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Osteoarthritis increases the risk of inflammatory arthritis due to immune checkpoint inhibitors associated with tissue-resident memory T cells

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ABSTRACT

Objective Immune checkpoint inhibitors (ICIs) have significantly advanced cancer treatment, but they can also lead to immune-related adverse events (irAEs), including inflammatory arthritis. Understanding the risk factors and underlying mechanisms of irAE pathogenesis is crucial for optimal patient management. Increasing evidence suggests that ICI-mediated activation of tissue-resident memory T cells (T_{RM}) significantly eliminates cancer cells and is associated with irAE-related colitis and dermatitis. However, it remains unknown why the development of these irAEs is restricted to a subset of patients. We hypothesized that osteoarthritis (OA) associated tissue damage and chronic inflammation lead to the recruitment and differentiation of joint T_{RM} cells, predisposing individuals to ICI-induced arthritis.

Methods Using a comprehensive approach, we compared the prevalence of OA in patients with irAE-arthritis to those with irAE non-arthritis and those without irAEs. Additionally, we used advanced immunophenotyping techniques to characterize T-cell populations in the blood and synovial fluid of patients with OA and irAE-arthritis.

Results Our findings revealed a significantly higher prevalence of OA in patients who developed irAE-arthritis than controls. Furthermore, the multivariable analysis identified OA, body mass index, and smoking as independent risk factors for the development of irAE-arthritis. T_{RM} cells expressing programmed cell death protein-1 (PD-1) were the predominant synovial T cells in OA joints. These cells were directly targeted by ICIs, resulting in an inflammatory immune response and the transition from OA to irAE-arthritis.

Conclusion This study, the first of its kind, identifies OA as a significant risk factor for irAEarthritis. It reveals a potential mechanism by which ICIs activate PD-1-positive T_{RM} cells in OA joints, resulting in tissue inflammation and irAE-arthritis. This research could significantly enhance the management and treatment of patients with cancer receiving ICIs.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Immune-related adverse events (irAEs), including inflammatory arthritis, are a significant burden associated with immune checkpoint inhibitor (ICI) therapy.

WHAT THIS STUDY ADDS

⇒ Our study has made a novel discovery: osteoarthritis (OA) is a crucial predisposition risk factor for developing irAE-arthritis. Mechanistically, we found that programmed cell death protein-1-positive T cells residing in OA joints are directly targeted by ICIs, leading to the inflammatory immune response characteristic of irAE-arthritis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study uncovered a subset of T cells that may link OA to the development of irAE-arthritis. These findings enable healthcare providers to stratify patients with cancer based on their risk of developing irAE-arthritis.

INTRODUCTION

Osteoarthritis (OA) is a degenerative joint disease characterized by cartilage loss and structural changes affecting the entire joint.[1] A global health burden, OA is a leading cause of disability, particularly among older adults.[2] Traditionally viewed as a "wear and tear" condition, OA is now recognized as a complex interplay of genetic, inflammatory, and mechanical factors.[3 4] While OA typically presents with limited clinical inflammation, underlying joint damage triggers low-grade inflammation, cytokine production, and T-cell recruitment.[5 6] A recent randomized placebo-controlled trial of methotrexate demonstrated a statistically significant decrease in knee pain in the treated group after 6 months.[7]

Additionally, T-cell depletion in murine models of OA limits OA progression.[8 9] Cartilage-reactive T cells have been detected in patients with OA and rheumatoid arthritis (RA), suggesting joint damage can prime

autoreactive T cells.[10 11] Although these data indicate that T cells are implicated in OA pathogenesis, their role in disease progression remains largely misunderstood.[5 6]

Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment by unleashing the immune system's potential to combat tumors. These therapies target immune checkpoints, such as programmed cell death protein-1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte associated protein 4 (CTLA-4), to unleash the pre-existing antitumor immunity. However, the heightened immune response can also lead to immune-related adverse events (irAEs), affecting various organs, including the nervous, ocular, endocrine, cardiovascular, pulmonary, gastrointestinal, renal, dermatological, musculoskeletal, and hematopoietic systems.[12] Notably, over half of ICI-treated patients experience irAEs.[13] Increasing evidence suggests that ICI mediates anticancer T-cell response and irAE-colitis and irAE-dermatitis by activating tissue-resident memory T cells (T_{RM}).[14–16] The risk factors and pathogenesis of irAEs remain poorly understood.[17] Although the colon and skin are naturally rich in T_{RM} cells, it remains unknown why irAE-colitis and dermatitis, the most investigated irAEs, occur in a fraction of the patients. Understanding the etiology of irAEs is crucial for developing effective prevention and management strategies. Investigating specific organ involvement can provide valuable insights into the underlying cellular mechanisms driving these adverse reactions.

This study grew from our observation of a high frequency of pre-existing OA in patients developing ICI-induced inflammatory arthritis (irAE-arthritis). Previous reports have described a worsening of OA symptoms following ICI treatment, termed "activated OA", distinct from inflammatory irAE-arthritis.[18 19] While the association between OA and irAE-arthritis has been suggested, its nature remains unclear.[18 20–22] Machine learning models further support a link between these conditions.[23] PD-L1 blockade can also increase inflammatory response in a murine model of OA.[8]

We hypothesized that joint damage, as seen in OA, predisposes to irAE-arthritis through the recruitment and activation of resident joint-specific memory T cells by ICIs. To test this hypothesis, this study investigates the association between OA and irAE-arthritis and aims to understand potential underlying mechanisms better.

PATIENTS AND METHODS

Study design

This was a case–control study of 108 patients who had received ICI treatment at the Columbia University Irving Medical Center (CUIMC) between September 2018 and February 2024 and who had one of the following outcomes: ICI-induced inflammatory arthritis (irAE-arthritis, cases), irAE without arthritis (irAE non-arthritis, first control group, see type of irAE listed in table 1) or no development of any irAE (no irAE, second control group) (figure 1A). The diagnosis of irAE-arthritis required: (1) the development of persistent joint pain after the initiation of ICI treatment, (2) a clinical diagnosis of inflammatory arthritis made by a consulting rheumatologist and based on inflammatory signs and symptoms of the affected joints, (3) a ruling out of other primary causes for inflammatory arthritis such as RA or spondyloarthropathy, and (4) the initiation of prednisone or another immunosuppressant drug for the treatment of arthritis that resulted in the improvement of symptoms.[24] We collected patient data from a broader database of 209 patients who received ICI treatment. After the chart review, we excluded 24 patients who did not receive the ICI drug. From this group, we identified 31 patients who developed irAE-arthritis. We consecutively selected 77 age-matched controls from the remaining cohort who did not develop irAE-arthritis following ICI. Among these, 39 experienced no irAEs, and 38 had irAEs other than arthritis (figure 1A and table 1). OA diagnosis was based on the international classification of disease-10 codes (ICD-10)[25] for the following: knee OA (M17, M17.0, M17.1, M17.2, M17.3, M17.4, M17.5, and M17.9), hip OA (M16, M16.0, M16.1, M16.2, M16.3, M16.4, M16.5, M16.6, M16.7, and M16.9), hand OA (M15.1, M15.2, M18, M18.0 to M18.5 and M18.9), or on the X-ray of the affected joint, with OA defined according to Kellgren and Lawrence radiographic criteria.[26] We analyzed X-rays obtained at the time of irAE diagnosis or the most recent X-ray dated within 10 years of the study enrollment date (figure 1B). Musculoskeletal radiologists at the CUIMC Department of Radiology interpreted all radiographs and were blinded to the clinical irAE outcome. Only patients who had peripheral joint OA were considered in the study. Treatment-naive synovial fluid and peripheral blood from patients with OA and ICI-treated patients were obtained from the Columbia B3 biorepository program.

Flow cytometry

Synovial and peripheral blood mononuclear cells were isolated using Lymphoprep Density Gradient Medium (07811, STEMCELL Technologies, Vancouver, British Columbia, Canada). 2×10^6 cells were incubated with 1:200 diluted Zombie NIR (BioLegend San Diego, California, USA) in phosphate buffered saline (PBS) for 30 min at room temperature and protected from light. After a wash with staining buffer (PBS supplemented 2% bovine serum albumin (BSA) and 0.1% sodium azide) and centrifugation at 500 g for 5 min, cells were incubated with Fc Receptor Blocking Solution (Human TruStain FcX, BioLegend) for 10 min. Cells were stained with a master mix of 41 antibodies (listed in online supplemental table S1) supplemented with CellBlox Blocking Buffer and Super Bright Complete Staining Buffer (Invitrogen,

Table 1 Patient characteristics

	no irAEs (n=39)	irAE non-arthritis (n=38)	irAE-arthritis (n=31)
Mean age at ICI initiation (±SD)	65.1±13.6	64.1±15.1	64.9±12.1
Sex, n (%)			
F	14 (35.9)	22 (57.9)	15 (48.4)
M	25 (64.1)	16 (42.1)	16 (51.6)
Race and ethnicity, n (%)			
White	20 (51.3)	16 (42.1)	24 (77.4)
Hispanic or Latino/a	10 (25.6)	9 (23.7)	4 (12.9)
Black or African American	4 (10.3)	5 (13.2)	0 (0)
Asian	1 (2.6)	3 (7.9)	2 (6.5)
Other	4 (10.3)	5 (13.2)	1 (3.2)
BMI	25.0±6.0	25.6±6.1	27.3±5.3
Ever smoker, n (%)	24 (61.5)	14 (36.8)	17 (54.9)
Cancer type, n (%)			
Breast	1 (2.6)	4 (10.5)	1 (3.2)
Bladder	4 (10.3)	4 (10.5)	5 (16.1)
Colorectal	2 (5.1)	2 (5.3)	0 (0)
Melanoma	4 (10.3)	7 (18.4)	8 (25.8)
Lung	7 (17.9)	4 (10.5)	5 (16.1)
Kidney	4 (10.3)	3 (7.9)	4 (12.9)
Uterus	2 (5.1)	6 (15.9)	1 (3.2)
Liver	2 (5.1)	2 (5.3)	1 (3.2)
Gastric	2 (5.1)	1 (2.6)	0 (0)
Head/neck squamous cell carcinoma	3 (7.7)	0 (0)	1 (3.2)
Esophagus	2 (5.1)	0 (0)	2 (6.5)
Biliary tract cholangiocarcinoma	3 (7.7)	0 (0)	0 (0)
Other	3 (7.7)	5 (13.2)	3 (9.7)
irAE type, n (%)			
Colitis	0 (0)	6 (15.9)	7 (22.6)
Dermatitis	0 (0)	13 (36.8)	7 (22.6)
Thyroiditis	0 (0)	12 (31.6)	5 (16.1)
Transaminitis	0 (0)	8 (21.0)	2 (6.5)
Neuropathy	0 (0)	2 (5.3)	4 (12.9)
Pneumonitis	0 (0)	2 (5.3)	1 (3.2)
Other	0 (0)	6 (15.9)	6 (19.4)
Positive autoimmune markers, n (%)			
ANA	--	--	8 (25.8)
RF/anti-CCP	--	--	4 (12.9)
ICI type, n (%)			
Anti-PD-1 (Pembro/Nivo)	27 (69.2)	24 (63.2)	22 (71.0)
Anti-CTLA-4+anti-PD-1 (Ipi+Nivo)	3 (7.7)	7 (18.4)	7 (22.6)
Anti-PD-L1 (Atezo/Durva)	8 (20.5)	4 (10.5)	2 (6.5)
Other*	1 (2.6)	3 (7.9)	0 (0)

*Different combination (i.e., anti-PD-1 and anti-LAG3); ±SD.
ANA, antinuclear antibodies; Atezo, atezolizumab; BMI, body mass index; CCP, cyclic citrullinated peptide; CTLA-4, cytotoxic T-lymphocyte associated protein 4; Durva, durvalumab; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event ; LAG-3, Lymphocyte-activation gene 3; Nivo, nivolumab; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; Pembro, pembrolizumab; RF, rheumatoid factor.

Waltham, Massachusetts, USA). Spectral flow data was obtained on the Cytek 5 L Aurora (Cytek Biosciences, Fremont, California, USA) and analyzed in FCS Express Research V.7 (De Novo Software, San Francisco, California, USA) and FlowJo V.10 software (BD Biosciences, Franklin Lakes, New Jersey, USA). Raw data was unmixed, cleaned using FlowCut, and downsampled to 10,000 events using weighted density

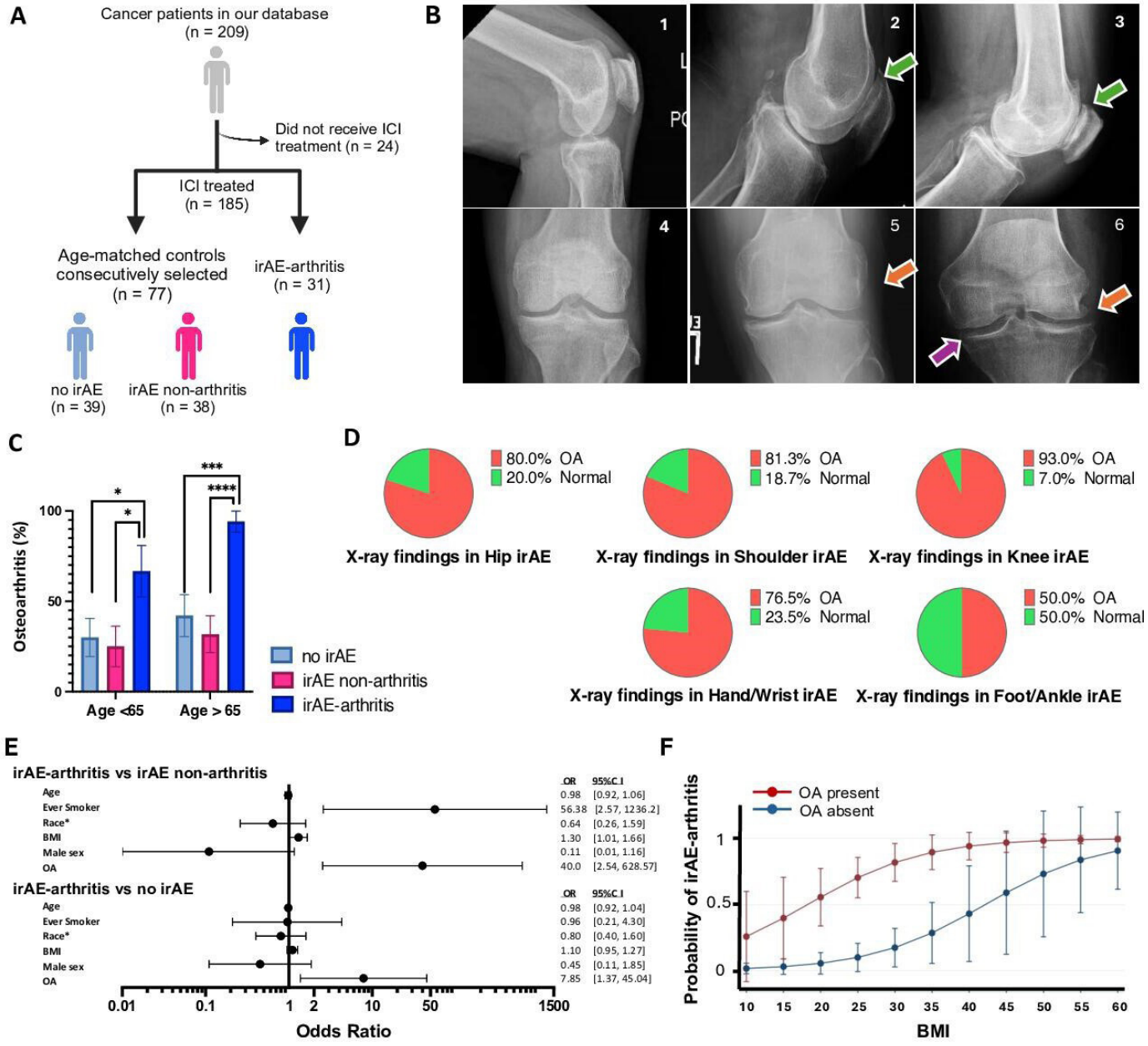

Figure 1 Osteoarthritis is a major risk factor for irAE-arthritis. (A) Graphical representation of patient enrollment. (B) Lateral and anteroposterior radiographic imaging of a healthy knee (1,4), a knee impacted with medial and patellofemoral compartmental OA, respectively, highlighted with a green and orange arrow (2, 5), and a knee impacted with tricompartmental OA and irAE-arthritis (3, 6) with the lateral OA being highlighted with a purple arrow. (C) Prevalence of osteoarthritis (mean±SE) in the no irAE, irAE non-arthritis, and irAE-arthritis groups, stratified by age less than 65 versus greater than or equal to 65 years. (D) X-ray findings in joints affected by irAE-arthritis. Red indicates the presence, and green means the absence of radiographic OA. (E) Forest plot showing the odds ratio for age, smoking history, race, BMI, sex, and OA from a logistic multivariable regression analysis comparing the outcomes of irAE-arthritis versus irAE non-arthritis (top) and irAE-arthritis versus no irAE (bottom). *White race was used as the reference in the analysis. (F) Predicted probability of developing irAE-arthritis, compared with irAE non-arthritis, with increasing BMI in the presence (red line) or absence (blue line) of underlying OA. BMI, body mass index; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; OA, osteoarthritis.

downsampling gated on Zombie NIR$^-$ CD15$^-$ CD19$^-$ CD14$^-$ TCR$\alpha\beta^+$ TCR$\gamma\delta^+$ cells with FCS Express Research software. Using FlowJo, samples were concatenated to create a single composite file with each constituent file specified. For dimensional reduction, after gating on CD4$^+$ or CD8$^+$ T cells or TCR alpha beta$^+$ cells when specified, unsupervised clustering was applied using FLowSOM (V.4.1.0), which was used to create supervised uniform manifold approximation and projection (UMAP) with the UMAP plugin (V.4.0.4) available on the FlowJo Exchange. For the comparison of T cells from OA synovial fluid (SF), irAE-arthritis

SF, and peripheral blood mononuclear cells (PBMC), the PD-1 and IgG4 parameters were excluded from the unsupervised clustering to prevent bias, as PD-1 expression is not detected by the antibodies used for flow cytometry staining when PD-1 is already bound to nivolumab/pembrolizumab.[27]

Statistical analysis

Summary statistics are presented as the mean and standard deviation (SD) for the normally distributed variables and medians with 25th and 75th quartiles for the non-normally distributed variables. Unadjusted comparisons were performed with a t-test (parametric) or Mann-Whitney U test (non-parametric) for continuous variables or χ^2 for counts data. Multivariable logistic regression was used to evaluate risk factors of irAE-arthritis following ICI treatment. Statistical analyses were conducted with GraphPad Prism V.10 (GraphPad Software, Boston, Massachusetts, USA) and Stata/IC V.15.1. The flow data are represented as median with 25th and 75th quartiles or mean and SD. The data sets were transformed using logarithm base 10 and checked for normality using the Shapiro-Wilk test. Experimental groups were compared using unpaired t-tests. The results were considered significantly different at an α-level of 5% ($p<0.05$).

Single-cell CITE-seq data analysis

Cellular indexing of transcriptomes and epitopes by sequencing (CITE-seq) data in RA and OA synovial T cells were visualized and analyzed using the cell browser website https:// immunogenomics.io/ampra2/ as previously published.[28]

RESULTS

Clinical characteristics of ICI-treated patients

The mean age was comparable across irAE-arthritis, irAE non-arthritis and no irAE groups: 65.1±13.6 years for the no irAE group, 64.1±15.1 years for the irAE non-arthritis group, and 64.9±12.1 years for the irAE-arthritis group (analysis of variance p=0.456; ±SD) (table 1). At the same time, the sex of the no irAE group was comprised of predominantly male subjects (64.1%), the irAE non-arthritis group tended to be female subjects (57.4%), with the irAE-arthritis group showing a slight non-significant male subject majority (51.6%) (χ^2 p=0.153). Racial distribution was 51% white in the no irAE group, 42% white in the irAE non-arthritis group, and 77% white in the irAE-arthritis group (χ^2 p=0.09). Smoking history was present in 63.2%, 36.8%, and 56.7% of subjects in the irAE, irAE non-arthritis, and irAE-arthritis groups, respectively (χ^2 p=0.06). Lung cancer was the most common malignancy in the no irAE group (17.9%), while melanoma predominated in both the irAE non-arthritis (18.4%) and irAE-arthritis groups (25.8%). Most group patients received adjuvant anti-PD-1 antibody monotherapy (table 1). Notably, 35.5% of patients in the irAE-arthritis group had detectable antinuclear antibodies, rheumatoid factor, or anti-cyclic citrullinated peptide (antibodies) levels identified during their evaluation for irAE-arthritis.

irAE-arthritis is associated with weight, history of smoking, and pre-existing osteoarthritis

A history of OA was present in 14 (35.9%), 11 (29.0%), and 26 (83.9%) of patients in the no irAE, irAE non-arthritis, and irAE-arthritis groups, respectively (χ^2 p<0.001). To determine if the association between OA and irAE-arthritis was limited to older patients, we conducted a stratified analysis using age ≥65 years as a cut-off. Although the overall OA prevalence was lower in patients younger than 65, the association between a history of OA and irAE-arthritis persisted (figure 1C). A sensitivity analysis restricted to only the patients with available X-rays for radiographic assessment resulted in a similarly significant association between OA and irAE-arthritis. Radiographic OA was present in 14 (54.5%), 11 (62.5%), and 26 (89.3%) of patients with no irAE, irAEs non-arthritis, and irAE-arthritis, respectively (χ^2 p=0.02). In irAE-arthritis-affected joints, OA was identified in 81.3% of shoulders, 80.0% of hips, 93.0% of knees, 76.5% of hands/wrists, and 50% of feet/ankles (figure 1D).

To control for factors associated with irAE-arthritis development in the univariate analysis, we performed a multivariable regression analysis evaluating the association between a history of OA and irAE-arthritis outcomes. Adjusting for age, sex, race, body mass index (BMI), and smoking history, the odds ratio (OR) for developing irAE-arthritis compared with no irAE, given a history of underlying OA, was 7.9 (95% CI 1.4 to 45.0, p=0.02) (figure 1E). Given a history of OA, the OR for developing irAE-arthritis compared with irAE non-arthritis was 40.0 (95% CI 2.5 to 628.5, p=0.009). Given a history of smoking, the OR for developing irAE-arthritis compared with irAE non-arthritis was 56.38 (95% Cl 2.57 to 1236.2, p=0.01). BMI was also significantly associated with irAE-arthritis development in the same analysis, with the OR increasing by 1.3 for each unit increase in BMI (p=0.045). A predicted probability plot of developing irAE-arthritis compared with irAE non-arthritis at different BMIs in patients with and without underlying OA was created from this regression model (figure 1F).

Additionally, we evaluated past joint surgery as a possible confounder. We found a history of surgery in any joint in 4/31 (12.9%) irAE-arthritis patients, 7/38 (18.4%) irAE non-arthritis patients, and 2/39 (5.1%) patients with no irAE. The statistical distribution of a history of joint surgery between the three subgroups of patients was not statistically significant (p=0.20). Specifically, the association between a history of joint surgery and the development of irAE-arthritis compared with irAE non-arthritis was non-significant at OR 0.67 (95% CI 0.17 to 2.49, p=0.54). The association between a history of joint surgery and the development of irAE-arthritis compared

with no irAE was also non-significant at OR 2.7 (95%CI 0.47 to 16.1, p=0.26).

Collectively, these data support a strong association between a history of OA and the development of irAE-arthritis following ICI treatment. Given OA's slow but typically progressive nature, which is associated with joint damage, we hypothesize that chronic joint-specific immunological memory underlies this observed association.

PD-1$^+$ resident memory T cells predominate among OA synovial fluid T cells

We hypothesized that specific T-cell subsets reside as dormant populations within OA joints, expressing PD-1 and becoming activated after anti-PD-1 antibody therapy. Using high-dimensional spectral flow cytometry, we analyzed SF from OA knees to characterize these T-cell subsets. We compared them to T cells from irAE-arthritis SF and PBMC from patients with cancer who did not receive ICI treatment.

OA SF contained an average of 419 nucleated cells/µL, with 43.5% lymphocytes. irAE-arthritis SF contained an average of 8,031 nucleated cells/µL, with 88% lymphocytes. OA SF lymphocytes comprised 39.42% αβ T cells and 13.50% γδ T cells. irAE-arthritis SF lymphocytes comprised 39.42% αβ T cells and 13.50% γδ T cells. Synovial αβ T cells were compared with PBMC αβ T cells from patients with cancer before ICI treatment (n=10).

Unsupervised cluster analysis of all αβ T cells identified clusters 13, 14, and 15 as predominant CD4$^+$ T-cell populations and cluster 2 as the predominant CD8$^+$ T-cell population in OA SF, representing, respectively, 20.96%, 23.57%, 23.63%, and 77.30% of CD4$^+$ or CD8$^+$ T cells (figure 2A). OA-derived cells in clusters 13, 14, and 2 exhibited PD-1, CD69, and CD103 expression compared with CD62L$^+$ CD45RA$^+$ CD95$^-$ naïve T cells (in cluster 19) and compared with irAE-arthritis and PBMC-derived clusters 13, 14, and 2 (figure 2B,C). Clusters 2, 13, and 14 also demonstrated heterogeneous major histocompatibility complex (MHC)-II expression and the absence of CD62L and CD45RA staining (figure 2 and online supplemental figure S1). The predominance of CD103 and CD69-positive T-cell memory cells suggested that T cells persist in the OA joint by adopting a T_{RM} cell phenotype. Their PD-1 expression identified them as potential targets for ICI therapies blocking the PD-1 signaling pathway. The cells targeted by anti-PD-1 therapies, such as nivolumab and pembrolizumab, can be identified using anti-human IgG4.[29] Nivolumab-bound T cells can be detected within 100 days and potentially up to 200 days post-treatment.[30 31] In irAE-arthritis SF, collected within 4 months of ICI treatment; we detected the anti-PD1 antibody-bound T cells in cluster 2 for CD8$^+$ T cells and clusters 10 and 13 for CD4$^+$ T cells. IgG4$^+$ irAE SF cells from clusters 2 and 13 exhibited activated phenotypes with higher MHC-II, Lymphocyte-activation gene 3(LAG-3), or T cell immunoglobulin and mucin-domain containing 3 (TIM-3) expression and lower CD27 and CD103 expression, indicating that drug-bound T cells in irAE-arthritis are not T_{RM} cells as previously suggested in irAE-colitis (figure 2C and online supplemental figure S1).[31] This shows that on PD-1 blockade, CD8$^+$ and CD4$^+$ T_{RM} cells differentiate into drug-bound effector T cells, as proposed in irAE-colitis based on T cell receptor (TCR) sharing between CD8$^+$ T_{RM} and effector CD8$^+$ T cells under ICI treatment.[32] T_{RM} cells are also outnumbered in irAE-arthritis SF because of the recruitment of blood-derived effector memory T cells.[29 33]

Additionally, we re-analyze the publicly available single-cell RNA sequencing data from biopsies taken from the infrapatellar fat pad/synovium of three healthy joints and three OA joints (GSE216651, online supplemental figure S3). CD3$^+$ T cells constituted 8.48% of the OA synovial cells and 4.77% of the healthy joint cells. Nevertheless, CD103$^+$CD69$^+$ T cells constituted 1.1% and 0.62% CD3$^+$ T cells in the OA and healthy joint, respectively. Thus, although present at low frequency, the proportion of T_{RM} cells in the OA joint increases compared with the healthy joint.

To further characterize OA-associated PD-1$^+$ joint T cells, we analyzed a cellular indexing of transcriptomes and epitopes by sequencing (CITE-seq) data set of OA and RA synovial T cells.[28] Within OA synovial T cells (6,343 cells from eight donors), PD-1 expression was detected in four clusters of αβ T cells: T-3, T-5, T-7, and T13, respectively, annotated as CD4$^+$ T_{FH}/T_{PH}, CD4$^+$ *GZMK*$^+$ memory, CD4$^+$ T_{PH}, and CD8$^+$ *GZMK/B*$^+$ memory (figure 3). These clusters expressed CD69 protein, integrin genes (*ITGAE* encoding CD103, *ITGA1*, *ITGA4*, *ITGAL*), and CD45RO protein. Analysis of additional canonical or published T_{RM} gene markers revealed that PD-1-expressing clusters also expressed *RUNX3*, *CXCR6*, *RGS1*, *CRTAM*, *PRDM1*, *CTLA4*, *EOMES*, and *TNFRSF18* (figure 3 and online supplemental figure S2). Importantly, these clusters exhibited lower *S1PR1*, *SELL*, *KLF2*, and *CCR7* transcript levels, consistent with a T_{RM} phenotype.[34–36]

These data confirm that, in OA-associated joint damage, T cells persist in the joint with a T_{RM} phenotype, expressing a high level of PD-1. This suggests that anti-PD-1 therapy triggers their activation, initiating joint inflammation and irAE-arthritis.

T-cell subsets enriched in patients with OA who develop irAE-arthritis

We analyzed the T-cell phenotype of blood and synovial T cells to investigate the role of PBMC T cells in irAE-arthritis. Previous studies demonstrated overlap between these compartments, suggesting the involvement of PBMC T cells, especially drug (anti-PD-1 antibodies)-bound T cells, in irAE-arthritis.[29 33] We hypothesized that PBMC T cells, particularly drug-bound T cells, in irAE-arthritis patients would differ from those in irAE non-arthritis and no irAE patients, regardless of OA status. We compared post-ICI treatment PBMC T-cell phenotypes in irAE-arthritis patients with OA (n=5), irAE non-arthritis patients with OA (n=9), and no irAE patients with or without OA (n=6 and 4, respectively, figures 4A

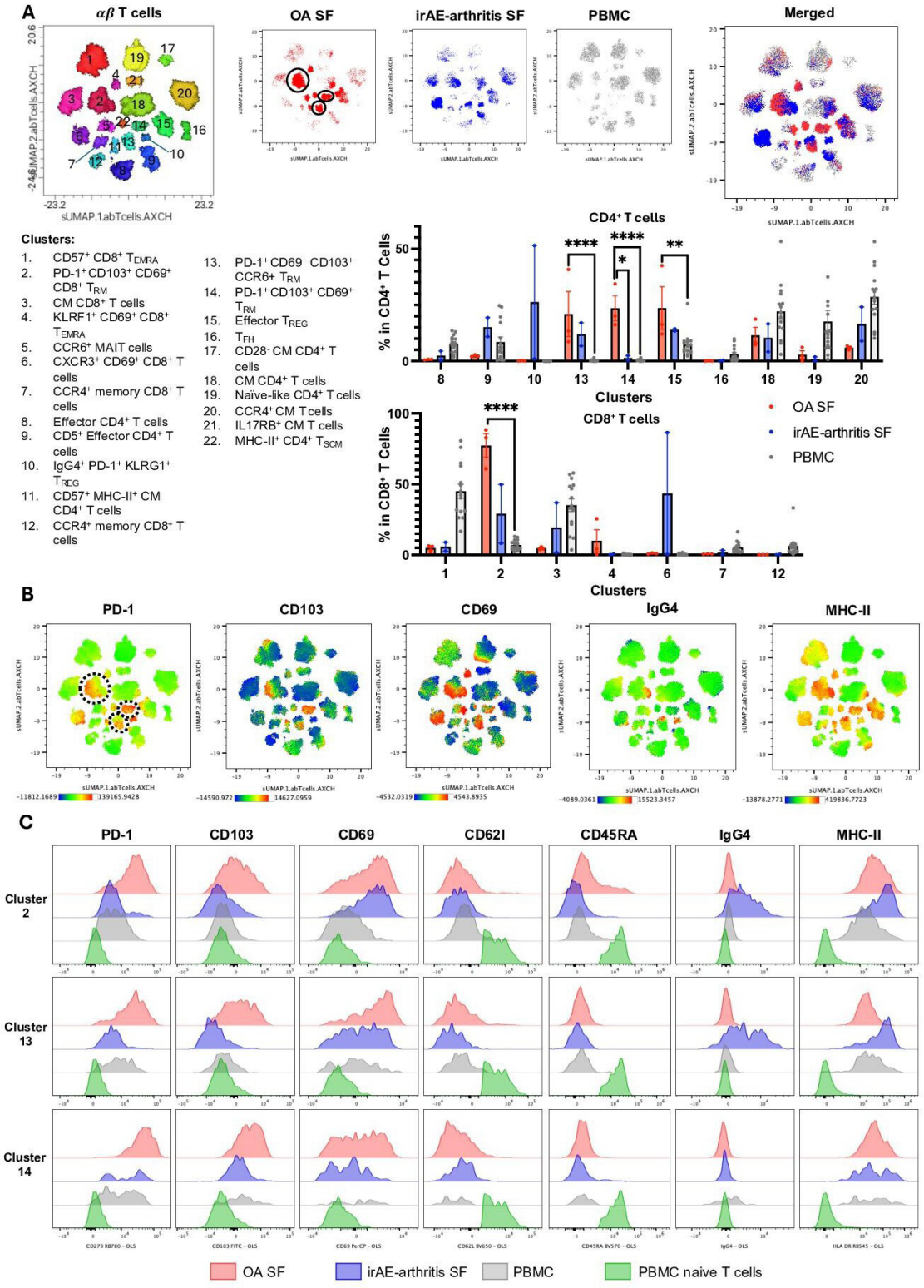

Figure 2 PD-1$^+$, CD8$^+$ and CD4$^+$ T_{RM} cells predominate synovial fluid T-cell populations in OA joints. (A) FlowSOM supervised UMAP analysis of merged OA synovial fluid (SF), irAE-arthritis SF, and peripheral blood mononuclear (PBMC) T cells subdivided into 22 FlowSOM clusters with the associated cluster annotation and proportions in the SF and PBMC CD8 and CD4 T cells. n=3 OA SF, n=2 irAE-arthritis SF and n=15 PBMC, *indicates statistical significance (t-test). (B) sUMAP corresponding heatmaps indicating the expression of OA SF, irAE-arthritis SF T_{RM} cell markers. (C) Histogram overlays indicated T_{RM} and activation marker staining in T_{RM} clusters 2, 13, and 14. CM, central memory; irAE, immune-related adverse events; MAIT cells, mucosa-associated invariant T cells; MHC, major histocompatibility complex; OA, osteoarthritis; PD-1, programmed cell death protein-1; PBMC, peripheral blood mononuclear cells; sUMAP, supervised uniform manifold approximation and projection ; PD-1, programmed cell death protein-1; SF, synovial fluid; T_{RM}, tissue-resident memory T cells; T_{FH}, follicular helper T cells; T_{REG}, regulatory T cells; T_{EMRA}, effector memory cells re-expressing CD45RA T cells; T_{SCM}, stem cells memory T cells.

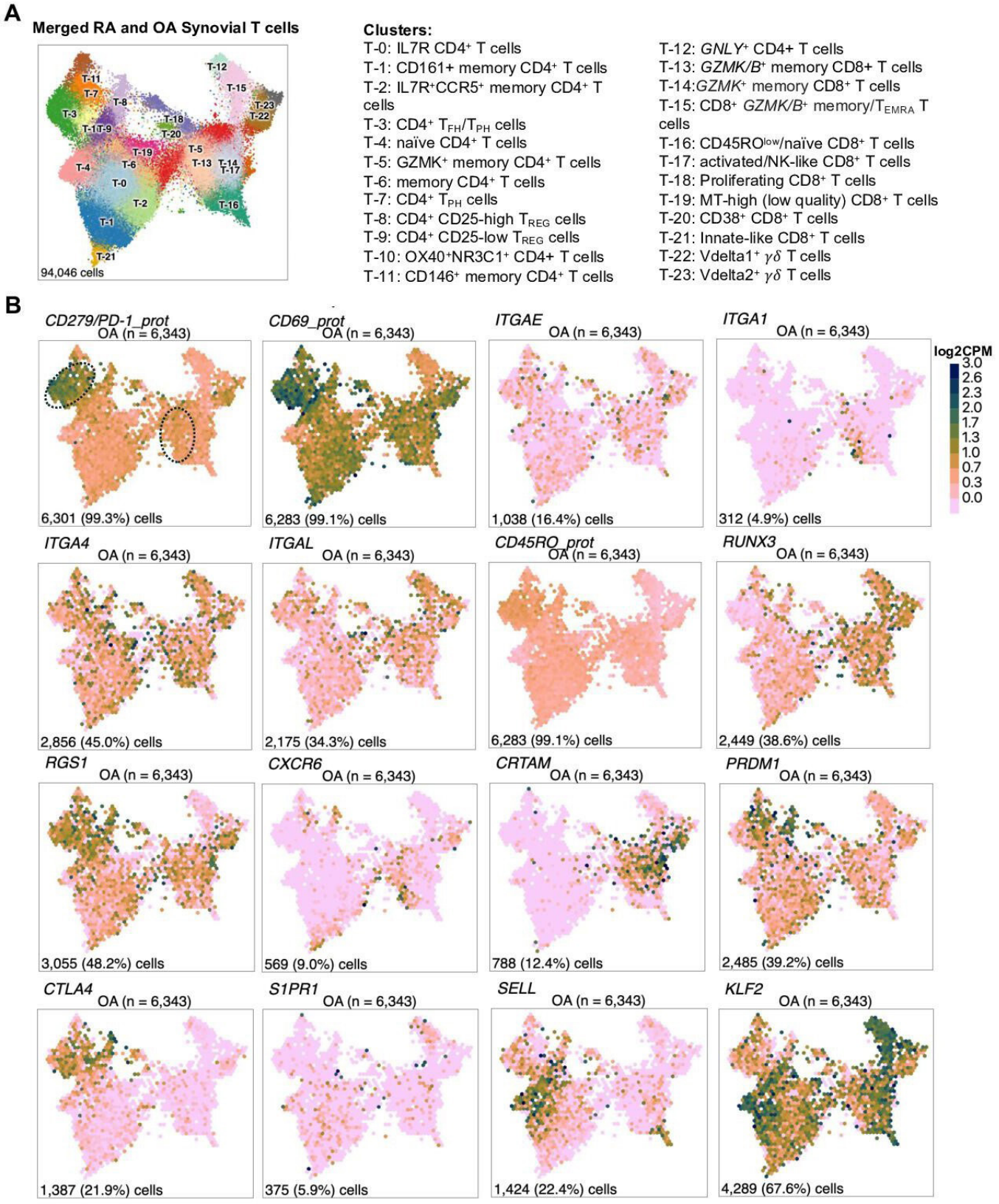

Figure 3 Synovial PD-1^{+}CD8^{+} and CD4^{+} T_{RM} cells are $T_{PH/FH}$-like, and GZMK/B^{+} T cells in OA synovium. (A) We reanalyzed publicly available joint synovium data (SynID: syn26710600): CITE-seq UMAP analysis of T cells from OA and rheumatoid arthritis (RA) synovium captured 24 clusters. (B) Expression of PD-1 and tissue-resident memory T cells protein and gene markers in OA synovium αβ T-cell clusters 3, 5, 7, and 13. CITE-seq, Cellular indexing of transcriptomes and epitopes by sequencing; OA, osteoarthritis; PD-1, programmed cell death protein-1; RA, rheumatoid arthritis; T_{PH}, peripheral helper T cells; T_{FH}, follicular helper T cells; T_{EMRA}, effector memory cells re-expressing CD45RA T cells; UMPA, uniform manifold approximation and projection.

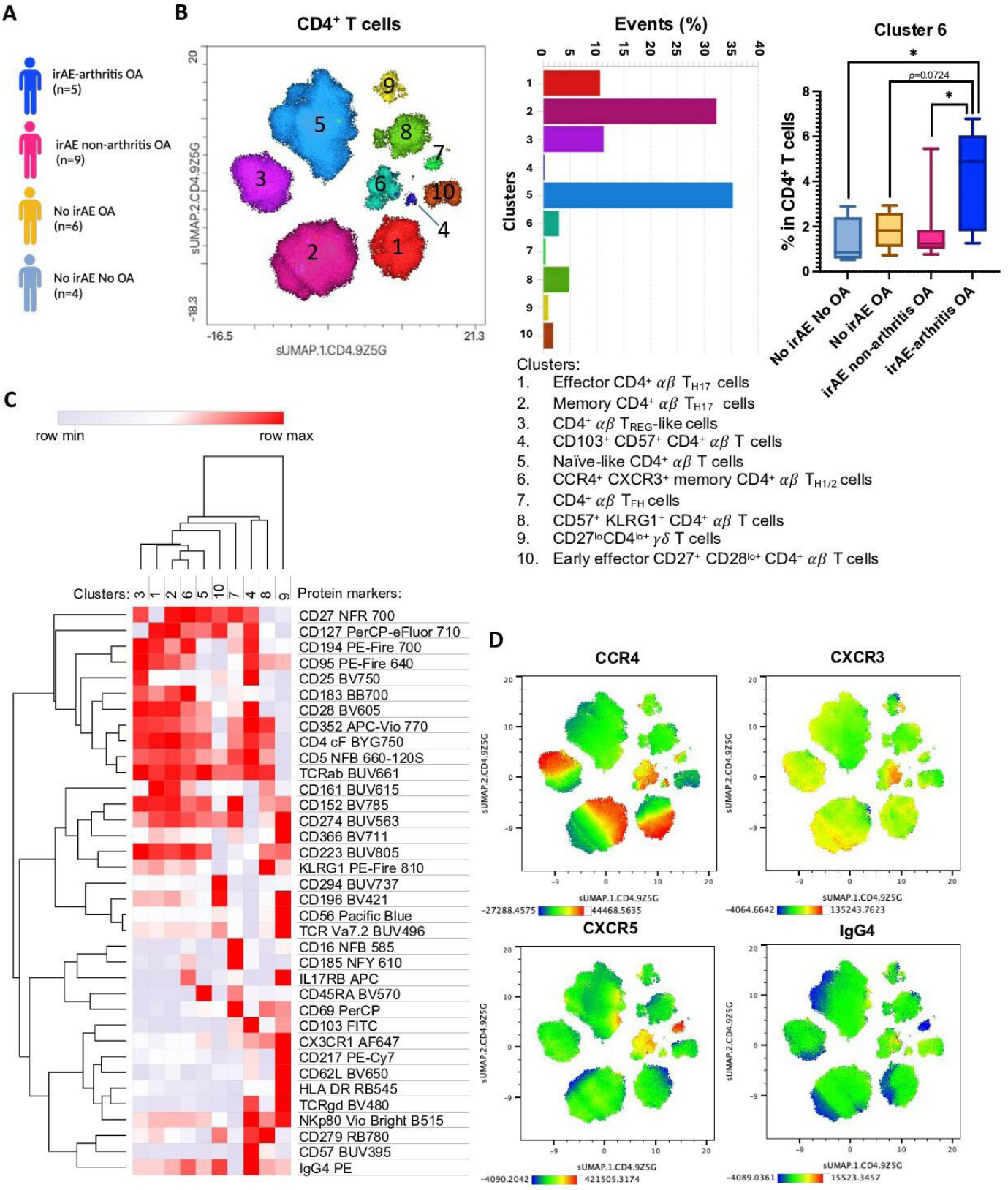

Figure 4 36 protein marker-based cluster annotation identifies abundant memory $T_{H1/2}$ in the peripheral blood mononuclear cell of patients with irAE-arthritis. (A) Study design. (B) FlowSOM supervised UMAP analysis of 10 clusters with their relative abundance and their annotations. *Indicates statistical significance (t-test). (C) Heatmaps indicate the relative abundance of each marker in clusters. (D) FlowSOM sUMAP heatmaps indicate the expression level of cluster 6 specific markers. irAE, immune-related adverse event; OA, osteoarthritis; sUMAP, supervised uniform manifold approximation and projection; T_{FH}, follicular helper T cells.

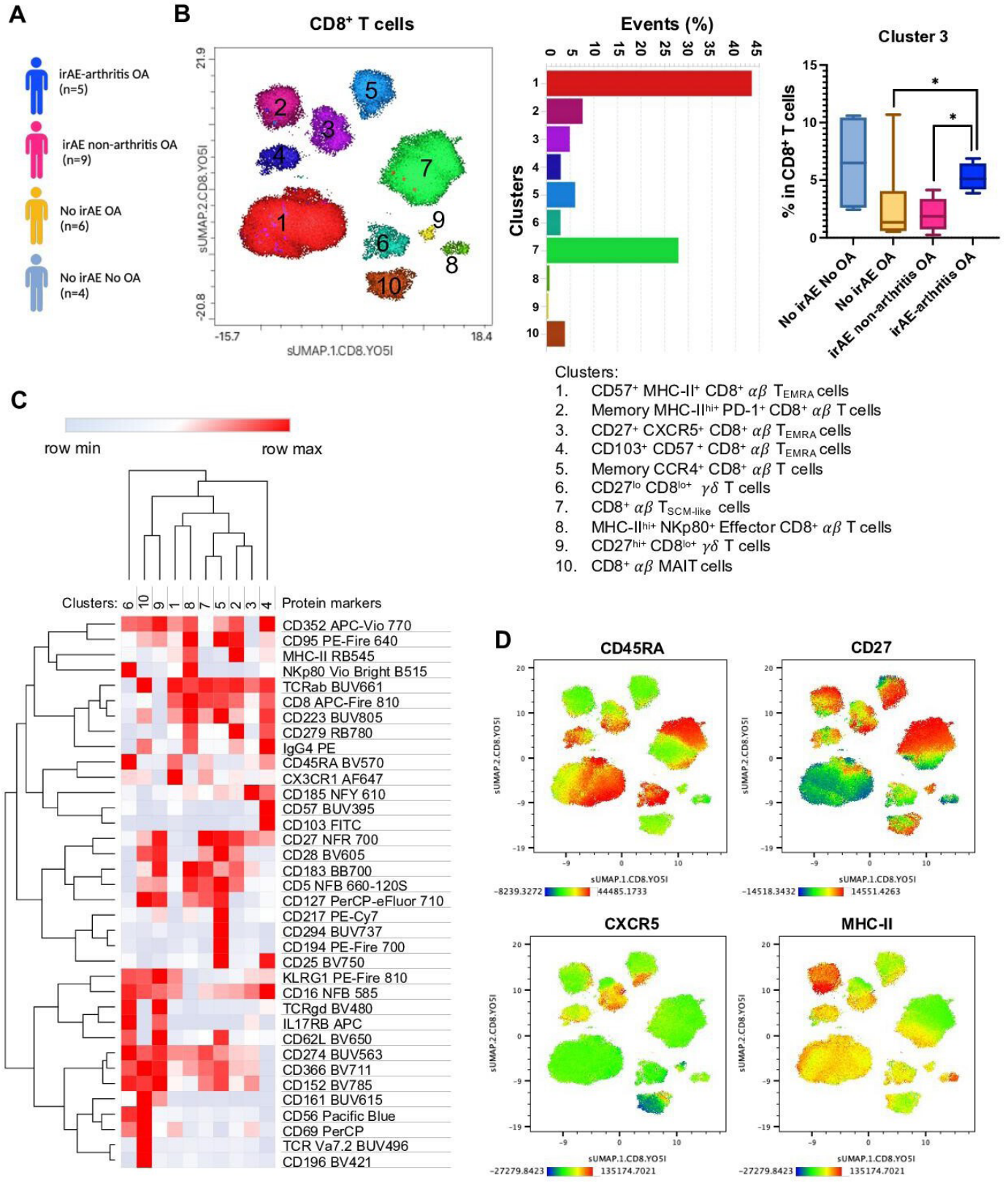

Figure 5 36 protein marker-based cluster annotation identifies abundant CD8+ T_{EMRA} cells in the peripheral blood mononuclear cell of patients with irAE-arthritis. (A) Study design. (B) FlowSOM supervised UMAP analysis of 10 clusters, with their relative abundance and annotations. *Indicates statistical significance (t-test). (C) Heatmaps indicate the relative abundance of each marker in clusters. (D) FlowSOM sUMAP heatmaps indicate the expression level of cluster 3 specific markers. irAE, immune-related adverse event; MHC, major histocompatibility complex; MAIT cells, mucosa-associated invariant T cells; OA, osteoarthritis; PD-1, programmed cell death protein-1; sUMAP, supervised uniform manifold approximation and projection; T_{EMRA}, effector memory cells re-expressing CD45RA T cells; T_{SCM}, stem cells memory T cells.

and 5A). Unsupervised cluster analysis identified cluster 6 as significantly more abundant in $CD4^+$ T cells of irAE-arthritis patients than patients with OA with other irAEs (p=0.0309, figure 4B) and patients without OA and irAEs (p=0.0375). Differences between patients with OA and those without irAEs were not statistically significant (p=0.0724). Cluster 6 exhibited $IgG4^+$ positivity indicative of bound anti-PD-1 antibodies, and a memory phenotype ($CD27^+$, $CD28^+$, $CD62L^-$), expressing intermediate levels of CXCR3, CCR4, and CXCR5 (figure 4C,D).

Unsupervised cluster analysis of $CD8^+$ T cells revealed cluster 3 as significantly more abundant in $CD8^+$ T cells of irAE-arthritis patients than patients with OA with irAE non-arthritis or without irAEs (p=0.0137and p=0.0336, respectively) (figure 5B). Cluster 3 represented a $CD8^+$ T_{EMRA} subpopulation characterized by CD45RA, CD27, intermediate CXCR5 expression, and MHC-II (figure 5C,D).

These findings suggest that tissue-specific irAEs, such as irAE-arthritis, are mediated by the "on-target, off-organ" activation of tissue-specific T-cell subpopulations. Our results support the hypothesis that OA-related tissue damage, which precedes ICI treatment and is associated with tissue-specific $PD\text{-}1^+$ T_{RM} cell differentiation, contributes to joint pathology during irAE-arthritis.

DISCUSSION

Our study found a strong association between a history of OA and the development of inflammatory irAE-arthritis after ICI therapy. Both univariate and multivariable analyses, controlling for potential confounders, revealed that patients with OA had significantly higher odds of developing irAE-arthritis than those without irAEs or irAE non-arthritis.

The notion of "activated OA", describing post-ICI OA exacerbation without inflammation, has been proposed.[19] Our findings reinterpret this observation by demonstrating that OA-damaged joints are predisposed to inflammatory arthritis post-ICI treatment, particularly in larger joints like knees, where radiographic OA was present in 93% of irAE-arthritis cases. Obesity, a known OA and irAE risk factor,[37 38] further modulates the OA-irAE-arthritis association. Adipose tissue and cigarette smoke likely contribute to systemic inflammation through cytokine release, including tumor necrosis factor-α, interleukin-1β, and adipokines.[38–40]

ICI-mediated anticancer T-cell response and non-arthritis irAEs such as colitis have been suggested to be mediated by direct activation of T_{RM}.[16] Nevertheless, the origin, role, and phenotype of the T_{RM} cells in irAEs remain to be fully established.[14 16] We found

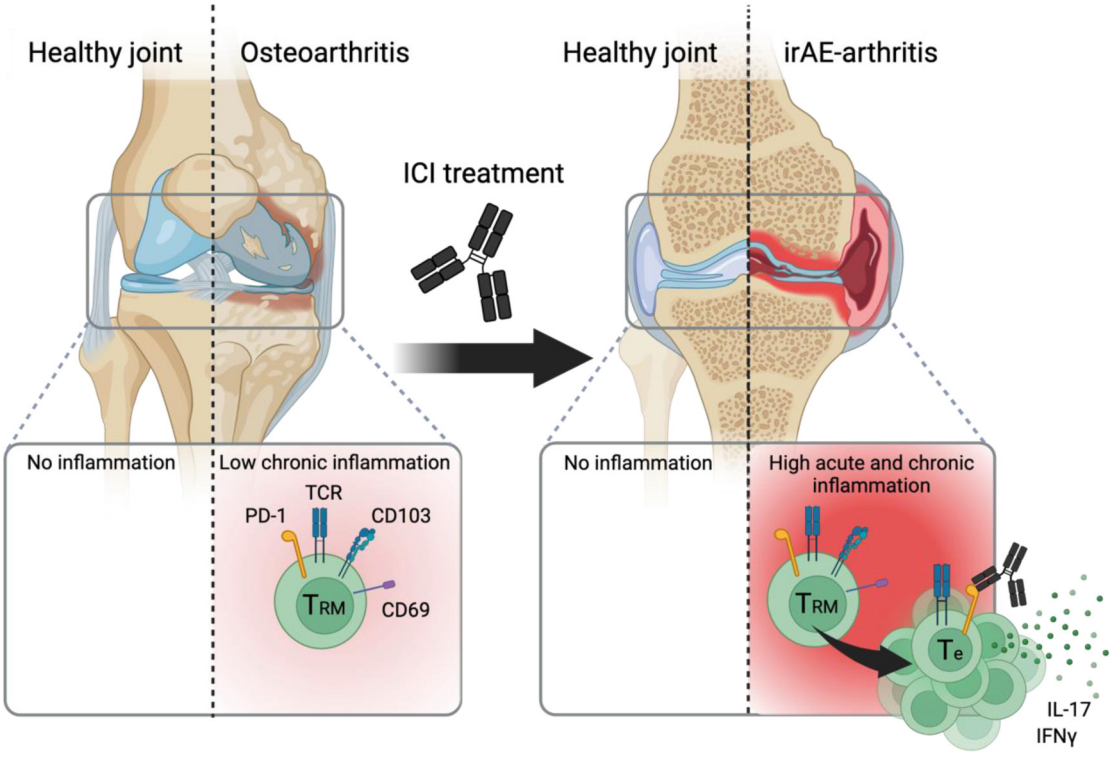

Figure 6 Proposed model of how OA predisposes for developing inflammatory arthritis during cancer immunotherapy using checkpoint inhibitors. Subclinical OA-associated tissue damage and chronic inflammation promote the recruitment, differentiation, and residency of autoreactive $PD\text{-}1^+$ $CD103^+$ $CD69^+$ memory T cells (T_{RM}) in the joint. Immune checkpoint inhibitor (ICI) treatment activates T_{RM} cells which initiate tissue inflammation by adopting an effector T-cell phenotype (Te) bound to ICI, secreting IL-17 or IFN-γ, and recruiting peripheral blood-derived effector memory T cells. This figure was created with BioRender. IFN, interferon; IL, interleukin; irAE, immune-related adverse event; OA, osteoarthritis; PD-1, programmed cell death protein-1; TCR, T cell receptor; T_{RM}, tissue-resident memory T cells.

that OA synovial fluid T cells predominantly exhibit a memory phenotype ($CD28^+$, $CD27^+$, $CD45RA^-$) expressing canonical tissue residency markers ($CD69^+$, $CD103^+$, $PD\text{-}1^+$, $CD62L^-$), similar to those described in lungs, intestines, skin, cancer, and RA-affected joints.[34–36] CITE-seq data confirmed $PD\text{-}1^+$ T cells in OA synovium expressing additional integrin genes (*ITGA1*, *ITGA4*, *ITGAL*) essential for tissue retention. These OA synovial T_{RM} cells also expressed *RUNX3*, *PRDM1*, *RGS1*, *CXCR6*, *CRTAM*, *GZMK*, and *CTLA-4* while exhibiting low *CCR7* and *KLF2* expression, characteristic of T_{RM} cells.[34–36] T_{RM} cells are known for persistence in non-lymphoid organs and to be poised for rapid response to pathogens. Recently, T_{RM} cells have been implicated in chronic inflammatory diseases, including those affecting the lung, brain, and RA-affected joints.[41 42] We observed the anti-PD-1 drug-bound activated T cells irAE arthritis cluster with OA $CD8^+$ and $CD4^+$ T_{RM}, indicating that anti-PD-1 drugs bind to T_{RM} and trigger their activation and differentiation. Although cancer-associated T_{RM} cells contribute to ICI-mediated anticancer $CD8^+$ T-cell responses.[35] Evidence of ICI-activated T_{RM} effector function exists in irAE-dermatitis, colitis, and pneumonitis.[16 32 43–45] Patients with RA under ICI treatment experience recurrent joint flares attributed to T_{RM} cell activation.[46]

Our data show that $PD\text{-}1^+$ T_{RM} cells in OA joints likely differentiate into activated effector memory T cells post-ICI treatment, mediating clinical joint inflammation and potentially recirculating and spreading to other joints.[15 47 48] Additionally, the ICI-mediated T_{RM} activation might recruit blood-derived T cells that are likely involved in the progression of joint inflammation.[29 33] Analysis of peripheral blood T cells from patients with OA exposed to ICI identified increased $CCR4^+$ $CXCR3^+$ $IgG4^+$ $CD4^+$ effector memory T cells and $CXCR5^+$ $CD27^{lo}$ $CD28^-$ $MHC\text{-}II^+$ $CD8^+$ T_{EMRA} cells in irAE-arthritis patients compared with those without irAEs or irAE non-arthritis. The presence of IgG4 on these T cells indicates anti-PD-1 drug binding. Previous studies demonstrated clonal expansion of $IgG4^+$ $CD8^+$ T cells shared between blood and synovial fluid in irAE-arthritis patients, suggesting their role in disease pathogenesis.[29] Notably, peripheral blood $CD4^+$ $T_{H1/2}$ cells have been linked to irAE-arthritis.[49] $CD8^+$ T_{EMRA} cells, known for cytotoxicity and pro-inflammatory cytokine secretion, are associated with tissue infiltration and chronic inflammation, including irAE-myocarditis.[50 51] The increased proportion of these activated effector $CD8^+$ and $CD4^+$ T cell populations in our patients with OA with irAE-arthritis PBMC supports their involvement in disease pathophysiology.

In conclusion, we propose that $PD\text{-}1^+$ T_{RM} cells in OA joints differentiate and contribute to developing irAE-arthritis following ICI treatment (figure 6). This joint-specific memory phenomenon is similar to that observed in other inflammatory arthritis.[36] It highlights OA as an inciting factor for developing inflammatory arthritis post-PD-1 blockade. The involvement of $PD\text{-}1^+$ T_{RM} cells in irAE-arthritis is substantiated by the rapid flare-up of this condition on ICI treatment.[22] Future work should investigate if other irAEs are associated with prior tissue damage and the associated T_{RM} cells, which might represent a distinct population from the microbiota-specific T_{RM} cells commonly enriched in mucosal tissues.

This work has limitations. This retrospective study cannot assess risk progression from OA to irAE-arthritis. While radiographic criteria and ICD-10 codes were used for OA diagnosis, ligamentous and muscle injuries, potential contributors to T_{RM} cell influx, were not assessed. The clinical pattern of joint involvement in arthritis-irAEs is not restricted to synovial inflammation and often resembles spondyloarthritis with extensive enthesitis.[17] We speculate that this entheseal component of the irAEs is initiated by an analogous mechanism where potentially autoreactive PD-1-expressing resident entheseal T cells or those held in check by regulatory T cells (T_{REG}) interactions are also activated by the checkpoint inhibitor therapy.[52] Another important limitation to recognize is the possibility that T_{RM} cells are present in healthy tissues, yet not all patients develop irAEs at these sites. The lack of healthy control tissue in our analyses is a limitation that stems from the ethical difficulty of obtaining samples from healthy joints. Instead, we used publicly available single-cell RNA sequencing dataset from an atlas of a "healthy" human joint to show that while T_{RM} cells can be isolated from a healthy joint, their frequency is lower than in an OA-affected joint. It is likely that the frequency of T_{RM} cells in the tissue and their degree of activation, as marked by PD-1 expression and TCR clonality, are important features that can influence whether irAE develops.

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