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Infrapatellar Fat Pad as an Immunometabolic Organ in Knee Osteoarthritis: Molecular Crosstalk, Clinical Relevance, and Therapeutic Implications

Anandanarayan Muruganandam [1, 2], Ashwini Raja [3], Bhoomika V. Badrinath [3], Naveen Jeyaraman [4, 5], Sankalp Yadav [6], Madhan Jeyaraman [5, 4]

1. Orthopaedics and Traumatology, Faculty of Medicine, Sri Lalithambigai Medical College and Hospital, Dr. M.G.R. Educational and Research Institute, Chennai, IND 2. Sports Medicine, Sri Ramachandra Institute of Higher Education and Research, Chennai, IND 3. Orthopaedics, Faculty of Medicine, Sri Lalithambigai Medical College and Hospital, Dr. M.G.R. Educational and Research Institute, Chennai, IND 4. Orthopaedics, ACS Medical College and Hospital, Dr. M.G.R. Educational and Research Institute, Chennai, IND 5. Regenerative Medicine, Agathisha Institute of Stemcell and Regenerative Medicine (AISRM), Chennai, IND 6. Medicine, Shri Madan Lal Khurana Chest Clinic, New Delhi, IND

Corresponding author: Sankalp Yadav, drsankalpyadav@gmail.com

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Abstract

Knee osteoarthritis (OA) is now recognized as a disease of the whole joint with disease processes affecting the cartilage, synovium, subchondral bone, and periarticular soft tissues. In particular, the infrapatellar fat pad (IPFP), also known as Hoffa's fat pad, has received growing interest as an active tissue within the knee joint, rather than a passive mechanical pad.

This narrative review critically evaluates the immunometabolic role of the IPFP, its molecular interactions with synovial tissues, cartilage, subchondral bone and menisci, links with knee pain and structural progression, and its potential as a biomarker and therapeutic target in knee OA. PubMed/MEDLINE and Scopus were searched from inception to 30 September 2026, supplemented by reference-list screening, and reporting followed the Scale for the Assessment of Narrative Review Articles (SANRA).

In human explant, histological and imaging studies, the osteoarthritic IPFP produces the adipokines (leptin, adiponectin, resistin and visfatin), cytokines (IL-1β, IL-6, TNF-α) and chemokines (CCL2) with a different immune infiltrate profile, where macrophages and T lymphocytes are the predominant cells. Cartilage and synoviocyte cultures are stimulated by IPFP-conditioned medium to show catabolic and inflammatory effects, which provide some biological plausibility for a pathogenic effect; however, the data are mostly correlative and cross-sectional. MRI-detected Hoffa synovitis was associated with pain in multiple, but not all, cohorts, and its association with histologically proven inflammation is not perfect. Fibrotic and angiogenic remodelling are documented in end-stage OA IPFP tissue; IPFP-derived stromal cells show in vitro chondrogenic capacity without proven superiority over other cell sources, and the independent contribution of metabolic syndrome, as distinct from obesity-related loading, remains unresolved.

The IPFP is much more than a mere structural filler; it is, more likely than not, an active member of the immunometabolic microenvironment of the osteoarthritic knee. The causal role in the primary driver, amplifier, or mostly a consequence of joint disease has yet to be determined, and human evidence is still limited. Its capacity to damage as well as repair suggests that it should not be indiscriminately suppressed by therapy or excised by surgery and should continue to be investigated in a phenotype-specific manner.

Categories: Pain Management, Quality Improvement, Orthopedics
Keywords: adipokines, adipose tissue, immunometabolism, infrapatellar fat pad, knee osteoarthritis, synovitis

Introduction And Background

Knee osteoarthritis (OA) is no longer thought of as an articular cartilage disease. It is, on the contrary, a disease of the joint as an organ, which involves a coordinated dysfunction of cartilage, subchondral bone, synovium, menisci, ligaments, and periarticular adipose and neuromuscular tissue [1-5]. In particular, synovitis has been repeatedly associated with both symptoms and structural progression, even when not considered within the context of classical inflammatory arthritis [6-9], and redefining OA as a condition with a significant low-grade inflammatory component [5,10-12].

OA is a leading cause of pain and disability worldwide: an estimated 595 million people were living with OA in 2020, the knee is the most frequently affected joint, and the number of knee OA cases is projected to increase by 74.9% by 2050 [13]. Clinically, the severity of knee pain correlates poorly with radiographic severity, so that patients with marked pain may have only mild radiographic change and vice versa; this discordance has directed attention to soft-tissue structures that are not visible on plain radiographs [14]. The

infrapatellar fat pad (IPFP), also known as Hoffa's fat pad, is one such structure. It is a recognized source of anterior knee pain, including Hoffa's syndrome (impingement and inflammation of the fat pad); IPFP signal abnormalities are frequent findings on knee magnetic resonance imaging (MRI), and whether the IPFP should be preserved or resected during total knee arthroplasty (TKA) remains debated [15-18].

In this overall joint picture, the IPFP is a structurally protected but not sufficiently analysed area of the body [19-21]. The IPFP is an intra-capsular, extra-synovial structure (that is, it lies inside the joint capsule but outside the synovial cavity), in direct continuity with the synovium, in apposition to the patellar tendon, the condyles of the femur and the tibial plateau and anterior meniscal horns, and also well vascularised and innervated [15,16,22]. It is in proximity to cartilage and bone, and constantly bathed in synovial fluid, unlike other adipose depots such as subcutaneous and visceral [23,24]. Adipose tissue in general is an endocrine and immune-active organ [25-27], and IPFP-specific explant studies confirm local secretory activity; together with its close anatomical relationship to the synovium and cartilage, this has prompted a shift in perspective: the IPFP is now proposed as a locally active inflammation-producing, immunometabolic, endocrine, paracrine, nociceptive and stromal organ in the osteoarthritic knee [19,23,28-32]. In this review, adipokines are hormone-like signalling proteins secreted by adipose tissue (for example, leptin and adiponectin); stromal refers to the non-adipocyte supporting cells of the tissue, including fibroblasts and progenitor cells; and immunometabolism describes the interplay between cellular metabolism and immune-cell function [33].

Several recent reviews have described the IPFP as an inflammatory and immunometabolic tissue in knee OA; however, the type and strength of the evidence behind each proposed function are rarely distinguished, and this is the knowledge gap addressed here [23,34]. Compared with these recent reviews, the present review specifically grades each proposed IPFP function by the type of evidence supporting it (human longitudinal, human cross-sectional, ex vivo, in vitro, animal) and summarizes the clinical implications for the differential diagnosis and management of knee pain. Its specific aims are to: (1) summarize the anatomy and cellular composition of the IPFP; (2) evaluate whether IPFP abnormalities are associated with the presence of knee OA; (3) evaluate whether they are associated with structural progression; (4) evaluate their contribution to knee pain; (5) assess their potential as imaging or soluble biomarkers; and (6) assess the IPFP as a therapeutic target. Throughout, human observational data are distinguished from mechanistic plausibility, and association is not interpreted as causation.

Review

This narrative review was prepared as follows. PubMed/MEDLINE and Scopus were searched from inception to 30 September 2026, supplemented by screening of the reference lists of retrieved articles and recent reviews. Search terms combined "infrapatellar fat pad" or "Hoffa's fat pad" with OA, synovitis, adipokine, inflammation, macrophage, pain, magnetic resonance imaging, mesenchymal stromal cells (MSCs), extracellular vesicles and arthroplasty. English-language human explant, histological, imaging, observational and interventional studies were eligible, together with ex vivo, in vitro and animal studies addressing mechanisms; case reports were included only where they informed differential diagnosis or safety. Each proposed IPFP function was graded according to the type of supporting evidence (human longitudinal, human cross-sectional, ex vivo, in vitro or animal). In total, 893 records were identified, 43 were screened, and 10 were included. Consistent with the narrative design, no formal risk-of-bias assessment or quantitative synthesis was performed, and reporting followed the Scale for the Assessment of Narrative Review Articles (SANRA) [35].

Anatomy and physiological functions of IPFP

The IPFP is located in the anterior compartment of the knee between the patellar tendon anteriorly and the femoral condyles and tibial plateau posteriorly, and it extends superiorly with the suprapatellar and parapatellar synovial folds through the ligamentum mucosum [15,22]. It is intracapsular but extrasynovial, and adjacent to the anterior horns of the medial and lateral menisci and lies lateral to the anterior cruciate ligament [15,24]. This helps it to absorb forces that pass through other joints, such as the patellofemoral and tibiofemoral, and fills in the dead space within it during flexion and extension, assists in distributing synovial fluid throughout the knee and lubricating the joint, and allows for a significant amount of volume changes during the knee's range of motion [16,36]. It is richly vascularized by the genicular anastomosis and innervated by branches of the femoral, obturator and posterior tibial nerves and by the infrapatellar branch of the saphenous nerve; because the femoral, obturator and saphenous contributions share L2-L4 segmental origins with the lumbar spine and hip, pain referred from these regions can mimic anterior knee pain. It contains free nerve endings, substance-P-positive sensory fibres and mechanosensitive elements relevant to proprioception and nociception, which are discussed later in this review [15,37,38]. Mechanical, vascular and neural integration make the IPFP a highly unique entity for detecting and potentially transmitting mechanical, biochemical signals to and from cartilage, synovium and bone [24,38].

IPFP - an endocrine and paracrine organ

The adipose tissue produces a wide range of adipokines, cytokines, chemokines, lipid mediators, and extracellular vesicles, working both locally and systemically [18,25,39]. To prove that the IPFP is not just infiltrated by immune cells, but also that these cells are not the only source of interleukin-6 (IL-6) and its

soluble receptor, human explant studies have shown that measurable amounts of these are present, and in some cohorts are greater than in matched subcutaneous fat [1,28]. Ushiyama and collaborators showed that the cytokines, such as IL-6 and IL-8, are secreted into the culture medium from the explants of IPFP, suggesting that the fat pad is another local source of cytokines in synovial fluid, apart from synovium itself [2,29]. Clockaerts et al. demonstrated that IL-1β stimulates the production of pro-inflammatory cytokines from the IPFP, but that the production of anti-inflammatory cytokines is reduced by activation of PPAR-α [3,30], suggesting that the tissue is not a constitutively inflammatory tissue but reacts to its microenvironment. Conditioned medium from OA IPFP explants directly drives an inflammatory, prodegradative phenotype in autologous fibroblast-like synoviocytes in which IL-6, IL-8, CCL2 and matrix metalloproteinases are all upregulated, giving direct evidence of the mechanism of fat-pad-to-synovium signalling in human tissues [4,31]. In addition to classical cytokines, the IPFP expresses adipokines such as leptin, adiponectin, resistin and visfatin/NAMPT with potential but variable effects on chondrocytes, synoviocytes and nerve fibres, angiogenic mediators such as vascular endothelial growth factor (VEGF), and fibrogenic mediators such as transforming growth factor beta (TGF-β) [5,7-9].

What does "immunometabolic organ" mean?

Immunometabolism refers to the dynamic cross-talk between the metabolic state of cells and the function of immune cells and includes the manner in which the availability of nutrients, hypoxia, and lipid handling dictate macrophage polarisation, cytokine production, and stromal-cell behaviour [10,11]. When applied to the IPFP, it's proposed that alterations in fat pad metabolism towards local hypoxia, oxidative stress, and lipid alterations elicit a shift toward pro-inflammatory macrophage recruitment and cytokine secretion, similar to that described in visceral adipose tissue during obesity [20,21,23,25]. This framing has led to the idea of a "metabolic OA phenotype" in which systemic and local metabolic dysfunction, separate from mechanical overload, is the cause of joint inflammation and progression, rather than mechanical overload alone [15,16,22]. The separation is only conceptual, not fully substantiated: most human IPFP studies have been unable to distinguish a true metabolic phenotype from confounding due to joint loading from obesity [40].

Cellular composition of IPFP

IPFP consists of mature adipocytes, preadipocytes, fibroblasts, and fibro-adipogenic progenitors, resident and recruited macrophages, T lymphocytes, mast cells, endothelial cells, pericytes, and a population of MSCs (Table *1*) [26,41,42]. Histological and flow-cytometric analysis of the OA IPFP tissue harvested at arthroplasty shows higher numbers of macrophages and lymphocytes than in subcutaneous fat from the same patients, and comparative studies indicate that the inflammatory-cell composition of the IPFP is more similar to that of neighbouring synovium than to that of more distant adipose tissue depots [27,43,44]. In addition, CD8+ T cells in the IPFP have been reported to be more abundant in knees with a higher radiographic OA grade [45]. It remains unclear whether this is a phenotype of the OA cell itself or simply a general reaction to intra-articular proximity, as there is a lack of similarly detailed information from young structurally normal knees [46]. Single-cell and spatial transcriptomic characterization of the IPFP is still only just underway and, when available, largely confined to the tissue at the end of the arthroplasty [34,47].

Cell type	Physiological role	OA-associated change	Major mediators	Proposed pathological effect	Evidence source (not formally graded)
Mature adipocytes	Energy storage, mechanical volume/deformability, adipokine secretion	Hypertrophy; altered secretory profile	Leptin, adiponectin, IL-6	Altered secretory profile associated with OA; causal contribution not established	Human IPFP expression/explant studies [23,27,28]
Macrophages	Tissue surveillance, homeostasis	Increased infiltration in many OA cohorts; mixed activation states	CCL2, IL-1β, TNF-α	May contribute to local and synovial inflammation	Human histology/flow cytometry [37,38]
Fibroblasts/fibro-adipogenic cells	Structural support, ECM turnover	Activation; myofibroblast differentiation; inflammatory fibroblast states	TGF-β, collagen	Fibrosis and stromal inflammatory signaling	Human histology plus single-cell transcriptomics [37,46]
T lymphocytes	Adaptive immune surveillance	Increased density reported in OA tissue	IFN-γ, IL-17 (proposed)	Possible contribution to chronic low-grade inflammation	Human flow-cytometry/tissue studies [38]
Endothelial cells/pericytes	Vascular supply	Neovascularization reported in OA tissue	VEGF	Angiogenesis; nociceptive coupling remains hypothetical	Human tissue/histology evidence [24,37]
Mesenchymal stromal/stem cells	Regenerative niche; immunomodulation	Present in healthy and OA tissue; functional shifts incompletely defined	Secretome; multiple stromal mediators	Potential reparative or immunomodulatory activity; clinical role unproven	Human isolation and in vitro differentiation studies [39-44]
Mast cells	Innate immune sentinels	Presence reported; limited characterization	Histamine, proteases (proposed)	Under-characterized in human IPFP	Human flow cytometry evidence; limited characterization [38]

TABLE 1: Cellular populations within the IPFP and their proposed roles in OA.

OA: osteoarthritis; IPFP: infrapatellar fat pad; IL-6: interleukin-6; CCL2 (MCP-1): C-C motif chemokine ligand 2 (monocyte chemoattractant protein-1); IL-1β: interleukin-1 beta; TNF-α: tumor necrosis factor alpha; ECM: extracellular matrix; TGF-β: transforming growth factor beta; IFN-γ: interferon gamma; IL-17: interleukin-17; VEGF: vascular endothelial growth factor

Macrophages and innate immunity

Macrophages are always the predominant immune cell type in OA IPFP tissue [24,41]. The classical M1/M2 paradigm, although convenient, is an oversimplification of the spectrum of activation states that are found within different types of macrophages, such as those in adipose tissue and synovial tissue, which actually have mixed and context-dependent marker expression rather than polarisation [48-50]. The chemokine CCL2 (MCP-1) is one of the more consistently upregulated chemokines in OA IPFP and is thought to recruit monocytes/macrophages through CCR2 signalling; a rat model with a CCL2/MCP-1 antagonist showed reduced IPFP fibrosis, which is mechanistically consistent [36,51]. Direct evidence of specifically human IPFP macrophage involvement (absent from the synovial or cartilage macrophages) is lacking, but the activation of the NF-κB and plausibly the NLRP3 inflammasome has been suggested to link macrophage activation with the release of IL-1β and IL-18 downstream [52-54]. In function, IPFP macrophages are proposed to mediate synovial inflammation through the secretion of paracrine cytokines, fibrosis by the secretion of profibrotic mediators, cartilage catabolism through the indirect secretion of cytokines by synovial cells and chondrocytes, and angiogenesis and peripheral sensitization, as detailed below [55,56].

Adipokines in knee OA

Leptin

Leptin is synthesized locally in joint adipose tissue, and, in experimental studies, leptin stimulates the expression of matrix metalloproteinases and nitric oxide in chondrocytes and thus contributes to cartilage matrix degradation [12,57,58]. In human cohorts, it is difficult to distinguish a local (joint-specific) effect from a systemic (obesity) effect, and findings on the relationship with radiographic severity are inconclusive [59,60].

Adiponectin

In the metabolic literature, adiponectin is considered anti-inflammatory, and in the OA joint, anti-inflammatory or pro-catabolic effects have been shown at concentrations of adiponectin present in synovial fluid, and the amounts of adiponectin expressed in IPFP compared to synovium vary from one cohort to another [33,61-63]. It should not be described as being protective throughout this tissue [64].

Resistin

In human tissue, the data on the effect of resistin on the induction of pro-inflammatory cytokines is more limited than that of leptin or adiponectin, and there is experimental evidence for its ability to induce cartilage matrix turnover [65,66].

Visfatin/NAMPT

Visfatin is an adipokine and an enzyme (NAMPT) in the salvage metabolism of NAD+, where it is associated with the induction of inflammatory mediators and matrix-degrading enzymes in OA tissue and has been proposed to be a mechanism connecting adipokine signalling to cartilage matrix turnover, with early interest in NAMPT-directed inhibition as a therapeutic approach [67-69].

No single adipokine can be considered entirely protective or entirely destructive; the effects of these factors are concentration-, context- and tissue-dependent; and most of the mechanistic evidence has come from chondrocyte or synoviocyte monocultures, and not from intact joint tissue (Table *2*) [70,71].

Mediator	Major cellular source	Principal target	Biological effect	Evidence in knee OA	Clinical implication
Leptin	Adipocytes, macrophages	Chondrocytes, synoviocytes	Upregulates MMPs and nitric oxide; promotes matrix catabolism	Human explant/experimental; correlates variably with severity	Candidate catabolic mediator; not a validated biomarker
Adiponectin	Adipocytes	Chondrocytes, synoviocytes	Context-dependent; not uniformly anti-inflammatory in joint tissue	Human explant studies show inconsistent, sometimes pro-catabolic effects	Effects likely concentration- and context-dependent
Resistin	Adipocytes, stromal cells	Chondrocytes, synoviocytes	Pro-inflammatory cytokine induction; matrix turnover	Mostly experimental; limited human IPFP-specific data	Mechanistically plausible, not clinically established
Visfatin/NAMPT	Adipocytes, immune cells	Chondrocytes, synoviocytes	Induces inflammatory mediators and matrix-degrading enzymes	Human IPFP and synovial expression studies	Early interest as a druggable target (NAMPT inhibition)
IL-1β	Macrophages, adipocytes	Chondrocytes, synoviocytes, IPFP itself	Amplifies local cytokine/MMP production	Human explant stimulation studies	Upstream amplifier rather than isolated target
IL-6	IPFP adipocytes/stroma	Synoviocytes, systemic circulation	Pro-inflammatory signalling; possible driver of local IL-6 pool	Elevated in human IPFP explants vs subcutaneous fat	Reflects local inflammatory burden
TNF-α	Macrophages	Chondrocytes, synoviocytes	Pro-inflammatory, catabolic co-mediator	Human IPFP tissue evidence	Randomized trials of TNF inhibition in OA have not shown clinical benefit
CCL2 (MCP-1)	Adipocytes, macrophages, fibroblasts	Monocytes/macrophages (CCR2)	Recruits monocytes; sustains macrophage infiltration	Human explant and preclinical (rat) fibrosis models	Candidate target for anti-fibrotic/anti-inflammatory strategy
VEGF	Endothelial cells, macrophages	Vascular endothelium	Drives pathological neovascularisation	Human imaging (DCE-MRI) and histology	Linked mechanistically to angiogenesis-nociception coupling
TGF-β	Fibroblasts, myofibroblasts	Fibroblasts (autocrine), stromal cells	Drives fibroblast-to-myofibroblast transition, collagen deposition	Human histological studies of IPFP fibrosis	Candidate anti-fibrotic target

TABLE 2: Major mediators produced by, or proposed to originate from, the IPFP and their putative roles in knee OA.

CCL2 (MCP-1): C-C motif chemokine ligand 2 (monocyte chemoattractant protein-1); CCR2: C-C motif chemokine receptor 2; DCE-MRI: dynamic contrast-enhanced magnetic resonance imaging; IL-1β: interleukin-1 beta; IL-6: interleukin-6; IPFP: infrapatellar fat pad; MMPs: matrix metalloproteinases; NAMPT: nicotinamide phosphoribosyltransferase; OA: osteoarthritis; TGF-β: transforming growth factor beta; TNF-α: tumor necrosis factor alpha; VEGF: vascular endothelial growth factor

IPFP-synovium crosstalk

Due to the anatomical continuity between the IPFP and the synovium (via the synovial layer investing the fat pad and the ligamentum mucosum), the concept of an IPFP-synovial functional unit is supported as opposed to two separate tissues [24,32,72]. Direct evidence for bidirectional signaling from humans comes from explant co-culture studies: IPFP-conditioned medium induces a pro-inflammatory (pro-degradative) phenotype of fibroblast-like synoviocytes; comparative immunophenotyping demonstrates that inflammatory-cell profiles of IPFP and adjacent synovium are more closely correlated than either is with remote fat [31,43]. This is an important caution to interpret: the presence of high levels of inflammatory markers in OA IPFP tissue does not automatically mean that the fat pad is responsible for initiating joint inflammation, because the inflamed synovium may equally be signalling to the adjacent fat pad; current data therefore do not establish whether the IPFP initiates, amplifies or responds to synovitis [31,43,73]. This is because it is difficult to differentiate between the initiator and amplifier in the current cross-sectional human data (Figure *1*) [74].

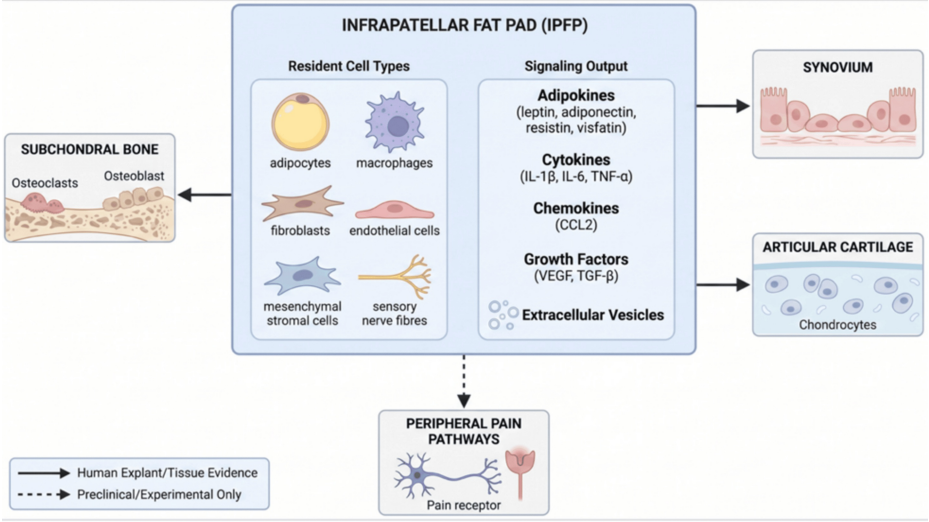


FIGURE 1: Infrapatellar fat pad as an immunometabolic organ.

Solid arrows denote pathways supported by human explant or tissue evidence; dashed arrows denote hypothesized pathways without direct IPFP-specific human evidence.

IPFP: infrapatellar fat pad; IL-1β: interleukin-1 beta; IL-6: interleukin-6; TNF-α: tumor necrosis factor alpha; VEGF: vascular endothelial growth factor; TGF-β: transforming growth factor beta

The image was created by Dr. Madhan Jeyaraman and Dr. Sankalp Yadav using BioRender (BioRender Inc., Toronto, Ontario, Canada).

IPFP-cartilage crosstalk

The co-culture experiments and conditioned-medium experiments show that the secretions generated by the IPF can induce chondrocyte catabolism by activating p38MAPK and ERK1/2 signalling pathways and inducing matrix-degrading enzymes in OA cartilage explants, respectively [75-77]. These in vitro effects are biologically consistent with the adipokine/cytokine profile described above, but are effects of the biologic system in an artificial culture system as opposed to effects on cartilage that can be attributed to the IPFP in vivo [78]. There are very few examples of longitudinal human data that directly correlate IPFP-derived mediator concentrations with subsequent cartilage volume loss, and this is one of the biggest gaps in the field that should be noted (Figure *2*) [79].

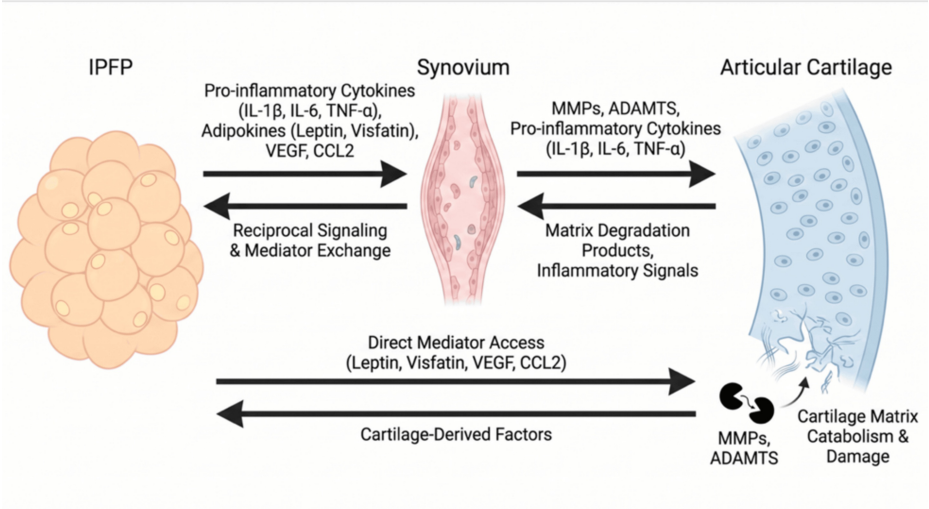


FIGURE 2: IPFP-synovium-cartilage crosstalk in knee osteoarthritis.

IPFP: infrapatellar fat pad; IL-1β: interleukin-1 beta; IL-6: interleukin-6; TNF-α: tumor necrosis factor alpha; VEGF: vascular endothelial growth factor

The image was created by Dr. Sankalp Yadav using BioRender (BioRender Inc., Toronto, Ontario, Canada).

IPFP-subchondral bone and meniscus crosstalk

There is limited mechanistic evidence for the relationship between IPFP biology and subchondral bone remodelling, osteophyte formation, or bone marrow lesions, and most provided evidence is of an anatomical or imaging-based association, which should be explicitly described and not assumed [80,81]. Anatomically, there is a direct relationship between the IPFP and the meniscus, with the fat pad directly touching the anterior meniscal horns, and there is no doubt that this relationship exists [82]. There have been some imaging cohorts that have identified a change in the volume or signal of the IPFP in conjunction with meniscal extrusion and degeneration, but there is no evidence of a direct causal relationship, let alone a clear directionality [83,84].

Fibrosis of the IPFP

Fibroblast activation, the differentiation of myofibroblasts, and collagen deposition are known characteristics of the OA IPFP, especially in tissue harvested following trauma or prior surgeries [41,85-87]. TGF-β signalling has been suggested as a central player, and resident stromal cells in the IPF have been demonstrated to develop an immunomodulatory phenotype when inflamed and made fibrotic, including degradation of substance P by CD10, which may be relevant to both fibrosis and local nociception [88,89]. Fibrosis makes the fat pad firmer and could limit fat pad deformability in the normal knee, possibly leading to anterior knee pain and loss of range of motion, especially in post-traumatic and post-surgical arthrofibrosis [85,90]. The interaction between inflammatory and fibrotic processes within the IPFP seems more like a sequential and overlapping process than mutually exclusive, as is the case in other chronically inflamed tissues, in which fibrosis can occur in the presence of inflammation [91].

Angiogenesis and hypoxia

Normally well vascularized, the IPFP has features of pathological neovascularisation, together with hypoxic and inflammatory signalling, and VEGF has been suggested as a major mediator of the process of pathological neovascularisation [41,92,93]. Dynamic contrast-enhanced MRI studies have shown that there is increased perfusion within the areas of Hoffa's fat pad signal abnormality in knees with OA, providing indirect human in vivo evidence for altered vascularity [94,95]. Angiogenesis and sensory nerve ingrowth are often seen to be co-localized in other chronically inflamed musculoskeletal tissues, and a similar coupling is plausible in the IPFP, although limited direct human histological evidence of a specific association between IPFP neovascularisation and nerve fibre density does exist [96,97].

IPFP and pain in knee OA

The severity of knee OA pain shows only a weak association with the severity of the radiographic joint damage, leading to an interest in the role of periarticular soft tissue sources in the experience of knee OA pain [14,53]. The IPFP is highly innervated and contains substance-P-positive fibres that are histologically present in the fat pad and in the adjacent synovium, as well as mechanosensitive channels that are thought to connect mechanical loading directly to nociceptive signalling [37,38]. Hoffa-synovitis signal alteration has

been associated with pain in some cohorts, and broader MRI synovitis measures, including contrast-enhanced synovitis, show similar but inconsistent pain associations; importantly, MRI signal alteration is not the same as histologically proven Hoffa synovitis and should be reported separately from it [17,98-101]. Each of these mechanisms is biologically plausible and could contribute to pain in an individual with IPFP, but cannot be non-invasively separated in the individual. Pain arising outside the knee must also be considered in the differential diagnosis: L3/L4 disc herniation with L4 nerve-root compression and loss of the patellar reflex has been documented, and because the L4 dermatome covers the anterior knee and medial leg, such radicular pain can be mistaken for intra-articular, including IPFP-related, pathology [102].

MRI and imaging biomarkers of IPFP

The volume, the alteration of signal intensity (Hoffa synovitis), and more recently texture and radiomic features are quantitative MRI metrics of the IPFP [103-105]. Hoffa synovitis is most commonly graded semi-quantitatively using the MRI Osteoarthritis Knee Score (MOAKS) or the Whole-Organ Magnetic Resonance Imaging Score (WORMS), whereas volume, signal-intensity, and radiomic metrics require dedicated segmentation [106,107]. Larger and well-characterized cohorts have investigated relationships between size of IPF or signal change in the IPF and the rates of symptomatic or structural progression, and some have reported that signal change (not necessarily volume) was more commonly associated with progression [103-105,108,109]. Longitudinal studies of IPFP morphology are ongoing in more recent studies as an independent prognosis marker for progression of OA [110-112]. Results are not fully harmonized between cohorts as a consequence of different segmentation approaches, sequence protocols, and population characteristics [101,113]. Reproducibility and external validation across scanners and populations are still to be systematically demonstrated to apply in clinical practice, and automated segmentation, texture analysis, and machine learning-based radiomics are at an early, largely exploratory stage [114].

Obesity, metabolic syndrome (MS), and IPFP

Obesity is one of the most powerful risk factors for knee OA in two ways: mechanically through loading, and through systemic metabolic pathways [66,68,115]. A comparative analysis of the expression of these adipokines in the synovium of MS patients and non-MS patients revealed that the expression levels of these adipokines in the synovium were influenced by systemic metabolic status, though not completely explained [62]. Determining whether the inflammation associated with IPFP is caused primarily by the inflammatory nature of the disease in the joint(s) or whether it is caused primarily by systemic adiposity and insulin resistance is not a "yes or no" question, but rather a mix of both and is truly not known [69]. Differential expression of adipokines and cytokines in paired-sample studies has provided evidence that IPFP biology differs qualitatively from subcutaneous and visceral fat, not simply quantitatively because of its size, but rather because of differential expression patterns, which, however, is limited to paired-sample studies [61,62]. Pharmacological weight reduction with glucagon-like peptide-1 (GLP-1) receptor agonists also improves knee OA pain: in the STEP 9 trial, once-weekly semaglutide reduced body weight by 13.7% versus 3.2% with placebo and improved WOMAC pain over 68 weeks [116]. Whether this is accompanied by changes in IPFP volume, signal, or inflammatory profile has not yet been reported and represents a tractable test of the metabolic hypothesis.

IPFP-derived MSCs

The first isolation of MSC-type stromal cells from the IPFP was performed more than 20 years ago, and these cells have been demonstrated to be chondrogenic, osteogenic, and adipogenic [117-119]. Later studies identified a chondrogenic potential that was enhanced after growth-factor expansion in IPFP-MSCs and attributed their expression of pericyte markers to the same chondrogenic potential; and found that the chondrogenic potential was not lost when the cells were isolated from osteoarthritic donors [120-122]. Comparisons with donor-matched bone-marrow- and subcutaneous-fat-derived MSCs reveal broadly similar (but not identical) chondrogenic and osteogenic differentiation capacity, with some studies favouring bone-marrow MSCs and others comparing or showing a benefit for IPFP-MSCs on the basis of the test used [123-125]. At this time, there is no consistent evidence that IPFP-MSCs are categorically better than other sources, and comparative claims should not be interpreted as any sort of ranking.

Extracellular vesicles and exosomes

It was recently reported that EVs isolated from OA IPFP tissue disrupt the metabolism of chondrocytes and cause chondrocytes to become senescent when challenged with EVs in vitro, potentially through the delivery of miRNA and protein cargo that can influence the behaviour of the recipient cell [39,126]. This work extends the potential signalling repertoire of the IPFP to the transmission of signals mediated by vesicles between chondrocytes, synoviocytes, and macrophages [127]. The field is still nascent: although a great deal of information about the composition of the cargo and the functional consequences has come from the work on explant and cell culture experiments, the bulk of this information is still of a preclinical/early translational nature and should not be considered clinically established.

Senescence and ageing

Similar to other adipose depots and cartilage, senescence and related senescence-associated secretory

phenotype (SASP) have been suggested as factors contributing to dysfunction of IPF with aging [23,39]. Direct longitudinal human evidence of the role of ageing in the development of a pro-inflammatory secretory phenotype of adipocytes and stromal cells, and of the connection of these changes to the onset of OA, is still limited, but oxidative stress and mitochondrial dysfunction in the ageing adipocytes and stromal cells are potential upstream mechanisms linking ageing, chronic low-grade inflammation, and OA progression [128].

Does the IPFP protect or damage the joint?

The question is central in the conceptual dimension of the review. These include mechanical cushioning and load distribution, maintenance of joint homeostasis, production/release of adipokines that may have reparative and/or anti-inflammatory effects under normal conditions, and function as a local source of MSC-like cells with potential for regeneration [121,129]. Pro-inflammatory cytokine and adipokine production and secretion, macrophage activation and recruitment, progressive fibrosis [41], nociceptive signalling [37], and synovial activation through paracrine crosstalk [31] are potential functions that might be harmful in the osteoarthritic state. The best available synthesis thus far is that the IPFP is not a tissue that is permanently stunted in either role, but is more likely to become a tissue that is incapable of maintaining homeostasis (mechanically supportive) and functioning as an immunometabolic tissue as it progresses through the stages of OA; this transition is likely triggered by chronic mechanical load, ageing, obesity, and injury, yet has not been longitudinally demonstrated within the same human joints over time [14]. Table *3* summarizes representative human studies evaluating the IPFP in knee OA.

Author/year	Study design	Population	n	IPFP assessment	Major finding	Clinical relevance	Limitation
Ushiyama et al. [29] (2003)	Human explant culture	Knee OA patients undergoing TKA	Not specified in review	Cytokine release from IPFP explants	IPFP releases IL-6, IL-8, and other cytokines into culture medium	Identifies IPFP as an additional local cytokine source beyond synovium	End-stage tissue only; no healthy controls
Distel et al. [28] (2009)	Human explant/tissue analysis	Knee OA patients	Small cohort	IL-6 and soluble IL-6 receptor secretion	IPFP is a substantial local source of IL-6/sIL-6R	Supports paracrine signalling to joint	Cross-sectional, arthroplasty tissue
Clockaerts et al. [30] (2012)	Human explant, stimulation study	Knee OA patients	Small cohort	Cytokine output under IL-1β/PPAR-α modulation	IPFP cytokine secretion is reactive, not fixed	Suggests targetable regulatory pathways	In vitro stimulation; physiological relevance uncertain
Eymard et al. [31] (2014)	Human explant co-culture	Knee OA patients	Small cohort	IPFP-conditioned medium effect on autologous synoviocytes	Induces inflammatory, prodegradative synoviocyte phenotype	Direct mechanistic evidence for IPFP-to-synovium signalling	Co-culture system; not in vivo confirmation
Klein-Wieringa et al. [43] (2016)	Human histology, comparative	End-stage knee OA	Cohort from a single center	Comparison of inflammatory cells in synovium vs IPFP	IPFP inflammatory profile parallels adjacent synovium	Supports IPFP-synovial functional unit concept	Cannot establish directionality of signalling
Favero et al. [41] (2017)	Histology and molecular analysis	Knee OA patients undergoing TKA	Moderate cohort	Histopathology of IPFP (fibrosis, vascularity, inflammation)	OA IPFP shows fibrosis, neovascularisation and inflammatory infiltrate	Characterises multi-domain IPFP pathology	Single time-point, end-stage sampling
Roemer et al. [17] (2009)	MRI cohort analysis	Knee OA/at-risk cohort	Cohort-level (MOST-related)	Hoffa synovitis on unenhanced MRI	MRI signal change is a feasible surrogate for patellofemoral synovitis	Enabled subsequent MRI-biomarker research	Signal change not directly validated against histology in same subjects
Cen et al. [112] (2023)	Longitudinal MRI cohort	Knee OA cohort	Cohort-level	Quantitative IPFP signal-intensity alteration	Signal-intensity alteration, not volume, associated with structural progression	Supports signal change as a progression marker	Observational; residual confounding possible
Pelletier et al. [110] (2025)	Longitudinal exploratory cohort	Knee OA patients	Cohort-level	IPFP morphology over time	IPFP morphology proposed as independent prognostic marker	Adds to longitudinal IPFP-progression evidence base	Exploratory; requires external replication
Cao et al. [39] (2024)	Human explant, EV isolation	Knee OA patients	Small cohort	IPFP-derived extracellular vesicles applied to chondrocytes	EVs impair chondrocyte metabolism and induce senescence in vitro	Extends IPFP signalling to vesicle-mediated pathways	In vitro exposure; concentrations may not reflect in vivo levels

TABLE 3: Key human studies evaluating the IPFP in knee OA.

OA: osteoarthritis; TKA: total knee arthroplasty; IPFP: infrapatellar fat pad; IL-6: interleukin-6; IL-8: interleukin-8; sIL-6R: soluble interleukin-6 receptor; IL-1β: interleukin-1 beta; PPAR-α: peroxisome proliferator-activated receptor alpha; MRI: magnetic resonance imaging; MOST: Multicenter Osteoarthritis Study; EVs: extracellular vesicles

IPFP resection during TKA

Partial or complete IPFP excision is a routine procedure when performing a TKA and is generally done to ensure better patellar visualization and surgical exposure [130]. There have been no consistent, clinically significant differences in patient-reported outcomes, range of motion, or anterior knee pain between preservation and resection in the literature; however, due to variability in the extent of resection and outcome measures used in the different trials, it is difficult to draw specific conclusions from the systematic reviews and meta-analyses of randomized trials comparing the two strategies [131]. A more recent double blind randomized study confirmed this with no impact of fat pad resection on functional outcome or gait parameters [132]. The absence of obvious harm from resection in current trials should be taken with a pinch of salt; conclusions should not be based on low-quality observational studies alone, and most trials have

limited follow-up and small numbers of patients.

Therapeutic targeting of IPFP

Weight loss and exercise are the best supported interventions to date to improve the metabolic and mechanical loading of the IPFP and the wider OA joint, upstream of many of the molecular pathways presented in this review [115,116]. The pharmacological approach is still experimental in OA, and clinical trial data are scarce and disappointing for several systemic cytokine inhibitors in unselected OA populations, other than cytokine-directed and adipokine-directed drugs, such as IL-1 pathway and/or NAMPT inhibitors [133,134]. Randomized placebo-controlled trials of TNF inhibition with adalimumab or etanercept in hand OA likewise did not show a clinically meaningful benefit on pain [135-137]. Conceptually, anti-fibrotic and macrophage-modulating strategies could be promising, and have reached only the pre-clinical and early exploratory stages, specific to IPFP [51]. Intra-articular delivery of therapeutic agents based on IPFP vascularity and stromal-cell content is still at the early stage of interest and is not yet a common practice (Table *4*). Patient safety should also be considered for commonly used non-prescription OA products: a generalized pruritic rash with facial swelling developing within hours of a glucosamine-chondroitin supplement, requiring antihistamines and corticosteroids, has been reported [138], so clinicians should ask about supplement use and counsel patients on possible adverse effects.

Target/pathway	Proposed intervention	Mechanistic rationale	Current evidence	Development stage	Key limitation
Systemic mechanical/metabolic load	Weight loss, structured exercise	Reduces joint loading and systemic/local metabolic drivers of inflammation	Well established in general knee OA literature	Established clinical practice	Not IPFP-specific; effect on IPFP biology inferred, not directly measured
IL-1/TNF-α signalling	Cytokine-pathway inhibition	Reduces downstream catabolic and inflammatory signalling	Limited, largely disappointing trial evidence in unselected knee OA	Experimental/largely discontinued for OA	Systemic inhibitors not tissue-selective; unclear IPFP-specific benefit
NAMPT/visfatin	Enzymatic inhibition	Reduces inflammatory mediator and MMP induction	Preclinical and early mechanistic studies	Preclinical	No validated human trial data in OA
CCL2/CCR2 axis	Chemokine-receptor antagonism	Limits monocyte/macrophage recruitment and fibrosis	Preclinical (rat) fibrosis model evidence	Preclinical	Not tested in human IPFP or clinical OA cohorts
TGF-β/fibrosis pathway	Anti-fibrotic agents	Limits myofibroblast differentiation and collagen deposition	Extrapolated from arthrofibrosis literature	Preclinical/conceptual	No IPFP-specific anti-fibrotic agent tested clinically
IPFP-resident MSCs	Autologous cell-based orthobiologic therapy	Chondrogenic and immunomodulatory potential of resident stromal cells	Human in vitro chondrogenesis data; limited comparative clinical data	Early clinical/investigational	Comparative efficacy vs other MSC sources not established
IPFP extracellular vesicles	EV-based diagnostic or therapeutic exploitation	Vesicle cargo modifies chondrocyte/synoviocyte behaviour	Single human explant study	Preclinical/exploratory	Cargo characterisation and reproducibility not yet established

TABLE 4: Potential therapeutic approaches targeting IPFP-associated pathways.

OA: osteoarthritis; IL-1: interleukin-1; TNF-α: tumor necrosis factor alpha; NAMPT: nicotinamide phosphoribosyltransferase; MMP: matrix metalloproteinase; CCL2: C-C motif chemokine ligand 2; CCR2: C-C motif chemokine receptor 2; TGF-β: transforming growth factor beta; IPFP: infrapatellar fat pad; MSCs: mesenchymal stromal cells; EV: extracellular vesicle

Orthobiologics and IPFP

In knee OA, one or more of the cell-based therapies using platelet-rich plasma (PRP), bone marrow aspirate (BMA), adipose-derived stem cells (ASCs), and MSCs are being used clinically or investigated; the IPFP is also a potential source tissue for the production of cell-based therapies and could be a resident tissue whose basal inflammatory phenotype may impact how it would respond to injected biologics [106,107,121,124]. To date, there have been no controlled clinical trials directly evaluating whether baseline inflammatory or fibrotic "phenotype" predicts differential response to orthobiologic treatment, and no claims of efficacy specifically for orthobiologic treatment for IPFP can be made beyond this hypothesis-generating rationale.

IPFP - potential role as a biomarker

Possible candidate biomarkers from the IPFP are MRI signal and volume metrics [103,110], and at an earlier stage, these may also include adipokine and cytokine levels, synovial fluid macrophage phenotype markers, and synovial fluid transcriptomic signatures (if available) [115,139]. None of these has been validated across prospective cohorts with multiple cohorts in the future to support clinical use to predict pain phenotype, structural progression, treatment response, or progression to arthroplasty, and current evidence is largely exploratory and based on single-center or cross-sectional cohorts [133].

Clinical phenotyping of knee OA using IPFP

Increasingly, the idea of inflammatory, metabolic, mechanical, fibrotic, and pain-dominant OA phenotypes is discussed broadly in the OA literature, and IPFP biology is plausible to be a differential contributor to each of these with the tissue's secretory profile, particularly the inflammatory and metabolic phenotypes [134,140,141]. There is currently no clinical phenotyping system with IPFP-specific parameters validated for clinical use, and this section should be considered as a framework for applying a precision medicine approach in future studies (Figure *3*).

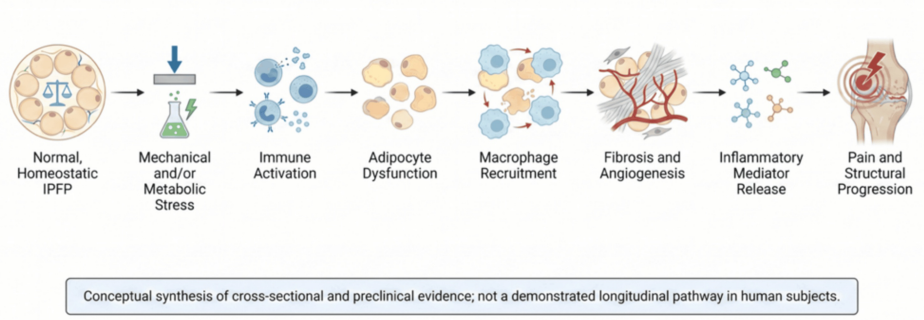


FIGURE 3: Proposed transition of the IPFP during osteoarthritis progression.

IPFP: infrapatellar fat pad

The image was created by the authors using BioRender (BioRender Inc., Toronto, Ontario, Canada).

Limitations of current evidence

Almost all the molecular and histological data in humans that are presented in the IPFP literature are cross-sectional studies from tissue samples taken at the time of arthroplasty, and so reflect end-stage disease [142]. Access to healthy control tissue is difficult to ethically achieve, and comparisons are often made with remote adipose depots (subcutaneous fat) as opposed to structurally normal IPFP tissue [143]. Explants and histology studies are often performed on small sample sizes and tissue processing, and the location of samples taken from the fat pad, as well as molecular assay methodology, is very variable between centres, which hinders the comparability of studies. BMI, age, sex, diabetes, severity of OA, and the use of medication and previous intra-articular injections are inconsistently addressed. Long-term human studies involving observations of IPF biology as well as pain and structural outcomes over time are limited, and much mechanistic understanding is derived from animal models or in vitro concentrations which may not be consistent with the physiological environment within the joint. Together, these restrictions seriously hinder the ability to draw firm conclusions about the role of the fat pad in the pathogenesis of OA from the majority of published associations between abnormalities of the fat pad and OA, and limit the ability to determine if it is a driver, amplifier, or consequence of disease.

Future directives

Longitudinal human cohorts that include early-stage OA, and where feasible and ethically appropriate, structurally normal comparator tissue; single-cell, spatial transcriptomic mapping of IPFP immune and stromal populations; integrated proteomic, metabolomic, lipidomic, and epigenomic profiling; systematic characterization of IPFP-derived extracellular vesicles; externally validated MRI radiomic and AI-assisted quantitative biomarkers; and, finally, studies that link molecular findings through imaging phenotypes to structural progression and patient-reported outcomes within the same longitudinal cohort, rather than as isolated cross-sectional associations.

Conclusions

The IPFP is an active, and far more than a passive, mechanical pad. Human explant, histological, and

imaging studies confirm significant endocrine, paracrine, immune, and nociceptive functions, and its close anatomical and molecular relationships with synovium and its proximity to cartilage strongly suggest that it can play an amplifying role in osteoarthritic joint pathology. But the causal evidence in humans is limited, based mainly on cross-sectional, end-stage tissue, and in vitro systems. The tissue function is likely both protective and pathological, and current surgical and pharmacological information does not support indiscriminate removal or suppression of the IPFP. Further research could clarify stage-specific and phenotype-specific IPFP biology in longitudinal human cohorts and make the IPFP a potential biomarker and a stage- and/or phenotype-specific therapeutic target of the precision-medicine approach to knee OA.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Sankalp Yadav, Anandanarayan Muruganandam, Ashwini Raja, Bhoomika V. Badrinath, Naveen Jeyaraman, Madhan Jeyaraman

Acquisition, analysis, or interpretation of data: Sankalp Yadav, Anandanarayan Muruganandam, Ashwini Raja, Bhoomika V. Badrinath, Naveen Jeyaraman, Madhan Jeyaraman

Drafting of the manuscript: Sankalp Yadav, Anandanarayan Muruganandam, Ashwini Raja, Bhoomika V. Badrinath, Naveen Jeyaraman, Madhan Jeyaraman

Critical review of the manuscript for important intellectual content: Sankalp Yadav, Anandanarayan Muruganandam, Ashwini Raja, Bhoomika V. Badrinath, Naveen Jeyaraman, Madhan Jeyaraman

Supervision: Sankalp Yadav, Anandanarayan Muruganandam, Naveen Jeyaraman, Madhan Jeyaraman

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