disintegrin and Metalloproteinase with Thrombospondin Motifs*
ADSC	: *Adipose Derived Stem Cells*
BMI	: *Body Mass Index*
BMSC	: *Bone Marrow Stem Cell*
Col	: *Collagen*
COX	: Siklooksigenase
DMM	: *Destabilization of The Medial Meniscus*
DNA	: *Deoxyribonucleic Acid*
ECM	: *Extracellular Matrix*
EGF	: *Epidermal Growth Factor*
ELISA	: *Enzyme-linked Immunosorbent Assay*
EMT	: *Epithel to Mesenchymal Transition*
ERK	: *Extracellular Signal-Regulated Kinase*
FADD	: *Fas-associated death domain protein*
FGF	: *Fibroblast Growth Factor*
GF	: *Growth Factor*
HGF	*: Hepatocvte Growth Factor*
HIF-1	: *Hypoxia-inducible factor*-1
IFN	: Interferon
IGF-1	: *Insulin-like Growth Factor*-1
IKKα	: IκB Kinase α
IL	: *Interleukin*
IKBα	: *Kappa-light Polypeptide Gene Enhancer in B-cells Inhibitor Alpha*
JNK	: c-*Jun N-Terminal Kinase*

KL : Kellgren-Lawrence

KOGS : *Knee Osteoarthritis Grading System*

LED : Laju Endap Darah

MAPK : *Mitogen-Activated Protein Kinase*

MIA : Monoiodoacetate

MMP : *Matrix Metalloproteinase*

MSC : *Mesenchymal Stem Cell*

NF- κB : *Nuclear Factor Kappa-B*

NO : Nitrat Oksida

NSAID : *Nonsteroidal Anti-inflammatory Drugs*

OA : Osteoarthritis

OD : *Optical Density*

PDGF : *Platelet-derived Growth Factor*

PGE2 : *Prostaglandin* E2

PI3K/AKT : Fosfatidylinositol-3-kinase

POA : Osteoarthritis Primer

PRP : *Platelet-rich Plasma*

PTOA : *Post-traumatic* OA

RANKL : *Receptor activator of nuclear factor kappa-B ligand*

RANTES : *Regulated Upon Activation, Normal T Cell Expressed and Presumably Secreted*

RF : *Rheumatoid Factor*

RIP-1 : *Receptor Interacting Protein*-1

SBP : *Subchondral Bone Plate*

SZ : *Superficial Zone*

TGF : *Transforming Growth Factor*

TGFBR : *Transforming Growth Factor Beta Receptor*

TIMP : *Tissue Inhibitor of Metalloproteinase*

TNF- α	: *Tumor Necrosis Factor-Alpha*
TNRF	: *Tumor Necrosis Factor Receptor*
TRADD	: TNFR-1 *associated death domain protein*
TRAF-2	: TNF *receptor-associated factor*-2
VEGF	: *Vascular Endothelial Growth Factor*
α-SMA	: *Alpha-Smooth Muscle Actin*

BAB 1
PENDAHULUAN

1.1 Latar Belakang

Osteoarthritis (OA) adalah gangguan sendi yang paling umum dan merupakan penyebab utama disabilitas dengan dampak sosial ekonomi yang besar.[1,2,3] Osteoarthritis merupakan penyakit endemik di seluruh dunia dan diperkirakan 300 juta orang di seluruh dunia hidup dengan mengalami OA.[2] OA berdampak pada lebih dari setengah populasi di atas 65 tahun, dengan tingkat kecacatan yang lebih tinggi pada wanita daripada pria. Di Indonesia, osteoarthritis terjadi pada 65% penduduk usia 61 tahun dengan prevalensi osteoarthritis lutut yang cukup tinggi yaitu 15,5% pada pria dan 12,7% pada wanita dari total penduduk Indonesia yang berjumlah 255 juta jiwa.[4,5,6] Osteoarthritis menyebabkan rasa nyeri, kehilangan fungsi, dan penurunan kualitas hidup (*Quality of Life*/QoL). Pada skala masyarakat, OA diperkirakan memakan biaya $303 miliar dolar per tahun untuk biaya medis.[2]

Kejadian osteoarthritis meningkat pada populasi tua, obesitas, pola makan yang tidak sehat, aktivitas fisik yang tidak aktif, mikrotrauma, dan stres kronis. Pada OA, terjadi kerusakan kartilago artikular sendi dan peradangan karena kelebihan beban kronis dan gangguan biomekanik pada sendi yang selanjutnya menyebabkan kekakuan, pembengkakan, dan kehilangan mobilitas pada sendi karena itu OA menjadi perhatian besar.[6,7,8,9] Patogenesis OA sangat ditentukan oleh ketidakseimbangan mediator proinflamasi dan antiinflamasi atau aktivitas anabolik dan katabolik. Peningkatan faktor katabolik dipertahankan oleh sejumlah sitokin proinflamasi hingga terjadi degradasi tulang rawan, remodeling tulang, proliferasi synovial, dan pembentukan osteofit yang mengarah ke gejala umum dan tanda klinis OA. [3,10,11]

Sampai saat ini, belum ada perawatan medis yang mampu mengurangi degradasi tulang rawan, peradangan, dan perkembangan penyakit pada OA. Semua perawatan osteoarthritis saat ini bersifat paliatif.[12,13] Obat yang digunakan dalam

penanganan OA saat ini adalah obat anti-inflamasi nonsteroid (OAINS) yang memiliki efikasi yang sedikit lebih baik dibandingkan dengan parasetamol. Namun, OAINS menimbulkan risiko mortalitas dan morbiditas yang lebih tinggi akibat perforasi saluran pencernaan dan ulserasi, termasuk insufisiensi ginjal, gagal jantung koroner kongestif, hipertensi, infark miokard, stroke, dan asma yang diinduksi aspirin.[14] Perlu dilakukan eksplorasi mengenai tatalaksana OA yang lebih aman dan mampu mengurangi degradasi tulang rawan misalnya dengan memanfaatkan *growth-factor* yang merupakan salah satu komponen platelet.

Platelet adalah fragmen sitoplasma megakariosit berdiameter sekitar 2 μm dan mengandung lebih dari 30 protein bioaktif yang memiliki peran mendasar dalam hemostasis atau penyembuhan jaringan.[15] Platelet mengandung tiga jenis granula utama yang melepaskan isinya begitu platelet diaktifkan. Setiap granul mengandung molekul berbeda yang terlibat dalam aktivasi trombosit, modulasi proses inflamasi, dan imunitas.[16] *Growth-factor* (GF) dan protein dikeluarkan oleh α-granul dari platelet dan penting untuk kaskade koagulasi yang setelah aktivasi, dapat membantu regenerasi jaringan.[17]

Growth-factor atau faktor pertumbuhan adalah molekul aktif biologis yang disekresikan untuk mempromosikan atau menghambat mitosis atau mempengaruhi diferensiasi sel.[18] *Growth-factor* dilepaskan oleh α-granul dari platelet,[19] sehingga baru-baru ini ditemukan strategi baru untuk mempromosikan kaskade penyembuhan luka dengan memanfaatkan GF, yaitu dengan menyiapkan konsentrat platelet autologus yang tersuspensi dalam plasma, yang mengandung faktor pertumbuhan dan menyalurkannya ke tempat luka.[20]

Penelitian oleh Moussa et. al. pada tahun 2017 melaporkan bahwa platelet memiliki efek anabolik pada tulang rawan. Platelet telah dieksplorasi secara ekstensif sebagai pengobatan kondroprotektif untuk OA lutut.[12] Aktivasi platelet adalah langkah penting yang mempengaruhi ketersediaan molekul bioaktif yang akan membantu penyembuhan jaringan. *Growth-factor* akan dilepaskan oleh butiran α-granul dari degranulasi platelet.[21] Alpha-granul mengandung faktor pertumbuhan dan protein penting untuk kaskade koagulasi yang setelah aktivasi, dapat membantu regenerasi jaringan.[17]

Platelet melalui aktivasi granula alfa dan degranulasi proteinnya seperti PDGF, TGF-β, CTGF, dan FGF akan berikatan dengan reseptornya masing-masing pada kolagen, osteoklas, dan kondrosit untuk merangsang sintesis matriks tulang rawan dan regenerasi jaringan sehingga menginduksi kondroproteksi.[12] Salah satu efek anti-inflamasi GF dari platelet adalah hasil dari TGF-β yang berikatan dengan reseptornya. Jalur TGF-β kanonik melibatkan fosforilasi SMAD2/3 yang dimediasi oleh TGFBR1, menyebabkan pensinyalan SMAD4 dan translokasi inti untuk aktivasi transkripsi dari program gen fibrotik dan ekspresi α-SMA (*α-smooth muscle actin*).[22]

Alpha-smooth muscle actin (α-SMA) yang dikodekan oleh gen ACTA2[23] adalah isoform aktin yang berperan penting dalam fibrogenesis dan dapat ditemukan di sel otot polos, miofibroblas, dan pembuluh darah.[24,25] Sel α-SMA-positif ditemukan pada jaringan kolagen padat, area perivaskular, dan sel-sel pelapis dalam selubung sinovial.[26] Ekspresi dari α-SMA sangat dipengaruhi oleh kehadiran TGF-β yang akan memfosforilasi SMAD2/3. Hal ini menjadi salah satu keunggulan α-SMA untuk diamati pada OA dengan intervensi GF karena sitokin anti inflamasi lain yang berperan pada kejadian OA, tidak dipengaruhi oleh kehadiran TGF-β.[27]

Pada OA, jaringan berada dalam proses penyembuhan dan fibroblas cenderung berproliferasi cepat untuk memperbaiki matriks yang rusak dan memungkinkan menghasilkan lebih banyak kolagen, komponen utama matriks ekstraseluler dalam ligamen.[28] Fibroblas juga membutuhkan fenotipe kontraktil, ditandai dengan pembentukan bundel mikrofilamen, dan dengan ekspresi de novo dari *α-smooth muscle actin* (α-SMA). Sel-sel aktif ini, disebut "miofibroblas" dan berpartisipasi dalam respon reparatif, dengan mengeluarkan sejumlah besar protein matriks ekstraseluler.[24,28] Sel ini akan menghasilkan kolagen dengan aktivitas yang lebih tinggi dibandingkan dengan fibroblas normal.[29] Dengan melihat potensi GF dalam mengatasi OA, penelitian ini dilakukan agar dapat menguji efikasi *Faktor Pertumbuhan Platelet* terhadap kadar alpha-SMA pada tikus putih galur wistar model osteoarthritis.

1.2 Rumusan Masalah

Bagaimana pengaruh faktor pertumbuhan platelet dari platelet terhadap kadar Alpha-SMA tikus putih model osteoarthritis?

1.3 Tujuan Penelitian

1.3.1 Tujuan Umum

Mengetahui adanya pengaruh faktor pertumbuhan platelet dari platelet terhadap kadar Alpha-SMA tikus putih model osteoarthritis.

1.3.2 Tujuan Khusus

1. Mengetahui rerata kadar Alpha-SMA pada setiap kelompok perlakuan hewan uji setelah diberikan faktor pertumbuhan platelet, yang dinilai menggunakan metode sandwich ELISA (*enzyme-linked immunosorbent assay).*
2. Mengetahui signifikansi injeksi faktor pertumbuhan platelet terhadap kadar alpha-SMA tikus putih model osteoarthritis.

1.4 Hipotesis

H0 : Tidak terdapat pengaruh faktor pertumbuhan platelet terhadap Alpha-SMA tikus putih model osteoarthritis.

H1 : Terdapat pengaruh faktor pertumbuhan platelet terhadap kadar Alpha-SMA tikus putih model osteoarthritis.

1.5 Manfaat Penelitian

1.5.1 Manfaat Teoritis

1. Diharapkan penelitian ini dapat menjadi sumber referensi bagi mahasiswa, peneliti, dan sejawat terkait penemuan pengobatan alternatif untuk osteoarthritis.

2. Diharapkan penelitian ini dapat menjadi kajian teoritis mengenai pengaruh faktor pertumbuhan platelet terhadap kadar Alpha-SMA tikus putih model osteoarthritis sebagai obat alternatif di masa depan.

1.5.2 Manfaat Praktis

1. Diharapkan faktor pertumbuhan platelet dapat diwujudkan sebagai terapi alternatif osteoarthritis jika memiliki efektivitas yang signifikan melalui uji klinis.
2. Melalui uji klinis, menjadi referensi uji klinis terkait faktor pertumbuhan platelet terhadap kadar Alpha-SMA pada tikus model osteoarthritis.

1.5.3 Manfaat Masyarakat

Pada penelitian ini, diharapkan masyarakat mendapatkan alternatif pengobatan osteoarthritis yang dapat mengurangi perkembangan osteoarthritis, bukan hanya mengurangi gejala yang dihasilkan oleh osteoarthritis.

DAFTAR PUSTAKA

1. Man GS, Mologhianu G. Osteoarthritis pathogenesis – a complex process that involves the entire joint. J Med Life [Internet]. 2014 Mar 3 [cited 2023 Jun 21];7(1):37. Available from: /pmc/articles/PMC3956093/
2. Abramoff B, Caldera FE. Osteoarthritis: Pathology, Diagnosis, and Treatment Options. Med Clin North Am [Internet]. 2020 Mar 1 [cited 2023 Jun 28];104(2):293–311. Available from: https://pubmed.ncbi.nlm.nih.gov/32035570/
3. Berenbaum F, Walker C. Osteoarthritis and inflammation: a serious disease with overlapping phenotypic patterns. https://doi.org/101080/0032548120201730669 [Internet]. 2020 May 18 [cited 2023 Jul 31];132(4):377–84. Available from: https://www.tandfonline.com/doi/abs/10.1080/00325481.2020.1730669
4. Ahmad IW, Rahmawati LD, Wardhana TH. Demographic Profile, Clinical and Analysis of Osteoarthritis Patients in Surabaya. Biomolecular and Health Science Journal. 2018 May 31;1(1):34.
5. Martel-Pelletier J. Pathophysiology of osteoarthritis. Osteoarthritis Cartilage [Internet]. 2004 Jan 1 [cited 2023 May 16];12(SUPLL.):31–3. Available from: http://www.oarsijournal.com/article/S106345840300267X/fulltext
6. Dobson GP, Letson HL, Grant A, McEwen P, Hazratwala K, Wilkinson M, et al. Defining the osteoarthritis patient: back to the future. Osteoarthritis Cartilage. 2018 Aug 1;26(8):1003–7.
7. Malemud CJ. The Biological Basis of Osteoarthritis: State of the Evidence. Curr Opin Rheumatol [Internet]. 2015 May 7 [cited 2023 Apr 30];27(3):289. Available from: /pmc/articles/PMC4492522/
8. Warnera SC, Valdesa AM. Genetic association studies in osteoarthritis: Is it fairytale? Curr Opin Rheumatol. 2017;29(1):103–9.
9. O'Connell B, Wragg NM, Wilson SL. The use of PRP injections in the management of knee osteoarthritis. Cell Tissue Res. 2019 May 13;376(2):143–52.
10. Molnar V, Matišić V, Kodvanj I, Bjelica R, Jeleč Ž, Hudetz D, et al. Cytokines and Chemokines Involved in Osteoarthritis Pathogenesis. Int J Mol Sci [Internet]. 2021 Sep 1 [cited 2023 Jul 13];22(17). Available from: /pmc/articles/PMC8431625/
11. Mueller MB, Tuan RS. Anabolic/Catabolic Balance in Pathogenesis of Osteoarthritis: Identifying Molecular Targets. PM&R. 2011 Jun;3:S3–11.
12. Moussa M, Lajeunesse D, Hilal G, El Atat O, Haykal G, Serhal R, et al. Platelet rich plasma (PRP) induces chondroprotection via increasing autophagy, anti-inflammatory markers, and decreasing apoptosis in human osteoarthritic cartilage. Exp Cell Res. 2017 Mar 1;352(1):146–56.
13. Mora JC, Przkora R, Cruz-Almeida Y. Knee osteoarthritis: pathophysiology and current treatment modalities. J Pain Res. 2018 Oct;Volume 11:2189–96.
14. Kumar A, Palit P, Thomas S, Gupta G, Ghosh P, Goswami RP, et al. Osteoarthritis: Prognosis and emerging therapeutic approach for disease

management. Drug Dev Res [Internet]. 2021 Feb 1 [cited 2023 Jul 26];82(1):49–58. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/ddr.21741
15. Dhurat R, Sukesh M. Principles and Methods of Preparation of Platelet-Rich Plasma: A Review and Author's Perspective. J Cutan Aesthet Surg [Internet]. 2014 [cited 2023 Jun 27];7(4):189. Available from: /pmc/articles/PMC4338460/
16. Garbin LC, Olver CS. Platelet-Rich Products and Their Application to Osteoarthritis. J Equine Vet Sci. 2020 Mar 1;86:102820.
17. Kennedy MI, Whitney K, Evans T, LaPrade RF. Platelet-Rich Plasma and Cartilage Repair. Curr Rev Musculoskelet Med [Internet]. 2018 Dec 1 [cited 2023 Jul 17];11(4):573–82. Available from: https://pubmed.ncbi.nlm.nih.gov/30203333/
18. Stone WL, Leavitt L, Varacallo M. Physiology, Growth Factor. StatPearls [Internet]. 2023 May 1 [cited 2023 Aug 2]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK442024/
19. Smith CW. Release of α-granule contents during platelet activation. In: Platelets. 2022. p. 491–502.
20. Eppley BL, Woodell JE, Higgins J. Platelet quantification and growth factor analysis from platelet-rich plasma: implications for wound healing. Plast Reconstr Surg [Internet]. 2004 Nov [cited 2023 Aug 2];114(6):1502–8. Available from: https://pubmed.ncbi.nlm.nih.gov/15509939/
21. Cavallo C, Roffi A, Grigolo B, Mariani E, Pratelli L, Merli G, et al. Platelet-Rich Plasma: The Choice of Activation Method Affects the Release of Bioactive Molecules. Biomed Res Int. 2016;2016.
22. Gibb AA, Lazaropoulos MP, Elrod JW. Myofibroblasts and Fibrosis. Circ Res. 2020 Jul 17;127(3):427–47.
23. Yuan SM. α-Smooth Muscle Actin and ACTA2 Gene Expressions in Vasculopathies. Braz J Cardiovasc Surg [Internet]. 2015 Nov 1 [cited 2023 Jul 4];30(6):644. Available from: /pmc/articles/PMC4762557/
24. Shinde A V., Humeres C, Frangogiannis NG. The role of α-smooth muscle actin in fibroblast-mediated matrix contraction and remodeling. Biochim Biophys Acta [Internet]. 2017 Jan 1 [cited 2023 May 25];1863(1):298. Available from: /pmc/articles/PMC5163362/
25. Anggorowati N, Kurniasari CR, Damayanti K, Cahyanti T, Widodo I, Ghozali A, et al. Histochemical and Immunohistochemical Study of α-SMA, Collagen, and PCNA in Epithelial Ovarian Neoplasm. Asian Pac J Cancer Prev [Internet]. 2017 Mar 1 [cited 2023 May 24];18(3):667. Available from: /pmc/articles/PMC5464482/
26. Hasegawa A, Nakahara H, Kinoshita M, Asahara H, Koziol J, Lotz MK. Cellular and extracellular matrix changes in anterior cruciate ligaments during human knee aging and osteoarthritis. Arthritis Res Ther [Internet]. 2013 [cited 2023 Jun 16];15:R29. Available from: http://arthritis-research.com/content/15/1/R29
27. Ricard-Blum S, Baffet G, Théret N. Molecular and tissue alterations of collagens in fibrosis. Matrix Biology [Internet]. 2018 Aug 1 [cited 2023 Jul

21];68–69:122–49. Available from: https://univ-rennes.hal.science/hal-01808771
28. Agarwal C, Britton ZT, Alaseirlis DA, Li Y, Wang JHC. Healing and normal fibroblasts exhibit differential proliferation, collagen production, alpha-SMA expression, and contraction. Ann Biomed Eng [Internet]. 2006 Apr [cited 2023 Jul 18];34(4):653–9. Available from: https://pubmed.ncbi.nlm.nih.gov/16568347/
29. Petrov V V., Fagard RH, Lijnen PJ. Stimulation of Collagen Production by Transforming Growth Factor-β1 During Differentiation of Cardiac Fibroblasts to Myofibroblasts. Hypertension [Internet]. 2002 Feb 1 [cited 2023 Jul 18];39(2 I):258–63. Available from: https://www.ahajournals.org/doi/abs/10.1161/hy0202.103268
30. Sen R, Hurley JA. Osteoarthritis. StatPearls [Internet]. 2023 Feb 20 [cited 2023 Apr 30]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK482326/
31. Remst DFG, Blaney Davidson EN, van der Kraan PM. Unravelling osteoarthritis-related synovial fibrosis: a step closer to solving joint stiffness. Rheumatology (Oxford) [Internet]. 2015 Aug 6 [cited 2023 May 25];54(11):1954–63. Available from: https://pubmed.ncbi.nlm.nih.gov/26175472/
32. Remst DFG, Blaney Davidson EN, Vitters EL, Blom AB, Stoop R, Snabel JM, et al. Osteoarthritis-related fibrosis is associated with both elevated pyridinoline cross-link formation and lysyl hydroxylase 2b expression. Osteoarthritis Cartilage [Internet]. 2013 Jan [cited 2023 May 25];21(1):157–64. Available from: https://pubmed.ncbi.nlm.nih.gov/23069856/
33. Kapoor M, Mahomed NN. Osteoarthritis: Pathogenesis, diagnosis, available treatments, drug safety, regenerative and precision medicine. Osteoarthritis: Pathogenesis, Diagnosis, Available Treatments, Drug Safety, Regenerative and Precision Medicine. 2015 Jan 1;1–278.
34. Sen R, Hurley JA. Osteoarthritis. StatPearls [Internet]. 2023 Feb 20 [cited 2023 May 16]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK482326/
35. Rim YA, Ju JH. life The Role of Fibrosis in Osteoarthritis Progression. 2020 [cited 2023 May 25]; Available from: https://dx.doi.org/10.3390/life11010003
36. Kulkarni K, Karssiens T, Kumar V, Pandit H. Obesity and osteoarthritis. Maturitas [Internet]. 2016 Jul 1 [cited 2023 Jun 28];89:22–8. Available from: https://pubmed.ncbi.nlm.nih.gov/27180156/
37. King LK, March L, Anandacoomarasamy A. Obesity & osteoarthritis. Indian J Med Res [Internet]. 2013 Aug [cited 2023 Jun 28];138(2):185. Available from: /pmc/articles/PMC3788203/
38. Hunter DJ, Felson DT. Osteoarthritis. BMJ. 2006 Mar 18;332(7542):639–42.
39. IRA. Diagnosis dan Penatalaksanaan Osteoartritis. 2014;

40. Jang S, Lee K, Ju JH. Molecular Sciences Recent Updates of Diagnosis, Pathophysiology, and Treatment on Osteoarthritis of the Knee. 2021 [cited 2023 May 22]; Available from: https://doi.org/10.3390/ijms22052619
41. Kohn MD, Sassoon AA, Fernando ND. Classifications in Brief: Kellgren-Lawrence Classification of Osteoarthritis. Clin Orthop Relat Res [Internet]. 2016 Aug 1 [cited 2023 Jun 13];474(8):1886–93. Available from: https://link.springer.com/article/10.1007/s11999-016-4732-4
42. Stewart HL, Kawcak CE. The Importance of Subchondral Bone in the Pathophysiology of Osteoarthritis. Front Vet Sci [Internet]. 2018 Aug 28 [cited 2023 May 16];5(AUG):178. Available from: /pmc/articles/PMC6122109/
43. Malemud CJ. The Biological Basis of Osteoarthritis: State of the Evidence. Curr Opin Rheumatol [Internet]. 2015 May 7 [cited 2023 Jun 21];27(3):289. Available from: /pmc/articles/PMC4492522/
44. Glyn-Jones S, Palmer AJR, Agricola R, Price AJ, Vincent TL, Weinans H, et al. Osteoarthritis. Lancet [Internet]. 2015 Jul 25 [cited 2023 Jun 21];386(9991):376–87. Available from: https://pubmed.ncbi.nlm.nih.gov/25748615/
45. Xia B, Di Chen, Zhang J, Hu S, Jin H, Tong P. Osteoarthritis Pathogenesis: A Review of Molecular Mechanisms. Calcif Tissue Int [Internet]. 2014 Nov 21 [cited 2023 Jun 21];95(6):495. Available from: /pmc/articles/PMC4747051/
46. Houard X, Goldring MB, Berenbaum F. Homeostatic mechanisms in articular cartilage and role of inflammation in osteoarthritis. Curr Rheumatol Rep [Internet]. 2013 Nov 27 [cited 2023 May 22];15(11):1–10. Available from: https://link.springer.com/article/10.1007/s11926-013-0375-6
47. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Care Res (Hoboken). 2020 Feb 1;72(2):149–62.
48. di Laura Frattura G, Filardo G, Giunchi D, Fusco A, Zaffagnini S, Candrian C. Risk of falls in patients with knee osteoarthritis undergoing total knee arthroplasty: A systematic review and best evidence synthesis. J Orthop [Internet]. 2018 Sep 1 [cited 2023 Apr 30];15(3):903. Available from: /pmc/articles/PMC6115537/
49. Kriz J, Seegenschmiedt HM, Bartels A, Micke O, Muecke R, Schaefer U, et al. Updated strategies in the treatment of benign diseases—a patterns of care study of the german cooperative group on benign diseases. Adv Radiat Oncol [Internet]. 2018 Jul 1 [cited 2023 Apr 30];3(3):240. Available from: /pmc/articles/PMC6127969/
50. Bortoluzzi A, Furini F, Scirè CA. Osteoarthritis and its management - Epidemiology, nutritional aspects and environmental factors. Autoimmun Rev [Internet]. 2018 Nov 1 [cited 2023 Apr 30];17(11):1097–104. Available from: https://pubmed.ncbi.nlm.nih.gov/30213694/
51. Mathiessen A, Conaghan PG. Synovitis in osteoarthritis: current understanding with therapeutic implications. Arthritis Res Ther [Internet].

2017 Feb 2 [cited 2023 Jul 3];19(1). Available from: https://pubmed.ncbi.nlm.nih.gov/28148295/
52. Li H, Xie S, Qi Y, Li H, Zhang R, Lian Y. TNF-α increases the expression of inflammatory factors in synovial fibroblasts by inhibiting the PI3K/AKT pathway in a rat model of monosodium iodoacetate-induced osteoarthritis. Exp Ther Med [Internet]. 2018 Dec 1 [cited 2023 Jul 21];16(6):4737–44. Available from: https://pubmed.ncbi.nlm.nih.gov/30542428/
53. Yunus MHM, Nordin A, Kamal H. Pathophysiological Perspective of Osteoarthritis. Medicina (B Aires) [Internet]. 2020 Nov 1 [cited 2023 Aug 8];56(11):1–13. Available from: /pmc/articles/PMC7696673/
54. Luo Y, Sinkeviciute D, He Y, Karsdal M, Henrotin Y, Mobasheri A, et al. The minor collagens in articular cartilage. Protein Cell [Internet]. 2017 Aug 1 [cited 2023 May 26];8(8):560. Available from: /pmc/articles/PMC5546929/
55. Sanchez Y Z C, Bay-Jensen Z X AC, Pap Z K T, Dvir-Ginzberg Z ¶ M, Quasnichka Z Yy H, Barrett-Jolley Z # R, et al. Chondrocyte secretome: a source of novel insights and exploratory biomarkers of osteoarthritis. 2017 [cited 2023 Jun 14]; Available from: http://dx.doi.org/10.1016/j.joca.2017.02.797
56. Samvelyan HJ, Hughes D, Stevens C, Staines KA. Models of Osteoarthritis: Relevance and New Insights. Calcif Tissue Int [Internet]. 2021 Sep 1 [cited 2023 May 26];109(3):243. Available from: /pmc/articles/PMC8403120/
57. Roseti L, Desando G, Cavallo C, Petretta M, Grigolo B. Articular Cartilage Regeneration in Osteoarthritis. Cells [Internet]. 2019 Nov 1 [cited 2023 May 26];8(11). Available from: /pmc/articles/PMC6912428/
58. Phull AR, Eo SH, Abbas Q, Ahmed M, Kim SJ. Applications of Chondrocyte-Based Cartilage Engineering: An Overview. Biomed Res Int [Internet]. 2016 [cited 2023 May 25];2016. Available from: /pmc/articles/PMC5007317/
59. Karuppal R. Current concepts in the articular cartilage repair and regeneration. J Orthop [Internet]. 2017 Jun 1 [cited 2023 May 25];14(2):A1. Available from: /pmc/articles/PMC5440635/
60. Armiento AR, Alini M, Stoddart MJ. Articular fibrocartilage - Why does hyaline cartilage fail to repair? Adv Drug Deliv Rev [Internet]. 2019 Jun 1 [cited 2023 May 25];146:289–305. Available from: https://pubmed.ncbi.nlm.nih.gov/30605736/
61. Charlier E, Deroyer C, Ciregia F, Malaise O, Neuville S, Plener Z, et al. Chondrocyte dedifferentiation and osteoarthritis (OA). Biochem Pharmacol [Internet]. 2019 Jul 1 [cited 2023 May 25];165:49–65. Available from: https://pubmed.ncbi.nlm.nih.gov/30853397/
62. Maldonado M, Nam J. The role of changes in extracellular matrix of cartilage in the presence of inflammation on the pathology of osteoarthritis. Biomed Res Int. 2013;2013.
63. Hall AC. The Role of Chondrocyte Morphology and Volume in Controlling Phenotype—Implications for Osteoarthritis, Cartilage Repair, and Cartilage Engineering. Curr Rheumatol Rep [Internet]. 2019 Aug 1 [cited 2023 Jun 29];21(8). Available from: /pmc/articles/PMC6571082/

64. Deroyer C, Charlier E, Neuville S, Malaise O, Gillet P, Kurth W, et al. CEMIP (KIAA1199) induces a fibrosis-like process in osteoarthritic chondrocytes. Cell Death Dis [Internet]. 2019 Feb 1 [cited 2023 May 25];10(2). Available from: /pmc/articles/PMC6362103/
65. Rim YA, Nam Y, Ju JH. The Role of Chondrocyte Hypertrophy and Senescence in Osteoarthritis Initiation and Progression. Int J Mol Sci [Internet]. 2020 Apr 1 [cited 2023 Jul 3];21(7). Available from: https://pubmed.ncbi.nlm.nih.gov/32235300/
66. Mathiessen A, Conaghan PG. Synovitis in osteoarthritis: current understanding with therapeutic implications. Arthritis Res Ther [Internet]. 2017 Feb 2 [cited 2023 Jul 3];19(1). Available from: /pmc/articles/PMC5289060/
67. Abbasi B, Pezeshki-Rad M, Akhavan R, Sahebari M. Association between clinical and sonographic synovitis in patients with painful knee osteoarthritis. Int J Rheum Dis [Internet]. 2017 May 1 [cited 2023 Jul 3];20(5):561–6. Available from: https://pubmed.ncbi.nlm.nih.gov/26915050/
68. Klingberg F, Hinz B, White ES. The myofibroblast matrix: implications for tissue repair and fibrosis. J Pathol [Internet]. 2013 Jan [cited 2023 Jul 25];229(2):298. Available from: /pmc/articles/PMC4005341/
69. Liu N, Fu D, Yang J, Liu P, Song X, Wang X, et al. Asiatic acid attenuates hypertrophic and fibrotic differentiation of articular chondrocytes via AMPK/PI3K/AKT signaling pathway. Arthritis Res Ther [Internet]. 2020 May 12 [cited 2023 May 25];22(1). Available from: /pmc/articles/PMC7218496/
70. de Paz-Lugo P, Lupiáñez JA, Meléndez-Hevia E. High glycine concentration increases collagen synthesis by articular chondrocytes in vitro: acute glycine deficiency could be an important cause of osteoarthritis. Amino Acids [Internet]. 2018 Oct 1 [cited 2023 Jul 21];50(10):1357. Available from: /pmc/articles/PMC6153947/
71. Zhang L, Xing R, Huang Z, Ding L, Zhang L, Li M, et al. Synovial Fibrosis Involvement in Osteoarthritis. Front Med (Lausanne) [Internet]. 2021 May 26 [cited 2023 Jul 21];8:684389. Available from: /pmc/articles/PMC8187615/
72. Zaleskas JM, Kinner B, Freyman TM, Yannas I V., Gibson LJ, Spector M. Growth factor regulation of smooth muscle actin expression and contraction of human articular chondrocytes and meniscal cells in a collagen-GAG matrix. Exp Cell Res [Internet]. 2001 Oct 15 [cited 2023 Jul 6];270(1):21–31. Available from: https://pubmed.ncbi.nlm.nih.gov/11597124/
73. Sun KH, Chang Y, Reed NI, Sheppard D. Translational Research in Acute Lung Injury and Pulmonary Fibrosis: α-Smooth muscle actin is an inconsistent marker of fibroblasts responsible for force-dependent TGFβ activation or collagen production across multiple models of organ fibrosis. Am J Physiol Lung Cell Mol Physiol [Internet]. 2016 May 5 [cited 2023 May 25];310(9):L824. Available from: /pmc/articles/PMC4867351/

74. Winter K, Dzieniecka M, Strzelczyk J, Wągrowska-Danilewicz M, Danilewicz M, Małecka-Wojciesko E. Alpha Smooth Muscle Actin (αSMA) Immunohistochemistry Use in the Differentiation of Pancreatic Cancer from Chronic Pancreatitis. J Clin Med [Internet]. 2021 Dec 1 [cited 2023 May 24];10(24):5804. Available from: /pmc/articles/PMC8707555/
75. Wang J, Zohar R, McCulloch CA. Multiple roles of α-smooth muscle actin in mechanotransduction. Exp Cell Res. 2006 Feb 1;312(3):205–14.
76. Hu B, Wu Z, Liu T, Ullenbruch MR, Jin H, Phan SH. Gut-Enriched Krüppel-Like Factor Interaction with Smad3 Inhibits Myofibroblast Differentiation. Am J Respir Cell Mol Biol [Internet]. 2007 Jan [cited 2023 Jul 6];36(1):78. Available from: /pmc/articles/PMC1899300/
77. Darby IA, Zakuan N, Billet F, Desmoulière A. The myofibroblast, a key cell in normal and pathological tissue repair. Cellular and Molecular Life Sciences 2015 73:6 [Internet]. 2015 Dec 17 [cited 2023 Jul 21];73(6):1145–57. Available from: https://link.springer.com/article/10.1007/s00018-015-2110-0
78. Stadtländer CTKH. diFiore's Atlas of Histology with Functional Correlations Victor P. Eroschenko. Microscopy and Microanalysis. 2005 Oct 28;11(5):472–472.
79. Garbin LC, Olver CS. Platelet-Rich Products and Their Application to Osteoarthritis. J Equine Vet Sci. 2020 Mar 1;86:102820.
80. Repsold L, Joubert AM. Platelet Function, Role in Thrombosis, Inflammation, and Consequences in Chronic Myeloproliferative Disorders. Cells [Internet]. 2021 Nov 1 [cited 2023 Aug 9];10(11):3034. Available from: /pmc/articles/PMC8616365/
81. Yun SH, Sim EH, Goh RY, Park JI, Han JY. Platelet Activation: The Mechanisms and Potential Biomarkers. 2016 [cited 2023 May 24]; Available from: http://dx.doi.org/10.1155/2016/9060143
82. Thomas MR, Storey RF. The role of platelets in inflammation. Thromb Haemost [Internet]. 2015 [cited 2023 May 24];114(3):449–58. Available from: https://pubmed.ncbi.nlm.nih.gov/26293514/
83. Piccin A, Pierro AM Di, Canzian L, Primerano M, Corvetta D, Negri G, et al. Platelet gel: a new therapeutic tool with great potential. Blood Transfusion [Internet]. 2017 [cited 2023 Jun 27];15(4):333. Available from: /pmc/articles/PMC5490729/
84. Tramś E, Malesa K, Pomianowski S, Kamiński R. Role of Platelets in Osteoarthritis—Updated Systematic Review and Meta-Analysis on the Role of Platelet-Rich Plasma in Osteoarthritis. Cells [Internet]. 2022 Apr 1 [cited 2023 Jul 6];11(7). Available from: /pmc/articles/PMC8997794/
85. Lee JW, Hyun Kwon O, Kim TK, Cho YK, Choi KY, Chung HY, et al. Platelet-Rich Plasma: Quantitative Assessment of Growth Factor Levels and Comparative Analysis of Activated and Inactivated Groups. Arch Plast Surg [Internet]. 2013 Sep [cited 2023 Jun 16];40(5):530. Available from: /pmc/articles/PMC3785585/
86. Seeger MA, Paller AS. The Roles of Growth Factors in Keratinocyte Migration. Adv Wound Care (New Rochelle). 2015 Apr;4(4):213–24.

87. Kushida S, Kakudo N, Morimoto N, Hara T, Ogawa T, Mitsui T, et al. Platelet and growth factor concentrations in activated platelet-rich plasma: a comparison of seven commercial separation systems. J Artif Organs [Internet]. 2014 [cited 2023 Jun 18];17(2):186–92. Available from: https://pubmed.ncbi.nlm.nih.gov/24748436/
88. Pourcho AM, Smith J, Wisniewski SJ, Sellon JL. Intraarticular platelet-rich plasma injection in the treatment of knee osteoarthritis: review and recommendations. Am J Phys Med Rehabil [Internet]. 2014 [cited 2023 Jun 18];93(11 Suppl 3):S108–21. Available from: https://pubmed.ncbi.nlm.nih.gov/24879553/
89. Bansal H, Leon J, Pont JL, Wilson DA, Bansal A, Agarwal D, et al. Platelet-rich plasma (PRP) in osteoarthritis (OA) knee: Correct dose critical for long term clinical efficacy. Sci Rep [Internet]. 2021 Dec 1 [cited 2023 Jun 21];11(1). Available from: /pmc/articles/PMC7889864/
90. Qian Y, Han Q, Chen W, Song J, Zhao X, Ouyang Y, et al. Platelet-Rich Plasma Derived Growth Factors Contribute to Stem Cell Differentiation in Musculoskeletal Regeneration. Front Chem [Internet]. 2017 Oct 1 [cited 2023 Jun 28];5:89. Available from: /pmc/articles/PMC5671651/
91. Van Le TH, Kwon SM. Vascular Endothelial Growth Factor Biology and Its Potential as a Therapeutic Target in Rheumatic Diseases. Int J Mol Sci [Internet]. 2021 May 2 [cited 2023 Jun 19];22(10). Available from: /pmc/articles/PMC8161097/
92. Zhang M, Yu W, Niibe K, Zhang W, Egusa H, Tang T, et al. The Effects of Platelet-Derived Growth Factor-BB on Bone Marrow Stromal Cell-Mediated Vascularized Bone Regeneration. Stem Cells Int [Internet]. 2018 [cited 2023 Jul 19];2018. Available from: https://pubmed.ncbi.nlm.nih.gov/30515221/
93. Zhu L, He J, Cao X, Huang K, Luo Y, Xu W. Development of a double-antibody sandwich ELISA for rapid detection of Bacillus Cereus in food. Sci Rep [Internet]. 2016 Mar 15 [cited 2023 Aug 13];6. Available from: /pmc/articles/PMC4792147/
94. Su W, Liu G, Liu X, Zhou Y, Sun Q, Zhen G, et al. Angiogenesis stimulated by elevated PDGF-BB in subchondral bone contributes to osteoarthritis development. JCI Insight [Internet]. 2020 Apr 4 [cited 2023 Jul 19];5(8). Available from: /pmc/articles/PMC7205438/
95. Andia I, Maffulli N. Platelet-rich plasma for managing pain and inflammation in osteoarthritis. Nature Reviews Rheumatology 2013 9:12 [Internet]. 2013 Oct 1 [cited 2023 Jul 12];9(12):721–30. Available from: https://www.nature.com/articles/nrrheum.2013.141
96. Zhu P, Wang Z, Sun Z, Liao B, Cai Y. Recombinant platelet-derived growth factor-BB alleviates osteoarthritis in a rat model by decreasing chondrocyte apoptosis in vitro and in vivo. J Cell Mol Med [Internet]. 2021 Aug 1 [cited 2023 Jul 19];25(15):7472. Available from: /pmc/articles/PMC8335691/
97. El-Seoudi A, Abd El Kader T, Nishida T, Eguchi T, Aoyama E, Takigawa M, et al. Catabolic effects of FGF-1 on chondrocytes and its possible role in osteoarthritis. J Cell Commun Signal [Internet]. 2017 Sep 1 [cited 2023 Jul 28];11(3):255. Available from: /pmc/articles/PMC5559396/

98. Xie Y, Zinkle A, Chen L, Mohammadi M. Fibroblast growth factor signalling in osteoarthritis and cartilage repair. Nat Rev Rheumatol [Internet]. 2020 Oct 1 [cited 2023 Jul 13];16(10):547–64. Available from: https://pubmed.ncbi.nlm.nih.gov/32807927/
99. Boehme KA, Rolauffs B. Onset and Progression of Human Osteoarthritis—Can Growth Factors, Inflammatory Cytokines, or Differential miRNA Expression Concomitantly Induce Proliferation, ECM Degradation, and Inflammation in Articular Cartilage? Int J Mol Sci [Internet]. 2018 Aug 3 [cited 2023 Jun 18];19(8). Available from: /pmc/articles/PMC6121276/
100. Wen C, Xu L, Xu X, Wang D, Liang Y, Duan L. Insulin-like growth factor-1 in articular cartilage repair for osteoarthritis treatment. Arthritis Res Ther [Internet]. 2021 Dec 1 [cited 2023 Jul 17];23(1). Available from: https://pubmed.ncbi.nlm.nih.gov/34717735/
101. Shen J, Li S, Chen D. TGF-β signaling and the development of osteoarthritis. Bone Res [Internet]. 2014 May 27 [cited 2023 Jun 18];2:14002. Available from: /pmc/articles/PMC4274935/
102. Zhen G, Wen C, Jia X, Li Y, Crane JL, Mears SC, et al. Inhibition of TGF–β signaling in subchondral bone mesenchymal stem cells attenuates osteoarthritis. Nat Med [Internet]. 2013 Jun [cited 2023 Jun 25];19(6):704. Available from: /pmc/articles/PMC3676689/
103. Yang X, Pu Q, Wen Y, Zhao Y, Wang J, Xu P, et al. Activation of the TGF-β1/Smads/α-SMA pathway is related to histological and functional changes in children with neurogenic bladder. Sci Rep [Internet]. 2022 Dec 1 [cited 2023 Jul 12];12(1). Available from: /pmc/articles/PMC9166803/
104. Du X, Cai L, Xie J, Zhou X. The role of TGF-beta3 in cartilage development and osteoarthritis. Bone Res [Internet]. 2023 Dec 1 [cited 2023 Jul 6];11(1). Available from: /pmc/articles/PMC9806111/
105. Hamilton JL, Nagao M, Levine BR, Chen D, Olsen BR, Im HJ. Targeting VEGF and its Receptors for the Treatment of Osteoarthritis and Associated Pain. J Bone Miner Res [Internet]. 2016 May 1 [cited 2023 Jun 19];31(5):911. Available from: /pmc/articles/PMC4863467/
106. Shen P, Jiao Z, Zheng JS, Xu WF, Zhang SY, Qin A, et al. Injecting vascular endothelial growth factor into the temporomandibular joint induces osteoarthritis in mice. Sci Rep [Internet]. 2015 Nov 4 [cited 2023 Jun 19];5. Available from: https://pubmed.ncbi.nlm.nih.gov/26531672/
107. Wei Y, Luo L, Gui T, Yu F, Yan L, Yao L, et al. Targeting cartilage EGFR pathway for osteoarthritis treatment. Sci Transl Med [Internet]. 2021 Jan 1 [cited 2023 Jul 18];13(576). Available from: /pmc/articles/PMC8027922/
108. Gato-Calvo L, Magalhaes J, Ruiz-Romero C, Blanco FJ, Burguera EF. Platelet-rich plasma in osteoarthritis treatment: review of current evidence. Ther Adv Chronic Dis [Internet]. 2019 [cited 2023 Jun 19];10:1–18. Available from: /pmc/articles/PMC6383098/
109. Garbin LC, Olver CS. Platelet-Rich Products and Their Application to Osteoarthritis. J Equine Vet Sci [Internet]. 2020 Mar 1 [cited 2023 Jun 15];86. Available from: https://pubmed.ncbi.nlm.nih.gov/32067662/

110. Drevet S, Favier B, Brun E, Gavazzi G, Lardy B. Mouse Models of Osteoarthritis: A Summary of Models and Outcomes Assessment. Comp Med [Internet]. 2022 Feb 1 [cited 2023 Jun 19];72(1):3. Available from: /pmc/articles/PMC8915410/
111. Fang H, Beier F. Mouse models of osteoarthritis: modelling risk factors and assessing outcomes. Nat Rev Rheumatol [Internet]. 2014 [cited 2023 Jun 19];10(7):413–21. Available from: https://pubmed.ncbi.nlm.nih.gov/24662645/
112. Bapat S, Hubbard D, Munjal A, Hunter M, Fulzele S. Pros and cons of mouse models for studying osteoarthritis. Clin Transl Med [Internet]. 2018 Dec [cited 2023 Jun 24];7(1):36. Available from: /pmc/articles/PMC6246759/
113. Teeple E, Jay GD, Elsaid KA, Fleming BC. Animal Models of Osteoarthritis: Challenges of Model Selection and Analysis. AAPS J [Internet]. 2013 Apr [cited 2023 Jun 24];15(2):438. Available from: /pmc/articles/PMC3675748/
114. Chawla S, Jena S. The Anatomy and Physiology of Laboratory Rat. Essentials of Laboratory Animal Science: Principles and Practices [Internet]. 2021 [cited 2023 Jun 23];187–209. Available from: https://link.springer.com/chapter/10.1007/978-981-16-0987-9_9
115. Maynard RL, Downes N. Introduction to Anatomical Terminology. Anatomy and Histology of the Laboratory Rat in Toxicology and Biomedical Research. 2019 Jan 1;7–9.
116. Hildebrand C, Öqvist G, Brax L, Tuisku F. Anatomy of the rat knee joint and fibre composition of a major articular nerve. Anat Rec [Internet]. 1991 Apr 1 [cited 2023 Aug 10];229(4):545–55. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/ar.1092290415
117. Hildebrand C, Öqvist G, Brax L, Tuisku F. Anatomy of the rat knee joint and fibre composition of a major articular nerve. Anat Rec [Internet]. 1991 [cited 2023 Aug 10];229(4):545–55. Available from: https://pubmed.ncbi.nlm.nih.gov/2048758/
118. Lorenz J, Grässel S. Experimental osteoarthritis models in mice. Methods Mol Biol [Internet]. 2014 [cited 2023 Jun 24];1194:401–19. Available from: https://pubmed.ncbi.nlm.nih.gov/25064117/
119. Kuyinu EL, Narayanan G, Nair LS, Laurencin CT. Animal models of osteoarthritis: classification, update, and measurement of outcomes. J Orthop Surg Res [Internet]. 2016 Feb 2 [cited 2023 Jun 20];11(1). Available from: /pmc/articles/PMC4738796/
120. Rao ZT, Wang SQ, Wang JQ. Exploring the osteoarthritis-related genes by gene expression analysis. Eur Rev Med Pharmacol Sci. 2014 Oct;18(20):3056–62.
121. Lampropoulou-Adamidou K, Lelovas P, Karadimas E V., Liakou C, Triantafillopoulos IK, Dontas I, et al. Useful animal models for the research of osteoarthritis. Eur J Orthop Surg Traumatol [Internet]. 2014 [cited 2023 Jun 24];24(3):263–71. Available from: https://pubmed.ncbi.nlm.nih.gov/23508348/
122. McCoy AM. Animal Models of Osteoarthritis: Comparisons and Key Considerations. Vet Pathol [Internet]. 2015 Sep 24 [cited 2023 Jun

24];52(5):803–18. Available from: https://pubmed.ncbi.nlm.nih.gov/26063173/
123. Fang H, Huang L, Welch I, Norley C, Holdsworth DW, Beier F, et al. Early Changes of Articular Cartilage and Subchondral Bone in The DMM Mouse Model of Osteoarthritis. Sci Rep [Internet]. 2018 Dec 1 [cited 2023 Jun 25];8(1):2855. Available from: /pmc/articles/PMC5809364/
124. Jia H, Ma X, Wei Y, Tong W, Tower RJ, Chandra A, et al. Subchondral bone plate sclerosis during late osteoarthritis is caused by loading-induced reduction in Sclerostin. Arthritis Rheumatol [Internet]. 2018 Feb 1 [cited 2023 Jun 25];70(2):230. Available from: /pmc/articles/PMC5788711/
125. Cosenza S, Ruiz M, Toupet K, Jorgensen C, Noël D. Mesenchymal stem cells derived exosomes and microparticles protect cartilage and bone from degradation in osteoarthritis. Sci Rep [Internet]. 2017 Dec 1 [cited 2023 Jun 26];7(1). Available from: /pmc/articles/PMC5701135/
126. Pitcher T, Sousa-Valente J, Malcangio M. The Monoiodoacetate Model of Osteoarthritis Pain in the Mouse. J Vis Exp [Internet]. 2016 May 16 [cited 2023 Jun 24];2016(111):53746. Available from: /pmc/articles/PMC4942175/
127. Yoh S, Kawarai Y, Hagiwara S, Orita S, Nakamura J, Miyamoto S, et al. Intra-articular injection of monoiodoacetate induces diverse hip osteoarthritis in rats, depending on its dose. BMC Musculoskelet Disord [Internet]. 2022 Dec 1 [cited 2023 Sep 1];23(1). Available from: /pmc/articles/PMC9131671/
128. Giknis MLA, Clifford CB. Clinical Laboratory Parameters for Crl:Wl(Han). 2008.
129. Vigneshwar R, Arivuchelvan A, Mekala P, Imayarasi K. Sex-specific reference intervals for Wistar albino rats: hematology and clinical biochemistry. Indian Journal of Animal Health. 2021 Jun 1;60(1):58–65.
130. Gonzalez RM, Seurynck-Servoss SL, Crowley SA, Brown M, Omenn GS, Hayes DF, et al. Development and validation of sandwich Elisa microarrays with minimal assay interference. J Proteome Res [Internet]. 2008 Jun [cited 2023 Aug 13];7(6):2406–14. Available from: https://pubs.acs.org/doi/abs/10.1021/pr700822t
131. Gaastra W. Enzyme-linked immunosorbant assay (ELISA). Methods Mol Biol [Internet]. 1984 Nov 14 [cited 2023 Aug 13];1:349–56. Available from: https://pubmed.ncbi.nlm.nih.gov/20512705/
132. Hidayat R, Patricia Wulandari. Enzyme Linked Immunosorbent Assay (ELISA) Technique Guideline. Bioscientia Medicina : Journal of Biomedicine and Translational Research. 2021 Jan 29;5(5):447–53.
133. Hidayat R, Patricia Wulandari. Euthanasia Procedure of Animal Model in Biomedical Research. Bioscientia Medicina : Journal of Biomedicine and Translational Research. 2021 Mar 8;5(6):540–4.
134. He Y, Li Z, Alexander PG, Ocasio-Nieves BD, Yocum L, Lin H, et al. Pathogenesis of Osteoarthritis: Risk Factors, Regulatory Pathways in Chondrocytes, and Experimental Models. Biology (Basel). 2020 Jul 29;9(8):194.

135. Ege F. Pathogenesis, Pathology and Genetics of Osteoarthritis. In: Rheumatoid Arthritis. IntechOpen; 2022.
136. Scanzello CR. Chemokines and inflammation in osteoarthritis: Insights from patients and animal models. Journal of Orthopaedic Research. 2017 Apr;35(4):735–9.
137. Hu B, Wu Z, Phan SH. Smad3 Mediates Transforming Growth Factor-β–Induced α-Smooth Muscle Actin Expression. Am J Respir Cell Mol Biol. 2003 Sep;29(3):397–404.
138. Sun K, Luo J, Guo J, Yao X, Jing X, Guo F. The PI3K/AKT/mTOR signaling pathway in osteoarthritis: a narrative review. Osteoarthritis Cartilage. 2020 Apr;28(4):400–9.
139. Romashkova JA, Makarov SS. NF-κB is a target of AKT in anti-apoptotic PDGF signalling. Nature. 1999 Sep;401(6748):86–90.
140. Brandl A, Angele P, Roll C, Prantl L, Kujat R, Kinner B. Influence of the growth factors PDGF-BB, TGF-beta1 and bFGF on the replicative aging of human articular chondrocytes during in vitro expansion. J Orthop Res [Internet]. 2010 Mar [cited 2023 Jul 25];28(3):354–60. Available from: https://pubmed.ncbi.nlm.nih.gov/19798738/
141. Guérit E, Arts F, Dachy G, Boulouadnine B, Demoulin JB. PDGF receptor mutations in human diseases. Cellular and Molecular Life Sciences 2021 78:8 [Internet]. 2021 Jan 15 [cited 2023 Aug 10];78(8):3867–81. Available from: https://link.springer.com/article/10.1007/s00018-020-03753-y
142. Namhong S, Wongdee K, Suntornsaratoon P, Teerapornpuntakit J, Hemstapat R, Charoenphandhu N. Knee osteoarthritis in young growing rats is associated with widespread osteopenia and impaired bone mineralization. Scientific Reports 2020 10:1 [Internet]. 2020 Sep 15 [cited 2023 Aug 11];10(1):1–11. Available from: https://www.nature.com/articles/s41598-020-71941-8
143. Parisa N, Hidayat R, Maritska Z, Prananjaya BA. Evaluation of the anti-gout effect of Sonchus Arvensis on monosodium urate crystal-induced gout arthritis via anti-inflammatory action - an in vivo study. Med Pharm Rep [Internet]. 2021 [cited 2023 Sep 5];94(3):358. Available from: /pmc/articles/PMC8357366/
144. Xu J, Yan L, Yan B, Zhou L, Tong P, Shan L. Osteoarthritis Pain Model Induced by Intra-Articular Injection of Mono-Iodoacetate in Rats. J Vis Exp [Internet]. 2020 May 1 [cited 2023 Aug 16];2020(159). Available from: https://pubmed.ncbi.nlm.nih.gov/32510505/
145. Guingamp C, Gegout-Pottie P, Philippe L, Terlain B, Netter P, Gillet P. Mono-iodoacetate-induced experimental osteoarthritis: A dose-response study of loss of mobility, morphology, and biochemistry. Arthritis Rheum. 1997 Sep;40(9):1670–9.
146. Ängeby Möller K, Klein S, Seeliger F, Finn A, Stenfors C, Svensson CI. Monosodium iodoacetate-induced monoarthritis develops differently in knee versus ankle joint in rats. Neurobiology of Pain [Internet]. 2019 Aug 1 [cited 2023 Nov 22];6:100036. Available from: /pmc/articles/PMC6744596/

147. De Sousa Valente J. The Pharmacology of Pain Associated With the Monoiodoacetate Model of Osteoarthritis. Front Pharmacol [Internet]. 2019 [cited 2023 Nov 22];10. Available from: /pmc/articles/PMC6759799/
148. Muronetz VI, Melnikova AK, Barinova K V., Schmalhausen E V. Inhibitors of Glyceraldehyde 3-Phosphate Dehydrogenase and Unexpected Effects of Its Reduced Activity. Biochemistry (Mosc) [Internet]. 2019 Nov 1 [cited 2023 Nov 22];84(11):1268–79. Available from: https://pubmed.ncbi.nlm.nih.gov/31760917/
149. Zheng L, Zhang Z, Sheng P, Mobasheri A. The role of metabolism in chondrocyte dysfunction and the progression of osteoarthritis. Ageing Res Rev. 2021 Mar 1;66:101249.
150. Tan C, Li L, Han J, Xu K, Liu X. A new strategy for osteoarthritis therapy: Inhibition of glycolysis. Front Pharmacol. 2022 Nov 10;13:1057229.
151. Jiang L, Li L, Geng C, Gong D, Jiang L, Ishikawa N, et al. Monosodium iodoacetate induces apoptosis via the mitochondrial pathway involving ROS production and caspase activation in rat chondrocytes in vitro. Journal of Orthopaedic Research [Internet]. 2013 Mar 1 [cited 2023 Nov 27];31(3):364–9. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/jor.22250
152. Lepetsos P, Papavassiliou AG. ROS/oxidative stress signaling in osteoarthritis. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. 2016 Apr 1;1862(4):576–91.
153. Ansari MY, Ahmad N, Haqqi TM. Oxidative Stress and Inflammation in Osteoarthritis Pathogenesis: Role of Polyphenols. Biomed Pharmacother [Internet]. 2020 Sep 1 [cited 2023 Nov 27];129:110452. Available from: /pmc/articles/PMC8404686/
154. Germolec DR, Shipkowski KA, Frawley RP, Evans E. Markers of inflammation. Methods in Molecular Biology [Internet]. 2018 [cited 2023 Nov 10];1803:57–79. Available from: https://link.springer.com/protocol/10.1007/978-1-4939-8549-4_5
155. Ren K, Torres R. Role of interleukin-1β during pain and inflammation. Brain Res Rev [Internet]. 2009 Apr [cited 2023 Nov 10];60(1):57. Available from: /pmc/articles/PMC3076185/
156. Perrot CY, Javelaud D, Mauviel A. Insights into the Transforming Growth Factor-β Signaling Pathway in Cutaneous Melanoma. Ann Dermatol. 2013;25(2):135.
157. Hu B, Wu Z, Phan SH. Smad3 mediates transforming growth factor-beta-induced alpha-smooth muscle actin expression. Am J Respir Cell Mol Biol [Internet]. 2003 Sep 1 [cited 2023 Nov 12];29(3 Pt 1):397–404. Available from: https://pubmed.ncbi.nlm.nih.gov/12702545/
158. Van Der Kraan PM. The changing role of TGFβ in healthy, ageing and osteoarthritic joints. Nat Rev Rheumatol [Internet]. 2017 Mar 1 [cited 2023 Jul 3];13(3):155–63. Available from: https://pubmed.ncbi.nlm.nih.gov/28148919/
159. Fabregat I, Caballero-Díaz D. Transforming Growth Factor-β-Induced Cell Plasticity in Liver Fibrosis and Hepatocarcinogenesis. Front Oncol

[Internet]. 2018 Sep 10 [cited 2023 Nov 26];8(SEP):357. Available from: /pmc/articles/PMC6139328/

160. Leivonen SK, Lazaridis K, Decock J, Chantry A, Edwards DR, Kähäri VM. TGF-β-Elicited Induction of Tissue Inhibitor of Metalloproteinases (TIMP)-3 Expression in Fibroblasts Involves Complex Interplay between Smad3, p38α, and ERK1/2. PLoS One [Internet]. 2013 Feb 28 [cited 2023 Nov 27];8(2). Available from: /pmc/articles/PMC3585359/
161. Baker AH, Edwards DR, Murphy G. Metalloproteinase inhibitors: biological actions and therapeutic opportunities. J Cell Sci [Internet]. 2002 Oct 1 [cited 2023 Nov 27];115(19):3719–27. Available from: https://dx.doi.org/10.1242/jcs.00063