Synovial chondromatosis: Novel advances in understanding the pathogenesis and in diagnostic strategies (Review)

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Abstract. Synovial chondromatosis (SC) is a relatively rare benign synovial disorder characterized by the abnormal chondroid metaplasia of synovial cells, leading to the formation of multiple cartilage nodules that affect both intra-articular and extra-articular synovial tissues. Although the pathogenesis of SC remains incompletely understood, various signaling pathways, the inflammatory microenvironment and mechanical stress carry out key roles in the progression of the disease. Given the advancements in imaging techniques and the pathological mechanisms at play, early diagnosis and lesion evaluation of SC have markedly improved. In terms of treatment, both arthroscopic and open surgeries remain the primary approaches, with total synovectomy is the preferred method given the reduction in recurrence rates. The exploration of biologic agents offers novel possibilities for non-surgical management. Despite the generally benign nature of SC, recurrent occurrences and the potential for malignant transformation require careful monitoring. Future research should focus on molecular-targeted therapies, early detection and precision therapeutics to optimize clinical management and long-term outcomes of patients with SC. The present review discusses the pathogenesis, diagnostic methods, treatment strategies and future research directions of SC, aiming to provide a comprehensive theoretical framework for its clinical management.

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Abbreviations: Bcl-2, B-cell lymphoma 2; BMP-2/4, bone morphogenetic protein 2/4; C-erbB-2, receptor tyrosine-protein kinase ErbB-2; Col2A1, collagen type IIα1; Col3A1, collagen type IIIα1; C-Myc, cellular Myc; FGF2/9, fibroblast growth factor 2/9; FGFR1/2/3, fibroblast growth factor receptor 1/2/3; GLI1, GLI family zinc finger 1; HLA-DR$^+$, human leukocyte antigen-DR; IFN-γ, interferon γ; IGF-1, insulin-like growth factor 1; IL-6/17/1β, interleukin 6/17/1β; IL-6R, IL-6 receptor; JAK/STAT, Janus kinase/signal transducer and activator of transcription; MAPK/ERK, mitogen-activated protein kinase/extracellular signal-regulated kinase; MMPs, matrix metalloproteinases; MTOR, mechanistic target of rapamycin; PI3K/Akt, phosphoinositide 3-kinase/protein kinase B; PTC1, Patched 1; Smad2/3/4, Smad family proteins 2/3/4; Sox9, SRY-box 9; TGF, transforming growth factor; TNF, tumor necrosis factor; TWIST1, twist family BHLH transcription factor 1; VEGF-A, vascular endothelial growth factor A; SC, synovial chondromatosis; PSC, primary SC; SSC, secondary SC; US, ultrasonography; MRI, magnetic resonance imaging; AI, artificial intelligence

Key words: synovial chondromatosis, pathogenesis, signaling pathways, imaging diagnosis, arthroscopic surgery, recurrence, malignant transformation, personalized treatment

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1. Introduction

Synovial chondromatosis (SC), also known as synovial osteochondromatosis, is a relatively rare benign synovial lesion. The hallmark feature of SC is the formation of multiple cartilage nodules within the synovium of joints, tendon sheaths and bursae. Some of these nodules may detach into the joint cavity, forming loose bodies (1,2) (Fig. 1). SC largely affects the knee joint, followed by the hip, shoulder, elbow, ankle and wrist joints (3). It is less commonly observed in the metacarpophalangeal, interphalangeal, acromioclavicular, temporomandibular and intervertebral joints (4-6). Extraglenoid SC is commonly observed in the hands, feet, wrists and ankles, typically presenting as localized, painless masses (7). Clinically, SC can range from asymptomatic to symptomatic, with manifestations including joint swelling, pain, limited range of motion, recurrent effusion, crepitus and locking phenomena (3,8). In certain cases, palpable masses may be detected and severe cases may involve neurovascular compromise (3,8,9). SC is generally classified

into primary SC (PSC) or secondary SC (SSC) based on its etiology and histopathological features. PSC originates from the normal synovium and is characterized by the abnormal chondroid metaplasia of synovial cells (Fig. 2), with an increased number of loose bodies that are widely distributed and a greater recurrence rate (9,10). By contrast, SSC is often induced by conditions such as osteoarthritis or joint trauma, with cartilage fragments embedded in the synovium, triggering chondroid metaplasia. SSC typically presents with fewer but larger loose bodies and imaging studies often show characteristic changes related to the underlying primary disease (10,11). Although SC is a benign lesion, it has a high recurrence rate, and certain cases may transform into low-grade synovial sarcoma (SS) (9). Therefore, in-depth research into the pathogenesis of SC is essential for optimizing clinical diagnosis and treatment. The present review summarizes the latest advancements in SC research, focusing on its epidemiological trends, pathogenesis, clinical strategies and malignant potential. The aim of the present review is to highlight avenues to improve clinical recognition, optimize treatment plans and reduce the risk of recurrence and malignant transformation.

2. Epidemiology of SC

Incidence rate. SC is a relatively rare condition with an incidence of ~1 case per 100,000 individuals. It primarily affects adults between the ages of 30 and 50 years, although both infants and the elderly can also be affected (1,12,13). Earlier studies suggested that the male-to-female ratio of SC was 1.8:1, indicating a higher prevalence in males (12,13). However, other studies suggest that this ratio may range from 2:1 to 4:1 (14). Notably, in areas such as the temporomandibular joint, hands and wrists, the incidence in females may be higher compared with males (15). Furthermore, due to the often-insidious symptoms of SC, the average time to diagnosis is ~5 years (15). However, with advancements in imaging technology, the detection rate of SC has markedly increased over the years (8). The higher incidence of SC in adults may be associated with long-term joint stress and a history of trauma, while the rarity of SC in children may be related to protective mechanisms during skeletal development (14). Additionally, PSC and SSC exhibit notable differences in epidemiology. PSC is generally more common and has a higher recurrence rate, whereas SSC is primarily associated with osteoarthritis or joint injuries, being relatively rare and often confused with primary diseases (9-11,16). Extraglenoid SC is rare, typically presenting as a painless mass and there is no notable trend associated with sex or age in these cases (14).

Recurrence rate and malignant transformation rate. The recurrence rate of SC ranges from 0-31%, with the recurrence rate being lower when loose body removal and synovectomy are carried out via arthroscopy (~7.1%) (17,18). However, if the synovectomy is incomplete, the recurrence rate may rise to 20-30% (19). PSC has an increased recurrence rate compared with SSC, suggesting that PSC may exhibit more biological activity (9-11). Multiple recurrences may increase the risk of transformation into SS. Overall, the risk of malignant transformation in SC is low, typically ~5% (20). However, a study has reported a malignant transformation rate of ≤11.1% in hip joint SC cases (21), although this value may be lower in actual clinical practice due to limited follow-up times. Malignant transformation in SC is typically observed in cases with a disease duration of >5 years or in recurrent cases. Symptoms such as pain, swelling and local destruction may occur, and certain patients may exhibit cartilage matrix calcification and nuclear atypia, which resemble the features of low-grade SS (14). Compared with SSC, PSC carries a higher risk of malignant transformation, and gene fusions such as FN1-ACVR2A and chromosomal abnormalities have been detected in certain cases (22). However, to the best of our knowledge, there are currently no clear predictive markers for malignant transformation, emphasizing the need for long-term follow-up and biological assessments.

In summary, SC has a low incidence, delayed diagnosis and a higher prevalence in males. The recurrence rate of PSC is higher than that of SSC, with stronger biological activity, which may increase the risk of malignancy. The overall malignancy rate of SC is low, but cases with long-term recurrence may have potential for malignant transformation. Currently, epidemiological data on SC are limited and the mechanisms of malignancy remain unclear, with no effective predictive indicators. Further research is required on its pathogenesis, diagnostic methods and long-term prognosis.

3. Novel advances in the pathogenesis of SC

Although the exact pathogenesis of SC remains incompletely understood, recent research has revealed several potential mechanisms underlying the disease. According to the 2020 edition of the World Health Organization classification, SC has been categorized as a neoplastic disease due to its local invasiveness and clonal chromosomal changes (23). Milgram (24) categorized the pathological progression of SC into three stages: Synovial hyperplasia (Stage I), free body formation (Stage II) and stabilization (Stage III), although this staging system does not accurately predict disease progression. By contrast, Gerard *et al* (25) classified SC into four stages based on changes in synovial activity: Early chondrification, free body formation, cartilage nodule maturation and synovial atrophy. This staging system is more effective for evaluating disease activity and determining the timing of surgical intervention (25).

Regarding the pathogenesis of SC, current studies primarily focus on the differential pathological origins of PSC and SSC (7,11,26,27). PSC is hypothesized to result from abnormal chondrification of synovial cells, potentially associated with genetic mutations, signaling pathway abnormalities, inflammatory stimuli and mechanical stress (7,11,26,27). By contrast, SSC is more commonly triggered by chronic stimuli such as osteoarthritis or joint injury, primarily resulting from prolonged exposure of the synovium to mechanical stress or the embedding of cartilage fragments into the synovium (7,11). In terms of risk factors, PSC is frequently associated with genetic susceptibility, immune abnormalities and signaling pathway activation, while SSC is more likely to be influenced by local inflammation and biomechanical factors (Fig. 3) (26,27). Recently, research on the pathogenesis of SC has shifted towards the regulation of signaling pathways,

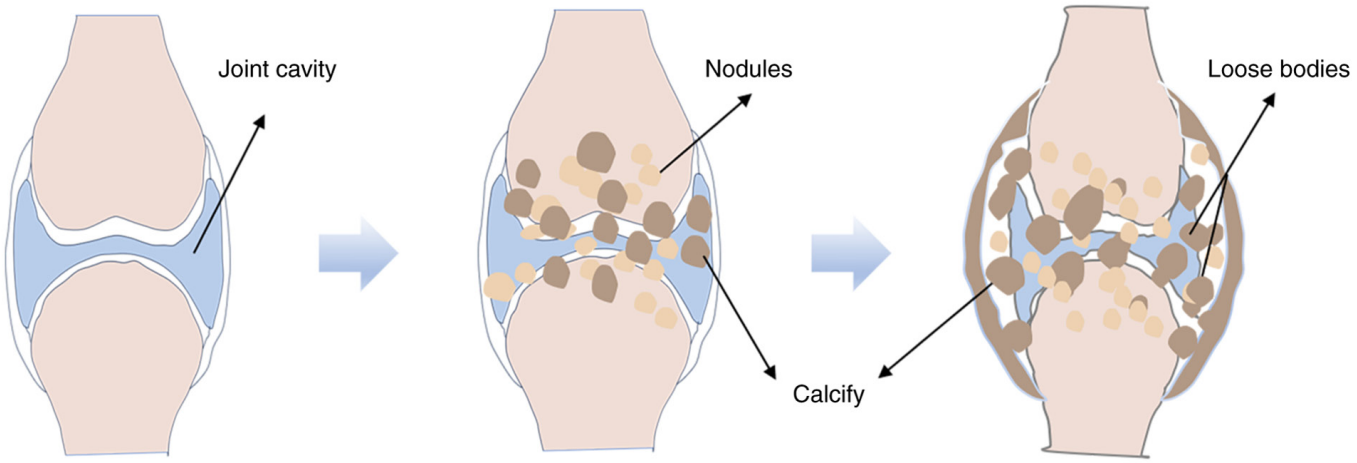

Figure 1. The progression of synovial cartilage nodule formation. As the nodules increase in size, certain areas may calcify, ultimately developing into mature synovial chondromatosis. In the later stages of the disease, normal joint structure and function are progressively destroyed, leading to joint instability and dysfunction, markedly impairing the mobility of the patient (in this figure, black arrows identify core structures such as 'joint cavity', 'nodules', 'calcifications' and 'loose bodies' at each stage; large blue arrows indicate the sequential process of synovial cartilage nodule formation).

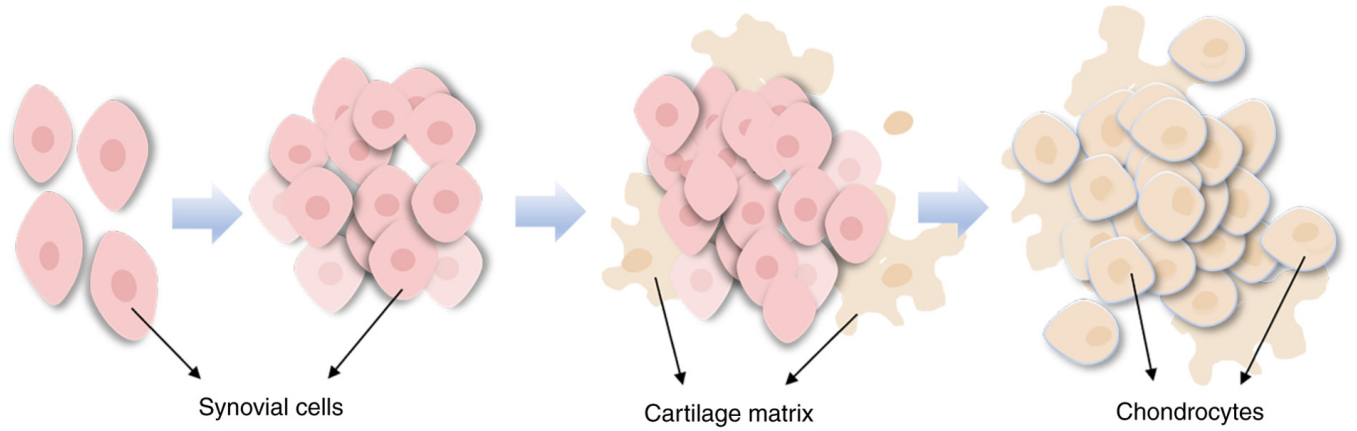

Figure 2. Schematic illustration of synoviocyte chondrogenic metaplasia in SC. This figure illustrates the process of chondroid metaplasia in synovial cells in SC. As the cells proliferate and secrete cartilage matrix, the matrix accumulates between the cells and synovial cells gradually differentiate into chondrocytes, ultimately leading to chondrogenesis and calcification. SC, synovial chondromatosis (in this figure, black arrows identify core components such as synovial cells, cartilage matrix and chondrocytes at each stage; large blue arrows indicate the sequential process of synoviocyte chondrogenic metaplasia).

changes in the synovial microenvironment and genetic characteristics. Several potential pathogenic mechanisms have been proposed in previous studies (28-33). This section discusses the pathogenesis of SC in terms of signaling pathway abnormalities, inflammatory microenvironment and mechanical stress (Table I).

The role of signaling pathways in the pathogenesis of SC. Occurrence of SC involves multiple signaling pathways, with the Hedgehog, FGF9/FGFR3 and TGF-β pathways being considered the most key (28-30) (Fig. 4). Overactivation of the Hedgehog signaling pathway induces abnormal proliferation of synovial cells and promotes their differentiation into chondrocytes. A study has shown that elevated expression of PTC1 and GLI1 genes in PSC patient tissues suggests that the Hedgehog signaling pathway may carry out a pivotal role in SC pathogenesis (28). Furthermore, the FGF9/FGFR3 pathway promotes chondrification of synovial cells through the abnormal activation of the MAPK/ERK signaling axis, accelerating disease progression. The notably elevated FGF9 levels in tissues of patients with PSC further corroborate this mechanism (29). The abnormal activation of the TGF-β signaling pathway also carries out a significant role in the pathogenesis of SC, as TGF-β1 promotes synovial cell proliferation and cartilage matrix formation via both Smad-dependent and independent pathways, exacerbating disease progression (30). In addition to these pathways, TGF-β3, FGF2 and IL-6 may also contribute to SC development (31,32,34). Although these signaling pathway abnormalities have been confirmed, their specific roles in different stages and subtypes of SC require further investigation (28-32,34).

Role of the inflammatory microenvironment in SC pathogenesis. The development of SC is associated with its inflammatory microenvironment (Fig. 5). A study has shown that IL-6 and VEGF-A levels are considerably elevated in the synovial fluid of patients with SC, where IL-6 enhances inflammation via the JAK/STAT signaling pathway and

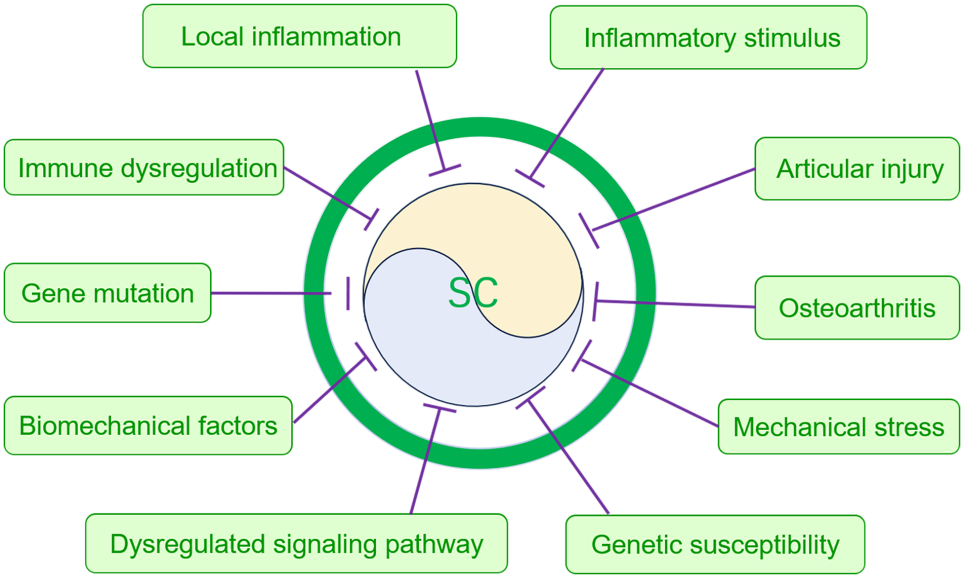

Figure 3. Schematic diagram of the key factors affecting SC. SC, synovial chondromatosis.

VEGF-A promotes angiogenesis, potentially leading to chronic inflammation and accelerating disease progression (31). In patients with PSC, an increase in CD68+ synovial macrophages and human leukocyte antigen-DR-positive cells indicates that immune dysregulation carries out a key role in the pathogenesis of PSC (35). At the molecular level, the co-expression of COL3A1 and CD90 synergistically promotes the synthesis of glycosaminoglycans and COL2A1, enhancing chondrocyte migration and proliferation. These molecules contribute to the pathogenesis of SC through immune and metabolic pathways and may serve as potential diagnostic markers to distinguish PSC from SSC (36). Additionally, the overlapping expression of biomarkers such as PCNA, CD90, CD105, IGF-1 and TGF-β1 in PSC cartilage nodules highlights the complex interactions between cell proliferation, mesenchymal stem cells and cartilage formation (37). Elevated expression of BMP-2 and BMP-4 in SC lesions further supports their key role in chondrification (38), while overexpression of C-erbB-2 in certain PSC tissue samples may be associated with synovial cell proliferation and disruptions in signaling pathways (39). Moreover, abnormal proliferation of CD34+ progenitor cells, in conjunction with TWIST1, TGF-β1 and Harmane, may promote osteogenic differentiation, accelerating chondrification and calcification processes (40). Synovial hyperplasia, angiogenesis and proteoglycan deposition are key pathological features of SC lesions (31). By contrast, the inflammatory microenvironment in SSC is primarily driven by joint damage, with its inflammatory state closely associated with the progression of the primary disease. Furthermore, synovial macrophages, through M1/M2 polarization, carry out a key role in cartilage degradation and regeneration. M1 macrophages promote inflammation and cartilage degradation, while M2 macrophages support cartilage repair and regeneration (35).

Role of mechanical stress in the pathogenesis of SC. Mechanical stress carries out a key role in the pathogenesis of SSC (Fig. 5). Prolonged mechanical stress can induce synovial cell proliferation and promote chondrification through the regulation of CD105 and CD90 (33,41). Moreover, mechanical stimulation may further enhance the expression of pro-inflammatory factors such as TNF-α and IL-1β, promoting synovial cell proliferation and chondrification (31). Under mechanical stress, synovial stem cells may differentiate into chondrocytes, ultimately leading to SC lesions. Patients with SSC often exhibit subchondral bone sclerosis, joint space narrowing and osteophyte formation in affected areas, suggesting that SSC may be an adaptive proliferative response of the synovium to prolonged mechanical stress (41).

Overall, PSC is primarily driven by signaling pathway abnormalities, while SSC is more influenced by inflammation and mechanical stress. Factors such as IL-6 and VEGF-A may promote disease progression, but the specific roles of these mechanisms in the disease process require further clarification. To the best of our knowledge, there is currently no unified pathogenic model and future research should focus on in-depth exploration of these mechanisms and their key regulatory factors. A deeper understanding of the pathogenesis of SC will provide theoretical support for clinical molecular biological diagnosis and targeted drug therapy.

4. Diagnosis and differential diagnosis of SC

Diagnosis. SC manifests with a range of clinical symptoms. The most common include persistent joint pain, typically rated between 5 and 7 on the VAS scale, which intensifies as the disease progresses (3,8,9). With SC, 75-85% of patients experience mechanical dysfunctions, such as joint popping, locking and a reduced range of motion, often associated with intra-articular loose bodies. A total of 85-90% of patients present with recurrent joint swelling and increased local skin temperature, indicating an inflammatory response. In patients with a disease duration >3 years, nerve compression symptoms (such as numbness in the branches of the trigeminal nerve) and secondary osteoarthritis may develop. These symptoms not only reflect the severity of the disease but also provide key

Table I. Key signaling pathways and their mechanisms in synovial chondromatosis with experimental evidence.

Signaling pathway	Key regulators and effectors	Biological function	Experimental evidence	(Refs.)
Hedgehog	GLI1, PTC1, Gli3, Cyclin D1, Col2A1	Synovial cell proliferation, accelerated chondrogenesis	PTC1 and GLI1 gene expression in PSC tissues increased 8-fold and 6-fold, respectively, compared with normal synovium tissue, in Gli3-deficient mouse models, Hedgehog pathway inhibition reduced SC lesion incidence by 50%.	(28)
TGF-β	TGF-β1, Smad2/3, Aggrecan, Sox9	Cartilage matrix synthesis, enhanced cell migration	Animal models confirmed TGF-β1 overexpression directly induces synovial fibroblast differentiation into chondrocytes (223-fold increase in type II collagen), TGF-β1 drives chondrometaplasia via MMP-13 (300-fold) and osteopontin (130-fold) upregulation.	(30)
FGF9/FGFR3	FGF9, MAPK/ERK, c-Myc, Bcl-2	Chondrometaplasia, apoptosis	FGF9 levels elevated 3-5-fold in PSC tissues, FGFR3 inhibitors reduced cartilage nodules by 62%.	(29,32)
IL-6	IL-6, STAT3, VEGF-A, MMPs	Angiogenesis, cartilage degradation	IL-6 concentration in SC synovial fluid was 150-fold higher than the controls, VEGF-A levels in the lesion group were 60-fold higher than in controls.	(31)
Mechanical stress	TNF-α, CD105, Ca^{2+}	Adaptive synovial hyperplasia, osteophyte formation	Stress stimulation upregulates TNF-α/CD105.	(31,33)

Bcl-2, B-cell lymphoma 2; Col2A1, collagen type IIα1; C-Myc, cellular Myc; FGFR3, fibroblast growth factor receptor 3; GLI1, GLI family zinc finger 1; IL-6, interleukin 6; MAPK/ERK, mitogen-activated protein kinase/extracellular signal-regulated kinase; MMPs, matrix metalloproteinases; PTC1, patched 1; Smad2/3, smad family proteins 2/3; Sox9, SRY-box 9; TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor α; VEGF-A, vascular endothelial growth factor A.

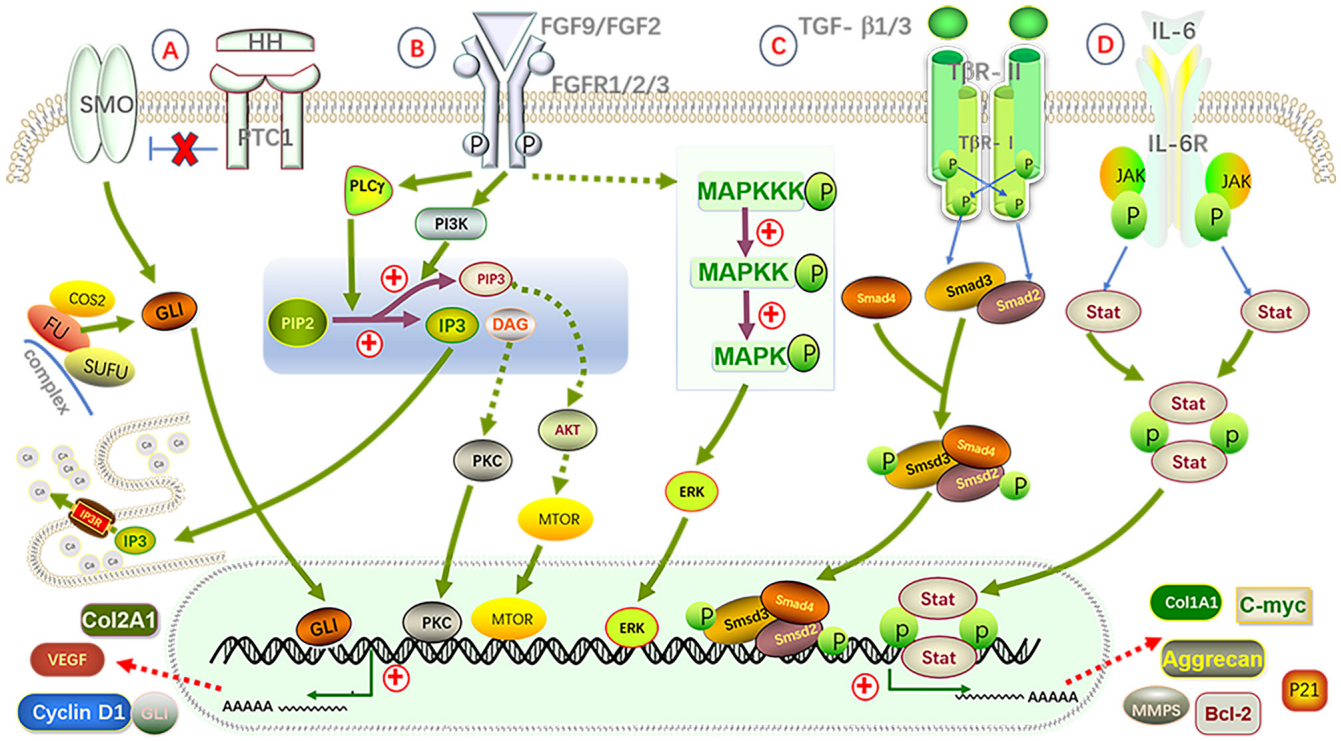

Figure 4. Schematic diagram of the roles of four major signaling pathways (Hedgehog, FGF, TGF-β and IL-6) in the pathogenesis of SC. (A) Hedgehog pathway: The HH ligand binds to the PTC1 receptor, relieving the inhibition of the SMO receptor, which activates Gli proteins and causes them to dissociate from the complex formed by COS2, FU and SUFU. This activation subsequently upregulates the expression of genes such as Cyclin D1, Col2A1 and Aggrecan. (B) FGF pathway: After the FGF ligand binds to the FGFR receptor, it activates the IP3-DAG-PKC, MAPK/ERK and PI3K/Akt signaling pathways, leading to the expression of genes including calcium ions, Cyclin D1, Bcl-2 and c-Myc. (C) TGF-β pathway: The TGF-β ligand binds to the TGF-βRII receptor, activating the tyrosine phosphorylation of the TGF-βRI receptor, which in turn activates the Smad2/3 signaling pathway. The activated Smad complex then enters the nucleus, regulating genes associated with chondrogenesis and cell proliferation, such as Col2A1, Aggrecan, Sox9 and Cyclin D1. (D) IL-6 pathway: IL-6 binds to its receptor IL-6R, activating the JAK/STAT signaling pathway, which promotes the expression of Cyclin D1, c-Myc, Bcl-2 and VEGF. Ultimately, the upregulation of these genes promotes cell proliferation, inhibits apoptosis, accelerates synovial cell differentiation and chondrogenesis, and thus facilitates the formation of SC. Bcl-2, B-cell lymphoma 2; c-Myc, cellular Myc; Col2A1, collagen type IIα1; DAG, diacylglycerol; FGFR, fibroblast growth factor receptor; FGF, fibroblast growth factor; Gli, Glioma-associated oncogene homolog; HH, Hedgehog; IL-6, interleukin 6; IL-6R, IL-6 receptor; IP3, inositol 1,4,5-trisphosphate; IP3R, inositol 1,4,5-trisphosphate receptor; JAK/STAT, Janus kinase/signal transducer and activator of transcription; MAPK/ERK, mitogen-activated protein kinase/extracellular signal-regulated kinase; MMPs, matrix metalloproteinases; mTOR, mechanistic target of rapamycin; PI3K/Akt, phosphoinositide 3-kinase/protein kinase B; PIP2, phosphatidylinositol 4,5-bisphosphate; PKC, protein kinase C; PTC1, Patched 1; SC, synovial chondromatosis; Smad2/3/4, Smad family proteins 2/3/4; Sox9, SRY-box 9; SMO, Smoothened; SUFU, suppressor of FU; TGF-βRI, transforming growth factor-β receptor I; VEGF, vascular endothelial growth factor; COS2, Costal 2; FU, Fused.

clues for clinical diagnosis and management (3,8,9). They offer clinicians essential insights to assess the severity of the disease and progression. In practice, doctors typically devise personalized treatment plans based on both the patient's subjective symptoms and imaging results.

The clinical presentation of early-stage SC is characterized by a lack of specificity, which poses considerable difficulties for accurate diagnosis. Ultrasonography (US), x-ray, computed tomography (CT), magnetic resonance imaging (MRI) and pathological examinations form a diagnostic system that progresses from basic to advanced methods, complementing each other. Among these, MRI is regarded as the most optimal imaging modality, capable of thoroughly evaluating synovial lesions and surrounding tissue involvement. However, pathological examination remains the definitive diagnostic tool (42). Furthermore, other diagnostic methods have become increasingly important in diagnosing SC.

US. US is primarily used for early screening and postoperative monitoring. It can detect synovial thickening, effusion and free bodies and dynamically assess the activity of the lesions (7,42). However, US has limited sensitivity for detecting non-calcified lesions and is inadequate in accurately determining the size and number of cartilage nodules, particularly in deep joints such as the hip, thus limiting its role in final diagnosis (14).

X-ray. X-ray remains the first choice for imaging in SC, effectively screening for lesions and providing preliminary staging information (14). The typical X-ray features of PSC include multiple spherical or ring-shaped calcifications within the joint cavity, while SSC typically involves calcification patterns that are irregular and may overlap with osteoarthritis calcifications, complicating the diagnosis (7,42). Additionally, x-ray is less sensitive for detecting extra-articular SC and soft tissue calcifications may be misdiagnosed as tendon calcifications. Non-calcified SC or early-stage cases may appear normal on x-rays, necessitating further evaluation with CT or MRI (43).

CT. CT carries out a key role in the early diagnosis of SC, especially in evaluating fine calcifications and bone destruction (7).

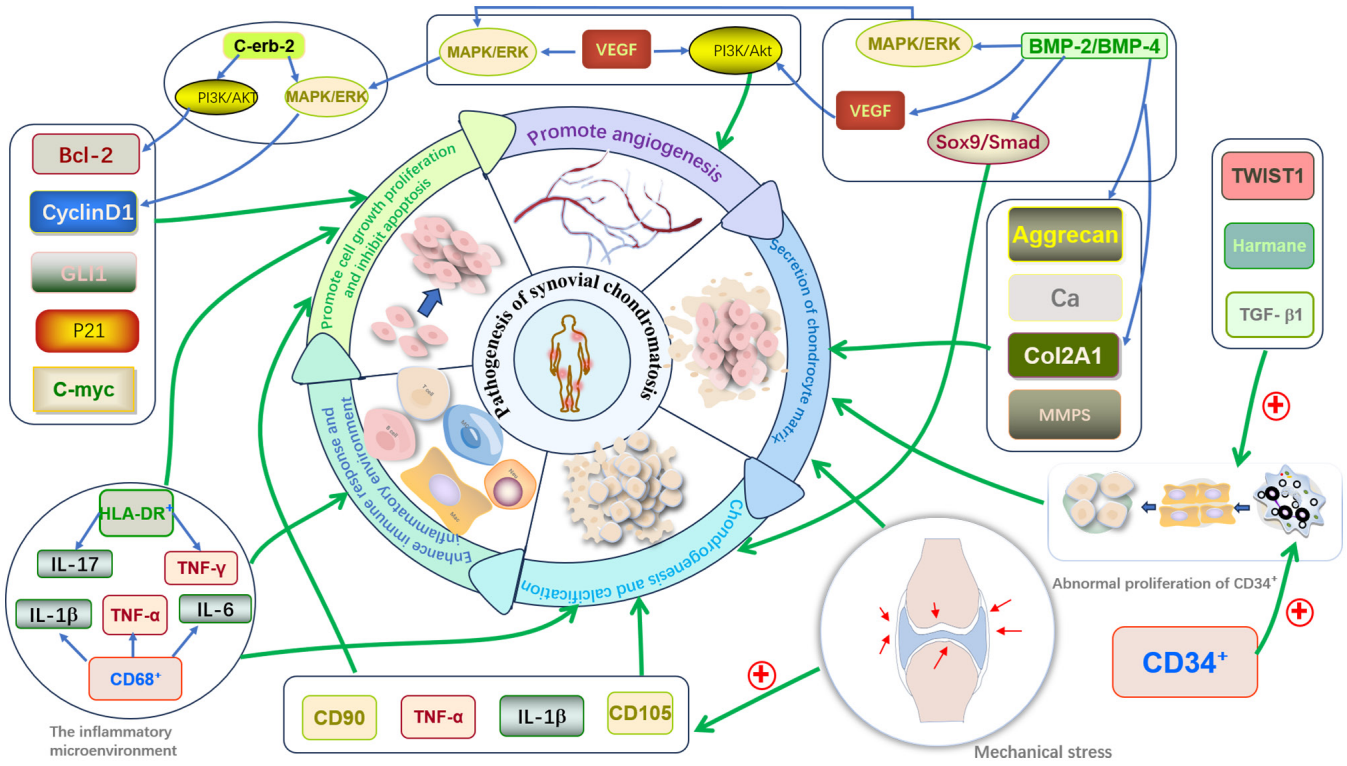

Figure 5. Schematic diagram of the impact of signaling pathway regulatory products, inflammatory microenvironment and mechanical stress on the pathogenesis of SC. i) Impact of factors: Bcl-2, Cyclin D1, GLI1, P21 and c-Myc primarily promote the growth and proliferation of synovial cells and inhibit apoptosis. Aggrecan, calcium ions, Col2A1 and MMPs promote the synthesis of cartilage matrix and cartilage repair. VEGF-A promotes cell proliferation and angiogenesis through the MAPK/ERK and PI3K/Akt pathways. ii) Impact of an inflammatory microenvironment: CD^+macrophages and $HLA\text{-}DR^+$cells secrete inflammatory cytokines, such as IL-1β, TNF-α, IL-6, IL-17 and IFN-γ. These cytokines enhance synovial inflammation, strengthen immune responses and accelerate synovial cell proliferation. iii) Impact of mechanical stress: Mechanical stress upregulates the expression of TNF-α, IL-1β, CD105 and CD90, promoting synovial cell proliferation, cartilage matrix synthesis, chondrogenesis and calcification, further driving the formation of chondromas. iv) Impact of other factors: Other factors, such as C-erbB-2, promote the proliferation of synovial cells through the MAPK/ERK and PI3K/Akt pathways and inhibit apoptosis. The abnormal proliferation of $CD34^+$progenitor cells provides a source of cells for chondrogenesis and calcification. TWIST1, TGF-β1 and harmine act synergistically to further promote the formation and progression of SC. These factors and mechanisms interact through different signaling pathways, collectively driving the occurrence and development of SC. Bcl-2, B-cell lymphoma 2; BMP-2/4, bone morphogenetic protein 2/4; c-Myc, cellular Myc; Col2A1, collagen type IIα1; erbB-2, receptor tyrosine-protein kinase ErbB-2; Gli1, glioma-associated oncogene homolog 1; $HLA\text{-}DR^+$, human leukocyte antigen-DR; IL-6/17/1β, interleukin 6/17/1β; MAPK/ERK, mitogen-activated protein kinase/extracellular signal-regulated kinase; MMPs, matrix metalloproteinases; PI3K/Akt, phosphoinositide 3-kinase/protein kinase B; SC, synovial chondromatosis; Smad, Smad family protein; Sox9, SRY-box 9; TGF-βRI, transforming growth factor-β receptor I; TNF-α/γ, tumor necrosis factor-α/γ; TWIST1, twist family BHLH transcription factor 1; VEGF, vascular endothelial growth factor.

The high resolution of CT allows clear visualization of small calcification points, ring-like calcifications and bone erosion, making it suitable for complex lesions or cases involving bone destruction (42,44). Furthermore, the multi-planar reconstruction function of CT helps analyze the relationship between calcified nodules, bone, synovium and soft tissues, which is especially advantageous in areas such as the hip, shoulder and ankle (44,45). However, CT is less effective for assessing synovial thickening and non-calcified cartilage nodules and MRI remains necessary for further analysis (7,45).

MRI. MRI is considered the gold standard for imaging diagnosis of SC, as it provides a comprehensive assessment of lesion extent, free body characteristics, soft tissue involvement and potential malignant transformation risks (7,46). MRI can detect non-calcified free bodies and clearly visualize synovial proliferation and cartilage matrix structure, demonstrating excellent diagnostic capability for both PSC, SSC and extra-articular SC (8). Compared with x-ray and CT, MRI offers considerable advantages in early detection of lesions, synovial activity assessment and postoperative follow-up (39). A study by Kramer *et al* (47) categorized the MRI presentation of SC into three patterns: Type A, typical calcified type, high T2 signal with focal low-signal areas, corresponding to Milgram Stage II; Type B, non-calcified type, high T2 signal without focal low-signal areas, corresponding to Milgram Stage I; and Type C, advanced ossification type, high signal intensity areas resembling fat, indicating cartilage matrix enrichment or malignant potential. This classification aids in determining the disease stage and selecting the most appropriate treatment (Table II). Additionally, MRI can help distinguish SC from SS, PVNS and other lesions, improving diagnostic accuracy (48). In early-stage SC, extra-articular SC and suspected malignant cases, the diagnostic value of MRI is irreplaceable. However, the high cost and longer examination time may necessitate complementary CT or X-ray evaluations for certain cases.

Histopathology. Although imaging carries out a key role in diagnosing SC, the final diagnosis depends on pathological analysis, which includes gross pathological and microscopic evaluations (29). Gross pathology in PSC

Table II. Milgram staging of synovial chondromatosis with corresponding Kramer MRI types and recommended surgical strategies (24,47).

Stage	Stage name	Pathological features	MRI findings (Kramer type)	Recommended surgical strategy	(Refs.)
Stage I	Synovial proliferation phase	Active cartilaginous metaplasia of the synovium without loose body formation. May be misdiagnosed as synovitis.	Kramer Type B: High T2 signal without low-signal calcification.	Early arthroscopic synovectomy is recommended to prevent disease progression and reduce recurrence risk.	(24,25,47,66,67)
Stage II	Transitional phase with loose bodies	Persistent synovial activity with formation of intra-articular loose bodies.	Kramer Type A: High T2 signal with focal low-signal calcifications.	Arthroscopic removal of loose bodies. Synovectomy as needed depending on synovial activity.	
Stage III	Loose body dominant phase	Synovial activity has diminished. Numerous mature loose bodies are present, often causing mechanical symptoms.	Kramer Type C: Mixed high signals with fat-like or erosive features.	Focus on loose body removal. Synovectomy is usually unnecessary and reserved for specific symptoms.	

MRI, magnetic resonance imaging.

typically reveals multiple translucent blue-white cartilage nodules with smooth surfaces; by contrast, SSC presents as localized cartilaginous metaplasia accompanied by chronic synovial inflammation and fibrosis (49,50). Microscopic examination of PSC reveals abundant undifferentiated chondrocytes within the synovium, rich matrix and uniform cellular arrangement, while SSC exhibits inflammatory cell infiltration, cartilage fragment deposition and fibrous tissue proliferation (49,50).

In pathological diagnosis, the gene fusion of FN1-ACVR2A and the overexpression of C-erbB-2 protein can indicate the clonal proliferation characteristics of PSC (22,38). This biomarker has considerable clinical value: In terms of diagnosis, the sensitivity of FN1-ACVR2A fusion for identifying SS is 92%, and the specificity is 100% (22); in terms of prognosis, patients with positive fusion have a 2.3-fold increased risk of recurrence, and the overexpression of C-erbB-2 is negatively associated with chemotherapy response (38). In terms of treatment, patients with positive fusion are recommended to undergo extensive synovectomy and extended follow-up for ≥5 years, while those with negative fusion can undergo local resection combined with routine 3-year follow-up (22,38). Although FN1-ACVR2A has not been included in the diagnostic criteria for malignancy, its status should be noted in the pathological report and integrated with imaging and clinical manifestations for risk-stratification management (23).

Other diagnostic methods. In addition to imaging and pathological examination, several auxiliary methods can aid in the diagnosis of SC. Electron microscopy can be used to observe the ultrastructural features of SC tissues, such as bone-cartilage differentiation, but its clinical application remains limited (51). Arthroscopy allows direct assessment of synovial proliferation and free bodies but is unable to precisely measure synovial thickness and the extent of soft tissue infiltration (10). Artificial intelligence (AI)-assisted diagnosis has shown promise in SC imaging analysis, particularly in using deep learning techniques to identify non-calcified SC, assess recurrence risks and predict malignant tendencies. However, this technology is still in the research phase and requires further validation before clinical implementation (52).

In summary, the diagnosis of SC should combine multiple diagnostic methods. US is useful for early screening and postoperative follow-up, while x-ray is the preferred method to identify calcified lesions, although non-calcified cases may be missed. CT can precisely assess calcification patterns and bone destruction, while MRI provides a comprehensive evaluation of synovial lesions, loose bodies and soft tissue involvement, making it suitable for early diagnosis and the assessment of malignancy. Definitive diagnosis still requires pathological analysis. The diagnosis of SC relies on a comprehensive evaluation of imaging and pathology, and AI-assisted diagnosis shows potential, but further research is needed for validation.

Differential diagnosis. SC must be differentiated from all diseases that may cause intra-articular free bodies or synovial proliferation, including crystal deposition diseases (such as calcific tendinitis and hydroxyapatite deposition), osteochondral free bodies (such as osteochondritis dissecans), arthritis-related lesions (such as rheumatoid arthritis,

Table III. Comparative analysis of SC and SS.

Category	SC	SS	(Refs.)
Clinical features	Benign lesion, rare malignant transformation (5%), predominantly affects large joints (knees/hips), presenting with joint pain, crepitus and limited mobility, peak incidence: Middle-aged adults (30-50 years).	Malignant tumor with aggressive behavior, typically occurs in deep soft tissues near joints, presenting as a rapidly growing mass with neuropathic pain/numbness, peak incidence: Young adults (15-40 years; median 25 years).	(1,12-14,20)
Imaging findings	MRI: Joint space expansion with homogeneous T2-hyperintense nodules/target sign of loose bodies, CT: Multiple calcified/ossified loose bodies.	MRI: Heterogeneously enhancing soft tissue mass with hemorrhage/necrosis, CT: Minimal calcification, frequent bone invasion.	(7,21,42,46, 47,52)
Histopathology	Synovial chondrometaplasia forming hyaline cartilage nodules, no cellular atypia, low proliferative activity, IHC: Strong VEGF-A expression.	Biphasic (epithelioid + spindle) or monophasic spindle patterns, Marked cellular atypia with frequent mitoses, IHC: EMA/CK/BCL-2 positive, SS18-SSX fusion+.	(29,42,49, 50,55,56)
Molecular markers	No specific mutations, potential Hedgehog/TGF-β pathway involvement.	Pathognomonic t(X;18)(p11.2;q11.2) translocation with SS18-SSX fusion (>95% cases).	(28,29, 30,55)
Management and prognosis	Surgical excision of loose bodies + synovectomy, low recurrence (<10%), excellent prognosis.	Wide resection + chemo/radiotherapy, high local recurrence, 5-year survival 50-80%, metastatic risk (lungs/bones).	(1,17,21,55)

SC, synovial chondromatosis; SS, synovial sarcoma; VEGF-A, vascular endothelial growth factor-A; IHC, immunohistochemistry; EMA, epithelial membrane antigen; CK, cytokeratin; BCL-2, B-cell lymphoma 2; SS18-SSX, SS18-SSX fusion gene; TGF-β, transforming growth factor β.

degenerative arthritis and osteoarthritis), synovial proliferative diseases [such as pigmented villonodular synovitis (PVNS) or synovial hemangiomas], and other conditions (such as giant cell tumors of the tendon sheath, elbow joint tuberculosis, tumor-induced calcification and periarticular scleroderma) (27,53,54). The majority of these diseases can be distinguished through clinical presentation, imaging and pathological examination. However, the differential diagnosis between PSC and SS is particularly notable, as misdiagnosis can lead to unnecessary overtreatment, while failure to diagnose may delay treatment and compromise the outcome (52).

Imaging differentiation. Imaging findings are the cornerstone for differentiating SC from SS (27). SC typically presents with cartilage nodules on the synovial surface, multiple free bodies in the joint and mild synovial thickening (2). By contrast, SS appears as an irregular soft tissue mass around the joint, with fewer free bodies (47). The calcification patterns in SC are typically ring-like, clustered or lobulated, which are characteristic of cartilage calcification (7,42). Conversely, SS presents as diffuse, patchy or punctate calcification with uneven distribution (52). SC lesions are generally confined to the synovium and rarely infiltrate deep tissues, whereas SS is more prone to invasion of muscles, nerves and blood vessels, with widespread edema and soft tissue infiltration visible on MRI (21,52). The degree of local tissue destruction also differs. SC shows mild bone erosion on the joint surface, with localized bone defects visible on CT and preserved bone cortex, while SS tends to cause bone destruction, periosteal reaction and marrow infiltration, indicating a higher degree of aggressiveness (7,21,52).

Histopathological differentiation. Histopathological examination further aids in distinguishing SC from SS. Microscopically, PSC shows translucent cartilage nodules with a regular arrangement of chondrocytes and few signs of atypia, necrosis or abnormal mitosis. By contrast, SS is characterized by high cellular density, disorganized arrangement of small round cells, active mitotic figures and may exhibit a biphasic pattern (epithelial-like and spindle cells) (42,55,56). Molecular markers can provide more definitive diagnostic evidence. In PSC, Bcl-2 protein expression is low, whereas SS shows high Bcl-2 expression. Additionally, SYT-SSX gene fusion [t (X;18) (p11.2; q11.2)] is a specific marker for SS, which is not present in SC (Table III) (55).

In summary, the typical imaging features of SC include loose bodies, multiple calcifications and localized synovial thickening, which are indicative of a benign mass, while SS is characterized by aggressive growth, soft tissue infiltration, bone destruction and specific gene fusions, suggesting malignancy. A combined approach of imaging, pathology and molecular testing can help improve diagnostic accuracy, reduce misdiagnosis and optimize clinical management. Although SC and SS show notable differences in imaging and molecular features, diagnosis remains challenging due to

overlapping imaging characteristics with other diseases and the need for improved sensitivity and specificity of molecular markers. Future research should focus on optimizing the combined use of imaging diagnostics and molecular testing, as well as exploring the potential of AI-assisted diagnosis to enhance early diagnostic accuracy and efficiency.

5. Treatment of SC

The treatment of SC should be individualized based on the extent of the lesion, symptom severity, and the functional requirements of the patient. Although SC has a certain degree of self-limitation, the mechanical irritation from free bodies and secondary joint damage can exacerbate symptoms, necessitating active intervention. Current treatment options include conservative and surgical approaches, with surgery remaining the primary treatment modality (57). However, the necessity of synovectomy continues to be debated (58).

Non-surgical treatment is appropriate for patients with mild or no symptoms, primarily involving non-steroidal anti-inflammatory drugs, activity modification and physical therapy to alleviate pain and delay disease progression (59,60). Additionally, biological agents such as FGF9 signaling pathway inhibitors and TNF inhibitors may provide novel strategies for non-surgical management of SC, although large-scale clinical validation is lacking (61,62). Currently, chemotherapy and radiotherapy lack clear evidence of efficacy in SC and are rarely used clinically, showing no significant advantages pre- or post-operatively. By contrast, radioactive synovectomy, especially with 188 rhenium-sulfide colloids, has shown potential in lesion removal and may reduce postoperative recurrence risk (63,64).

Surgical treatment remains the first-line option for patients with notable symptoms, impaired joint function or secondary joint damage (58). Arthroscopic surgery is widely used in cases with localized lesions and small joint cavities due to its minimally invasive nature, rapid recovery and preservation of post-operative function (65). Open surgery is suitable for patients with extensive synovial hyperplasia or involvement both inside and outside the joint, as it allows for more complete lesion removal and reduces the risk of recurrence, particularly in severe cases of knee SC (57,58).

The necessity of synovectomy in surgical treatment remains contested. Certain studies suggest that removing only the free cartilage bodies may suffice to control the condition, while others argue that combining synovectomy can reduce the recurrence rate (64,66,67). The Milgram staging system (24) may help explain this controversy: Stage I, where there is no free body, may necessitate synovectomy; Stage II, with free body formation, allows for arthroscopic removal of cartilage bodies while preserving the synovium; Stage III, with multiple free bodies that are no longer forming, prioritizes free body removal with less emphasis on synovectomy (66,67). Furthermore, while synovectomy can reduce recurrence rates, it may increase postoperative complications and decisions should be based on the stage of the lesion and individual risk of recurrence. Joint replacement surgery is indicated for patients with severe joint destruction and widespread osteoarthritis (68). As SC may continue to form free bodies, the long-term stability of joint replacements remains an area for further research (69).

In summary, the treatment of SC primarily involves surgery, with arthroscopy as the preferred method; open surgery is considered for extensive or recurrent cases. The necessity of synovectomy depends on the assessment of the stage of the disease and the risk of recurrence. In the future, SC treatment may move towards precision medicine, including molecular targeted therapy, imaging-assisted decision-making and novel surgical strategies, to optimize clinical management and improve long-term prognosis.

6. Conclusion

Despite pronounced progress in understanding the pathogenesis and therapeutic strategies of SC, challenges remain in elucidating the mechanisms of pathological transformation and in the pursuit of precision medicine for this condition. The pathogenesis of PSC is primarily driven by abnormalities in the Hedgehog, FGF9/FGFR3 and TGF-β signaling pathways, while SSC is more influenced by inflammatory microenvironments and mechanical stress. However, the molecular mechanisms underlying these processes are not yet fully understood and the risk of malignancy and the biological basis of SC remain inconclusive. Although MRI is considered the gold standard for diagnostic imaging, and AI-assisted diagnosis shows promising potential, further clinical validation is required for widespread implementation. Surgical intervention remains the cornerstone of treatment, with arthroscopy being suitable for localized lesions, while open surgery is preferred for extensive or recurrent cases. The necessity of synovectomy varies depending on the stage of the disease, and no unified standard currently exists. Current research is primarily focused on the molecular mechanisms of SC, predictive models for recurrence and risk of malignancy, exploration of molecular diagnostic techniques and the application of AI in early diagnosis and personalized treatment. Future research should continue to concentrate on the hierarchical regulation of signaling pathways, the role of the inflammatory microenvironment in disease progression and the optimization of precision treatment strategies to enhance early diagnosis, reduce the risk of recurrence and improve long-term patient outcomes.

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Authors' contributions

HL conceived the topic of study. XD made a substantial contribution to data interpretation and analysis and wrote and prepared the draft of the manuscript. HL supervised the present review and provided key revisions. XD, SL and HL contributed to manuscript revision and have read and approved the final version of the manuscript. Data authentication is not applicable.

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Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, ChatGPT-4.0 by OpenAI and DeepSeek-R1 were used for native language editing and proofreading for improving readability. AI tools were not used for any other purposes. The manuscript was subsequently revised and edited by the authors. The authors take full responsibility for the final content of this manuscript.

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