

Type-I interferon signature and DNA damage accumulation in peripheral blood of patients with psoriatic arthritis

George E Fragoulis*^{1,2}, Panagiotis A. Ntouros*¹, Andrianos Nezos³, Nikolaos I. Vlachogiannis¹, Iain B McInnes²,
Charalampos Skarlis³, Maria Tektonidou¹, Vassilis L. Souliotis^{1, 4}, Clio P Mavragani^{1, 3}, Petros P Sfikakis¹

1. Joint Academic Rheumatology Program, First Department of propedeutic and Internal Medicine, National and Kapodistrian University of Athens Medical School, Athens, Greece

2. Institute of Infection, Immunity and Inflammation, University of Glasgow. Glasgow, UK

3. Department of Physiology, National and Kapodistrian University of Athens Medical School, Athens, Greece

4. Institute of Chemical Biology, National Hellenic Research Foundation, Athens, Greece



ΙΑΤΡΙΚΗ ΣΧΟΛΗ ΕΚΠΑ
NKUA MEDICAL SCHOOL



University
of Glasgow

School of Infection
& Immunity



ΕΘΝΙΚΟ ΙΔΡΥΜΑ ΕΡΕΥΝΩΝ
National Hellenic Research Foundation

1. Introduction - objectives of our study

2. Study design

3. Results

4. Limitations - plans of action

5. Conclusion

DNA Damage Response (DDR) aberrations in patients with systemic autoimmunity

Article | May 18 2009

Deficiency of the DNA repair enzyme ATM in rheumatoid arthritis

Lan Shao, Hiroshi Fujii, Inés Colmegna, Hisashi Oishi, Jörg J. Goronzy, Cornelia M. Weyand 

> *Immunity*. 2015 Feb 17;42(2):332-343. doi: 10.1016/j.immuni.2015.01.012.

DNA damage primes the type I interferon system via the cytosolic DNA sensor STING to promote anti-microbial innate immunity

Anetta Härtlova ¹, Saskia F Erttmann ¹, Faizal Am Raffi ¹, Anja M Schmalz ¹, Ulrike Resch ¹, Sharath Anugula ¹, Stefan Lienenklaus ², Lisa M Nilsson ³, Andrea Kröger ², Jonas A Nilsson ³, Torben Ek ⁴, Siegfried Weiss ², Nelson O Gekara ⁵

> *Arthritis Res Ther*. 2016 Aug 4;18(1):182. doi: 10.1186/s13075-016-1081-3.

Defective DNA repair and chromatin organization in patients with quiescent systemic lupus erythematosus

Vassilis L Souliotis ^{1 2}, Konstantinos Vougas ³, Vassilis G Gorgoulis ^{3 4}, Petros P Sfikakis ⁵

> *Clin Immunol*. 2019 Jun;203:28-36. doi: 10.1016/j.clim.2019.03.009. Epub 2019 Mar 28.

DNA damage accumulation, defective chromatin organization and deficient DNA repair capacity in patients with rheumatoid arthritis

Vassilis L Souliotis ¹, Nikolaos I Vlachogiannis ², Maria Pappa ², Alexandra Argyriou ², Petros P Sfikakis ³

> *Front Immunol*. 2020 Oct 2;11:582401. doi: 10.3389/fimmu.2020.582401. eCollection 2020.

Association Between DNA Damage Response, Fibrosis and Type I Interferon Signature in Systemic Sclerosis

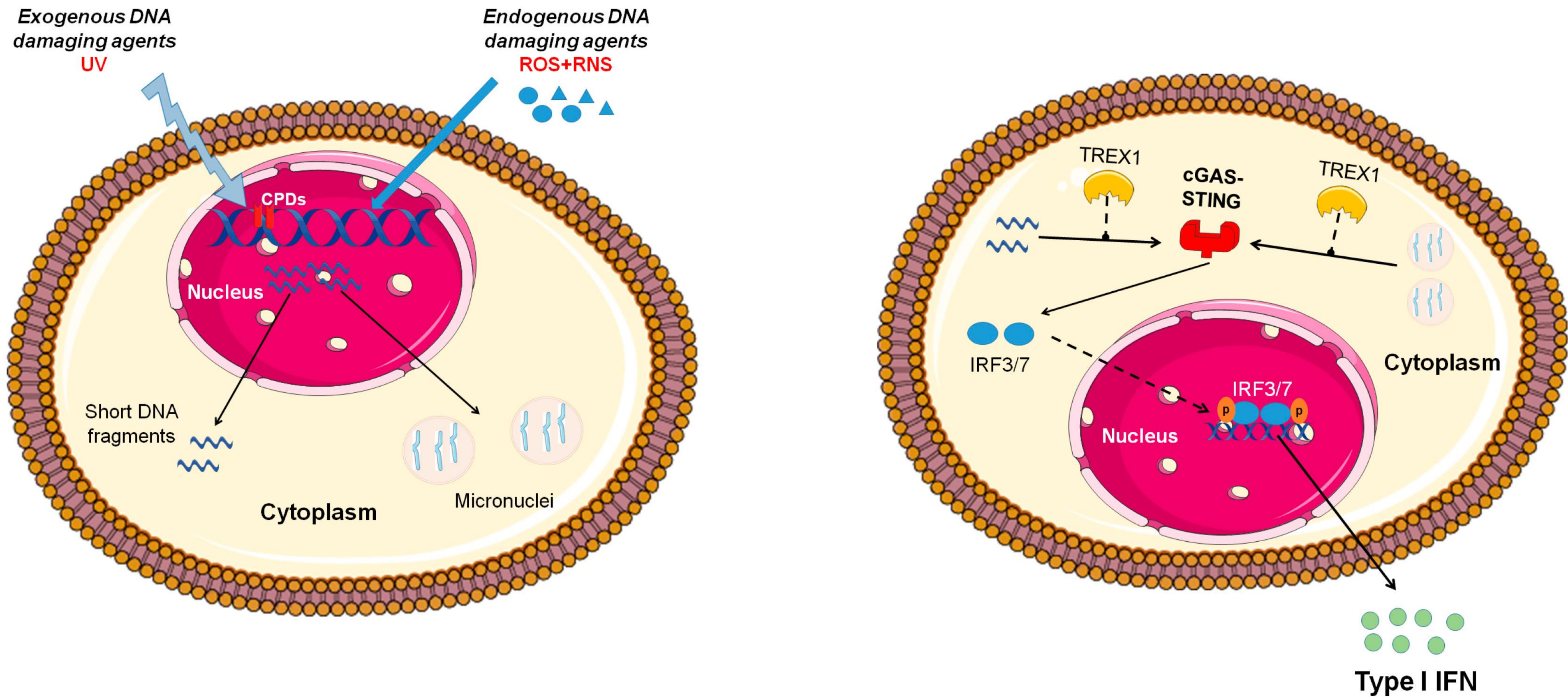
Nikolaos I Vlachogiannis ^{1 2}, Maria Pappa ^{1 2}, Panagiotis A Ntouros ^{1 2}, Adrianos Nezos ³, Clio P Mavragani ^{2 3}, Vassilis L Souliotis ^{1 4}, Petros P Sfikakis ^{1 2}

> *Clin Immunol*. 2023 Jan;246:109189. doi: 10.1016/j.clim.2022.109189. Epub 2022 Nov 16.

Deregulated DNA damage response network in Behcet's disease

Nikolaos I Vlachogiannis ¹, Panagiotis A Ntouros ², Maria Pappa ², Kleio-Maria Verrou ³, Aikaterini Arida ², Vassilis L Souliotis ⁴, Petros P Sfikakis ⁵

DNA damage formation can lead to type I IFN expression



Type I IFN aberrations may play a role in PSA pathogenesis

[J Exp Med](#) . 2005 Jul 4;202(1):135-43.

Article | July 05 2005

Plasmacytoid dendritic cells initiate psoriasis through interferon- α production

Frank O. Nestle, Curdin Conrad, Adrian Tun-Kyi, Bernhard Homey, Michael Gombert, Onur Boyman, Günter Burg, Yong-Jun Liu, Michel Gilliet



- activation and accumulation of plasmacytoid dendritic cells (pDCs) in psoriasis lesions
- type I IFN expression in psoriasis lesions

[Front Immunol](#). 2018; 9: 1936.

Anti-LL37 Antibodies Are Present in Psoriatic Arthritis (PsA) Patients: New Biomarkers in PsA

Loredana Frasca¹, Raffaella Palazzo¹, Maria S Chimenti², Stefano Alivernini^{3 4}, Barbara Tolusso³, Laura Bui⁵, Elisabetta Botti⁶, Alessandro Giunta⁶, Luca Bianchi⁶, Luca Petricca³, Simone E Auteri⁷, Francesca Spadaro⁸, Giulia L Fonti², Mario Falchi⁹, Antonella Evangelista⁵, Barbara Marinari⁶, Immacolata Pietraforte¹⁰, Francesca R Spinelli⁷, Tania Colasanti⁷, Cristiano Alessandri⁷, Fabrizio Conti⁷, Elisa Gremese^{3 4}, Antonio Costanzo¹¹, Guido Valesini⁷, Roberto Perricone², Roberto Lande¹



- LL-37 detects DNA and induces type I IFN expression - present in PSA synovia
- type I IFN signature in PSA synovia

[PLoS One](#). 2015; 10(6): e0128262.

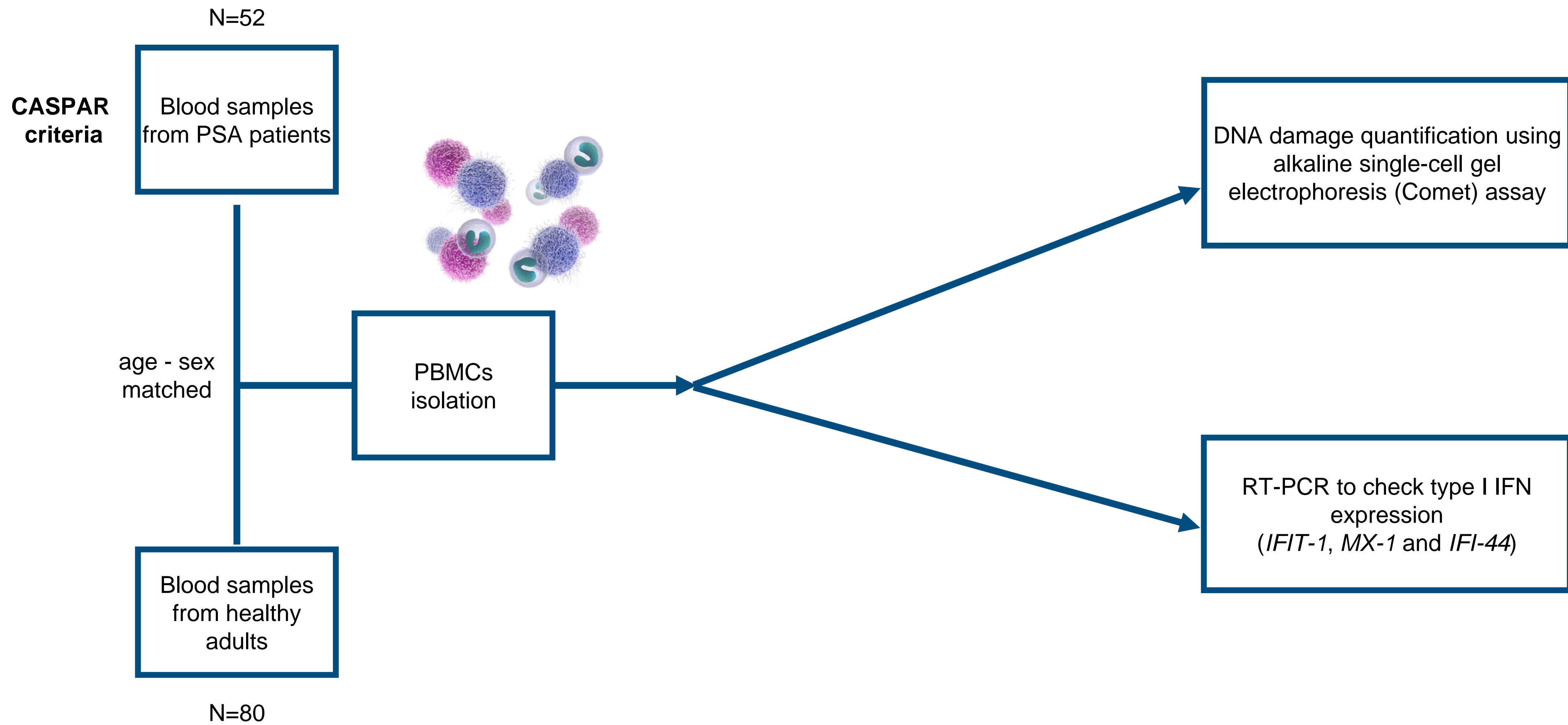
Gene Expression Profiling in Peripheral Blood Cells and Synovial Membranes of Patients with Psoriatic Arthritis

Marzia Dolcino,^{#1} Andrea Ottria,^{#3} Alessandro Barbieri,² Giuseppe Patuzzo,² Elisa Tinazzi,² Giuseppe Argentino,² Ruggero Beri,² Claudio Lunardi,^{2, †} and Antonio Puccetti^{1, 3, †*}



- elevated Type I IFN signature in PSA synovial membrane

Study design

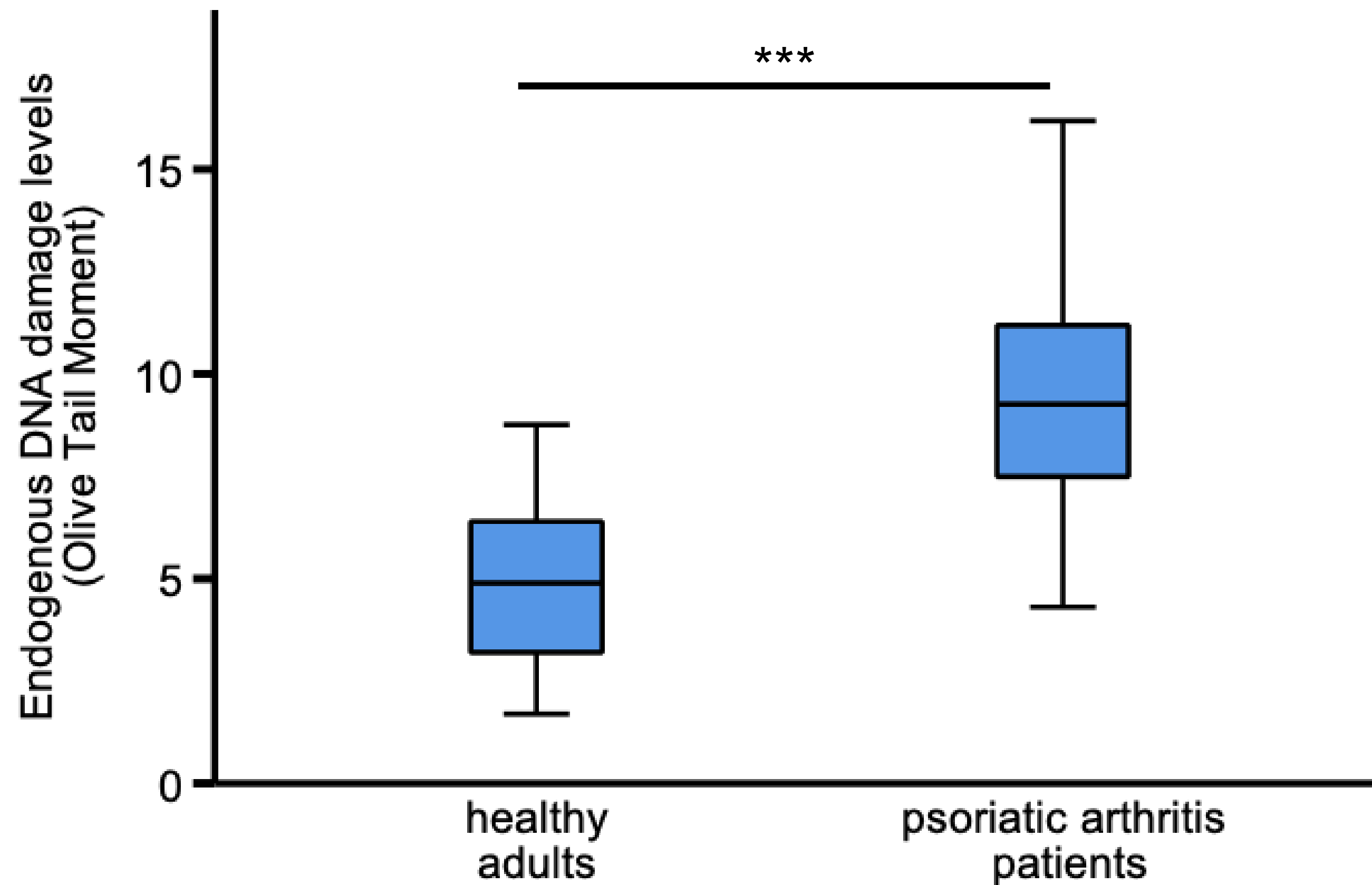


Excl. crit. : no active malignancy / no active and recent infection/vaccination
- for HCs : no personal history of SRDs

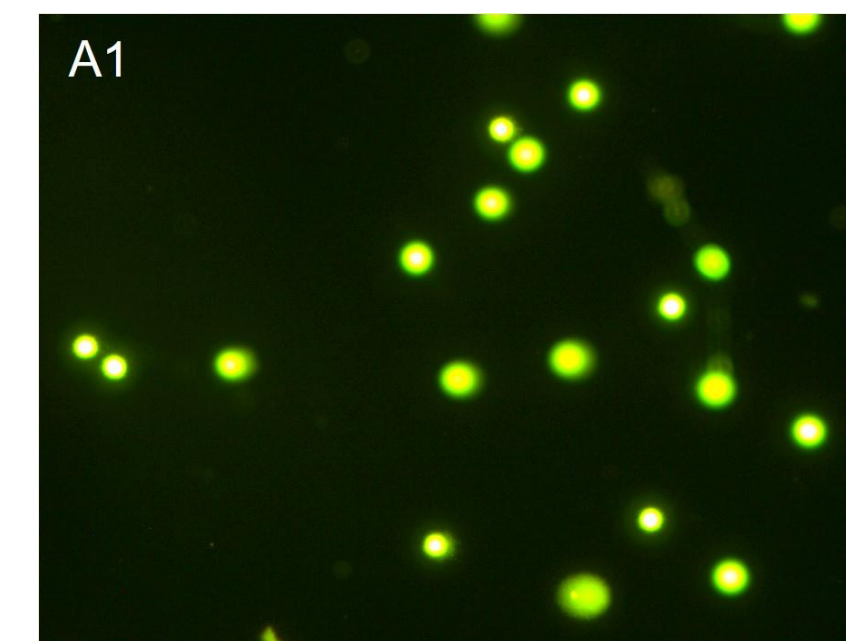
The cohort

Demographic features	PsA (n=52)
Age, mean \pm SD (years)	52.8 \pm 10.7
Female gender, n (%)	32 (61.5)
BMI, mean \pm SD	28.9 \pm 7.2
Smoking (current), n (%)	22 (42.3)
Follow-up time, mean \pm SD (months)	82.9 \pm 107.5
Clinical features (ever)	
Enthesitis, n (%)	18 (34.6)
Dactylitis, n (%)	15 (28.8)
Axial disease, n (%)	24 (46.1)
Nail disease, n (%)	33 (63.5)
DIP, n (%)	2 (3.8)
Eye involvement, n (%)	2 (3.8)
Bowel involvement, n (%)	4 (7.7)
Current treatment	
Steroids, n (%)	16 (30.8)
NSAIDs, n (%)	9 (17.3)
csDMARDs, n (%)	26 (50)
Apremilast, n (%)	2 (3.8)
TNF inhibitors, n (%)	24 (46.2)

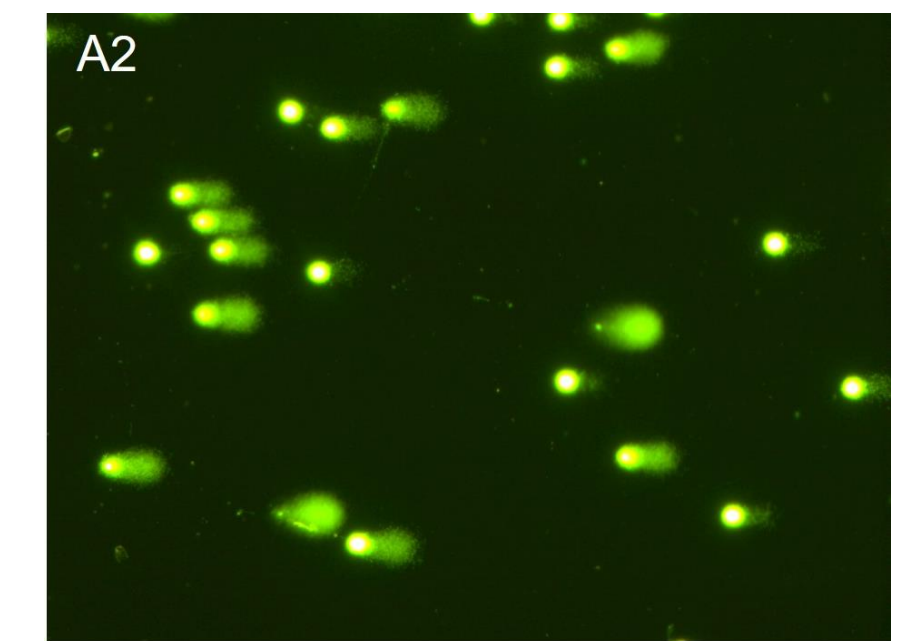
Increased endogenous DNA damage levels in PSA patients



	Healthy adults	Psoriatic arthritis patients
Number	80	52
DNA damage (OTM \pm SD)	4.88 \pm 1.98	9.42 \pm 2.71
P-value	p<0.001	



Healthy adults



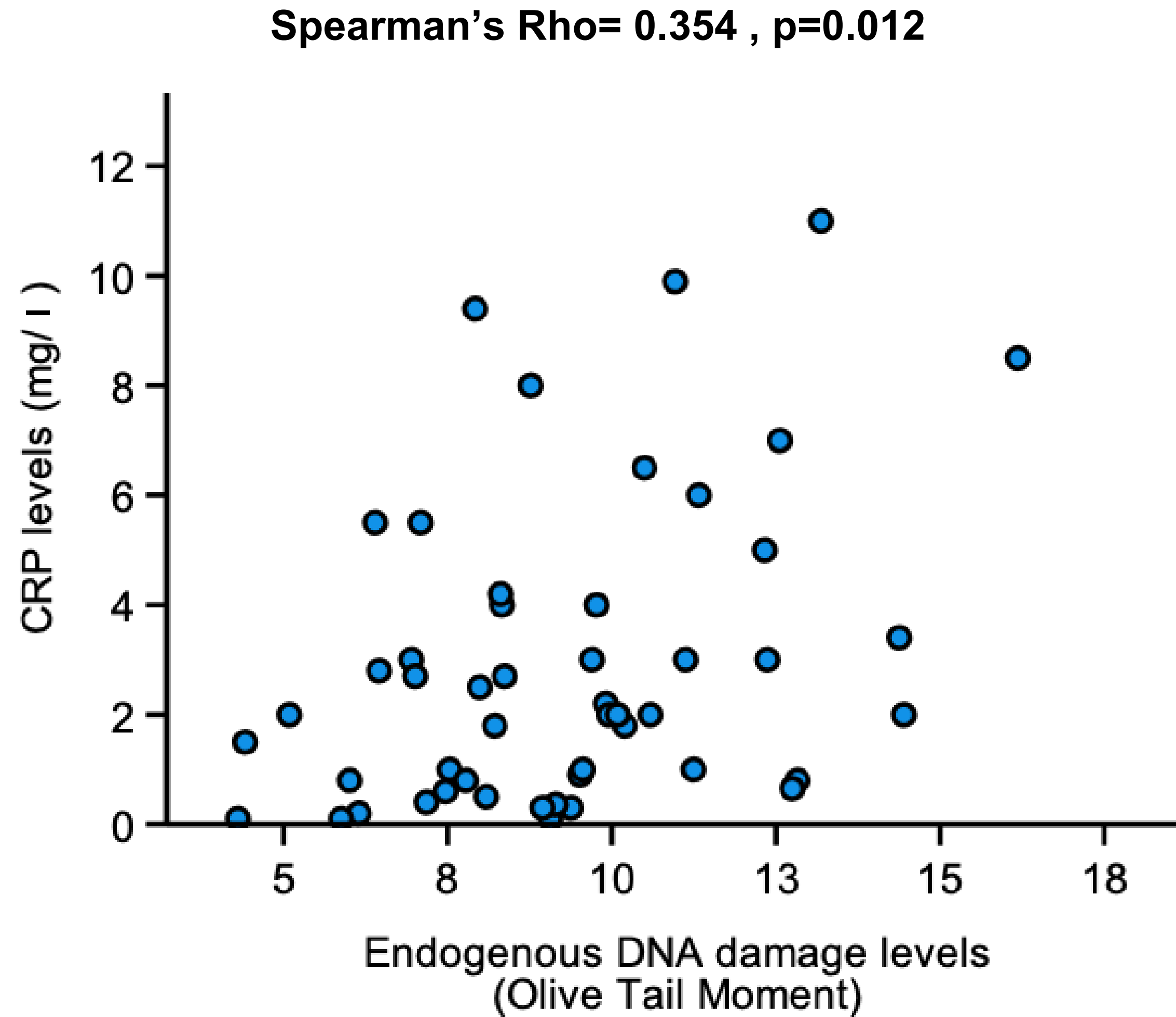
PSA patients

Endogenous DNA damage levels in PSA patients do not associate with patients' clinical characteristics

Disease Features	DNA damage score		
	presence	absence	
	mean ± SD		p-value
Female gender	9.13 ± 2.47	9.88 ± 3.07	0,339
Smoking	8.93 ± 2.63	9.78 ± 2.77	0,357
	R		p-value
Age	0,225		0,156
BMI	0,053		0,710
Disease duration	0,098		0,489
Ever present	mean ± SD		p-value
Enthesitis	8.89 ± 2.51	9.70 ± 2.81	0,306
Dactylitis	9.08 ± 2.82	9.56 ± 2.69	0,572
Nail disease	9.44 ± 2.78	9.38 ± 2.67	0,943
Axial disease	9.54 ± 2.55	9.30 ± 2.91	0,748
Uveitis	8.59 ± 5.25	9.47 ± 2.57	0,190
IBD	11.77 ± 3.03	9.22 ± 2.63	0,191

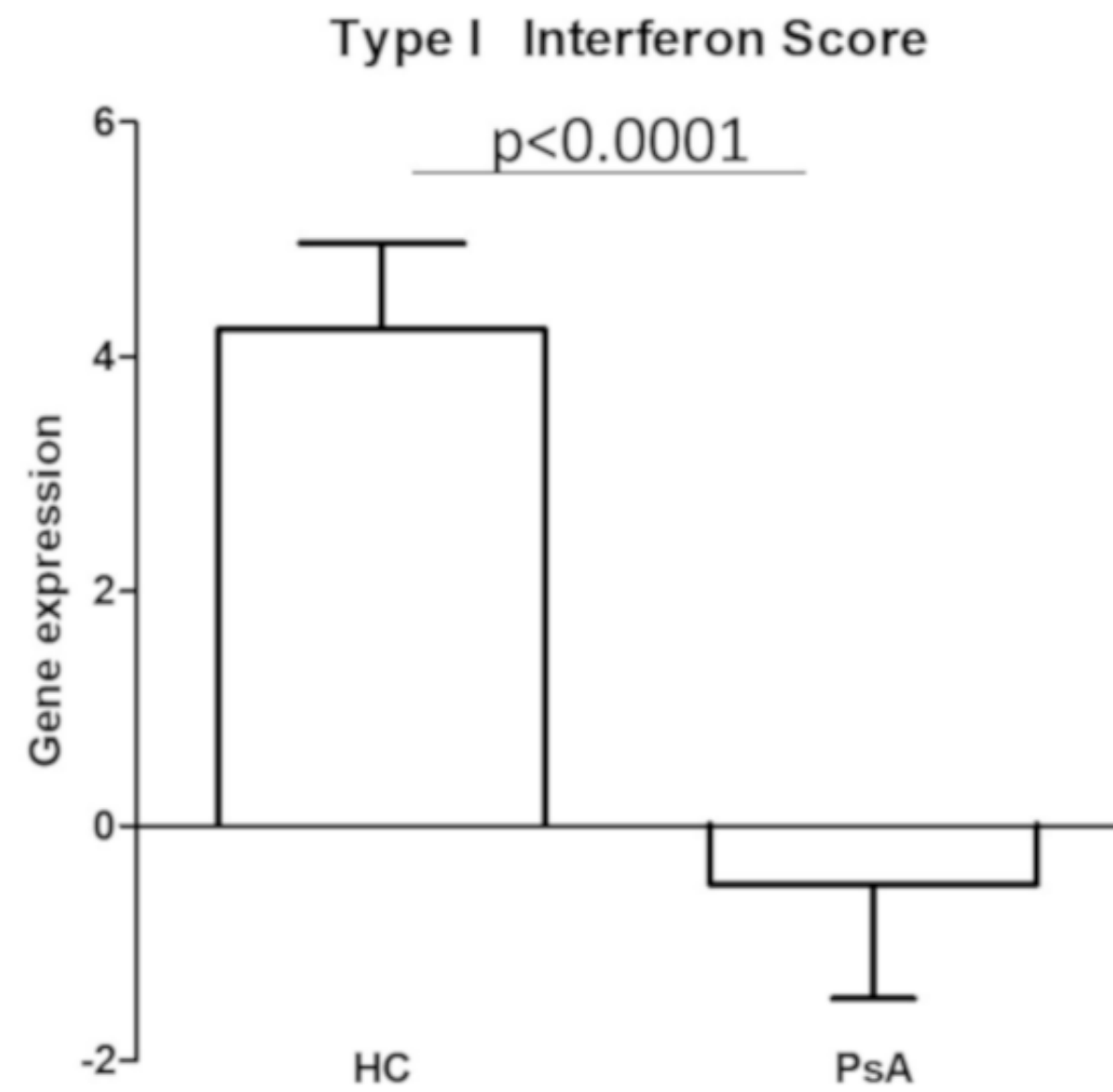
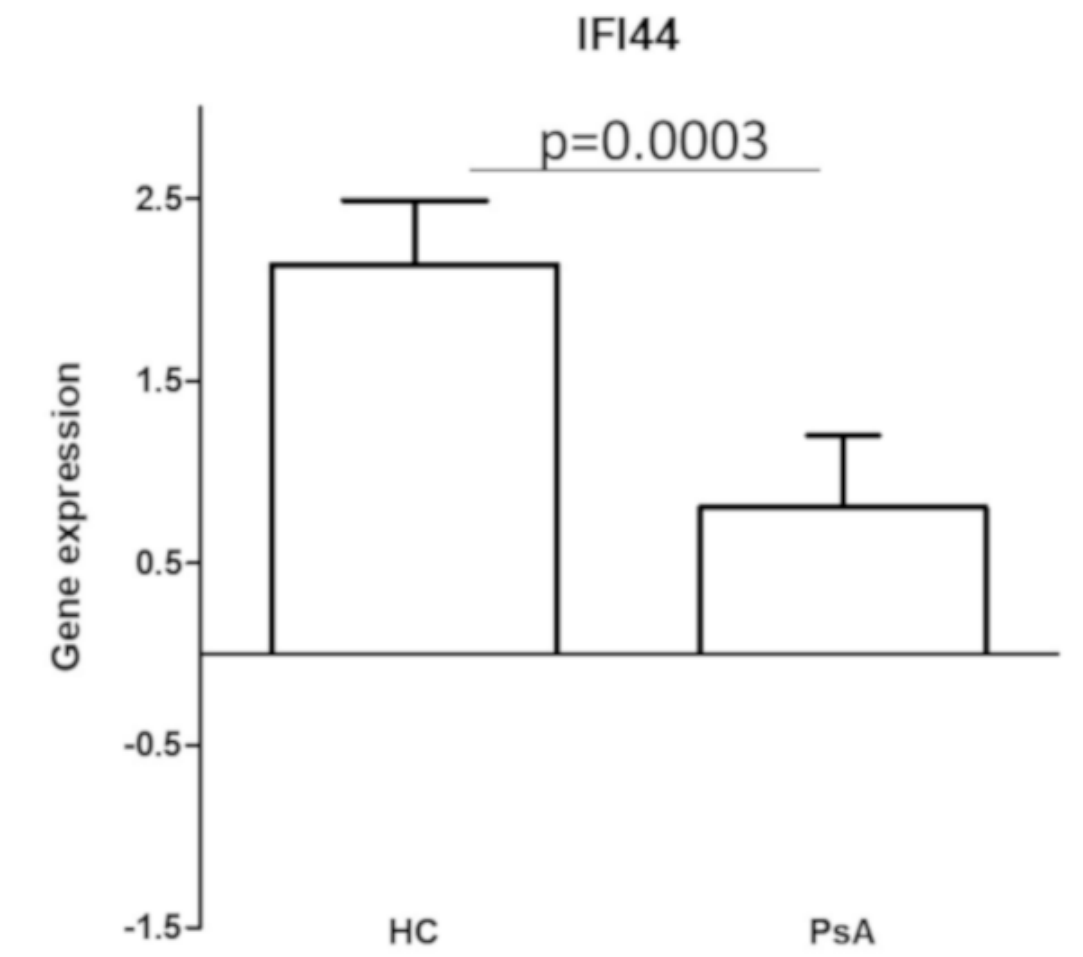
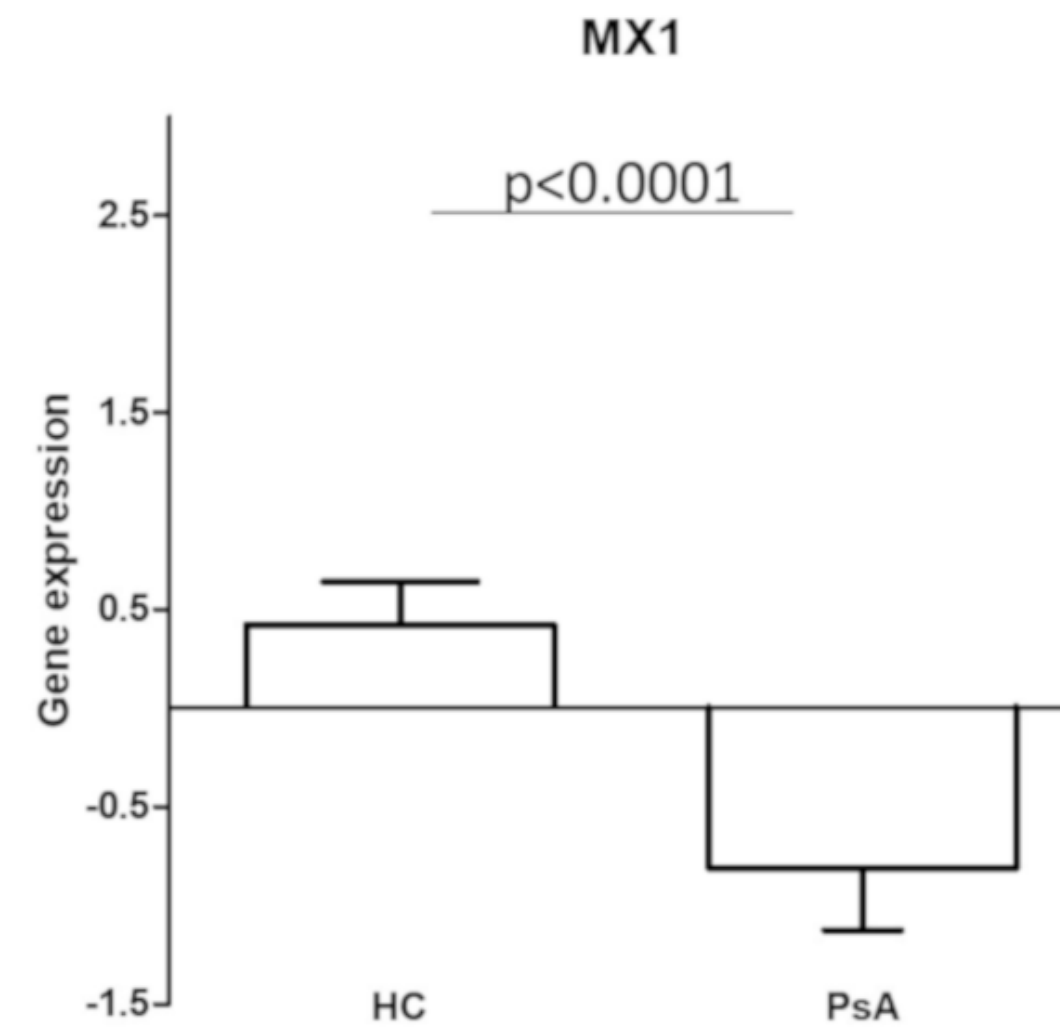
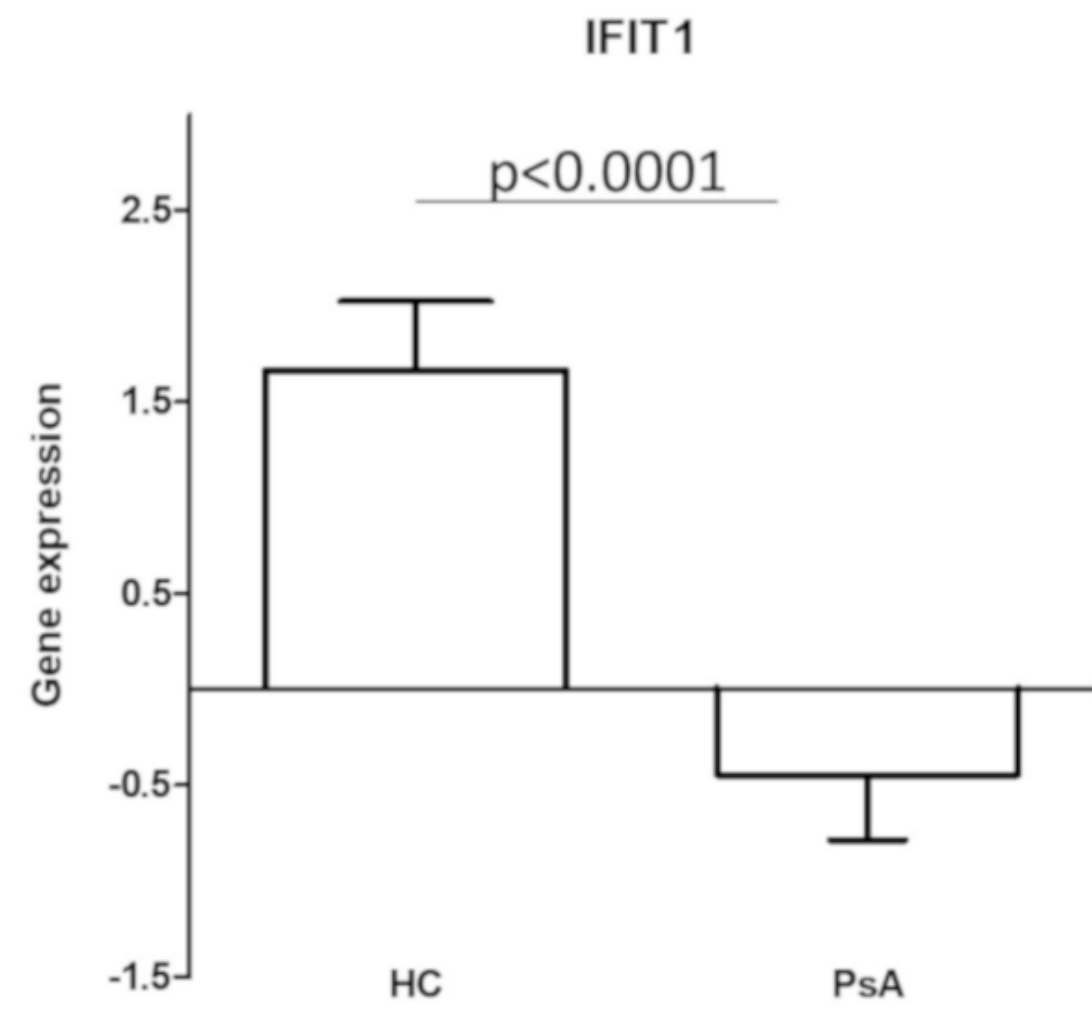
Disease Features	DNA damage score		
	presence	absence	
	mean ± SD		p-value
Current	mean ± SD	p-value	
Enthesitis	9.51 ± 2.33	9.40 ± 2.82	0,908
Dactylitis	8.97 ± 2.79	9.46 ± 2.73	0,732
Nail disease	9.34 ± 2.76	9.51 ± 2.71	0,942
BSA=0	9.56 ± 2.71	9.17 ± 2.77	0,594
MDA	9.57 ± 2.97	9.28 ± 2.51	0,706
Current Treatment	mean ± SD		p-value
Steroids	9.86 ± 2.82	9.22 ± 2.68	0,440
cDMARDs	9.16 ± 2.65	9.68 ± 2.80	0,475
Apremilast	11.14 ± 2.89	9.31 ± 2.70	0,217
TNFi	9.12 ± 3.28	9.74 ± 1.95	0,634
IL-23/17 inhibitors	10.12 ± 2.49	9.32 ± 2.76	0,469

Endogenous DNA damage levels correlate only with intercurrent CRP levels in PSA patients



CRP is elevated in half of PsA patients with active disease

Distinctive type I IFN signature in patients with PSA



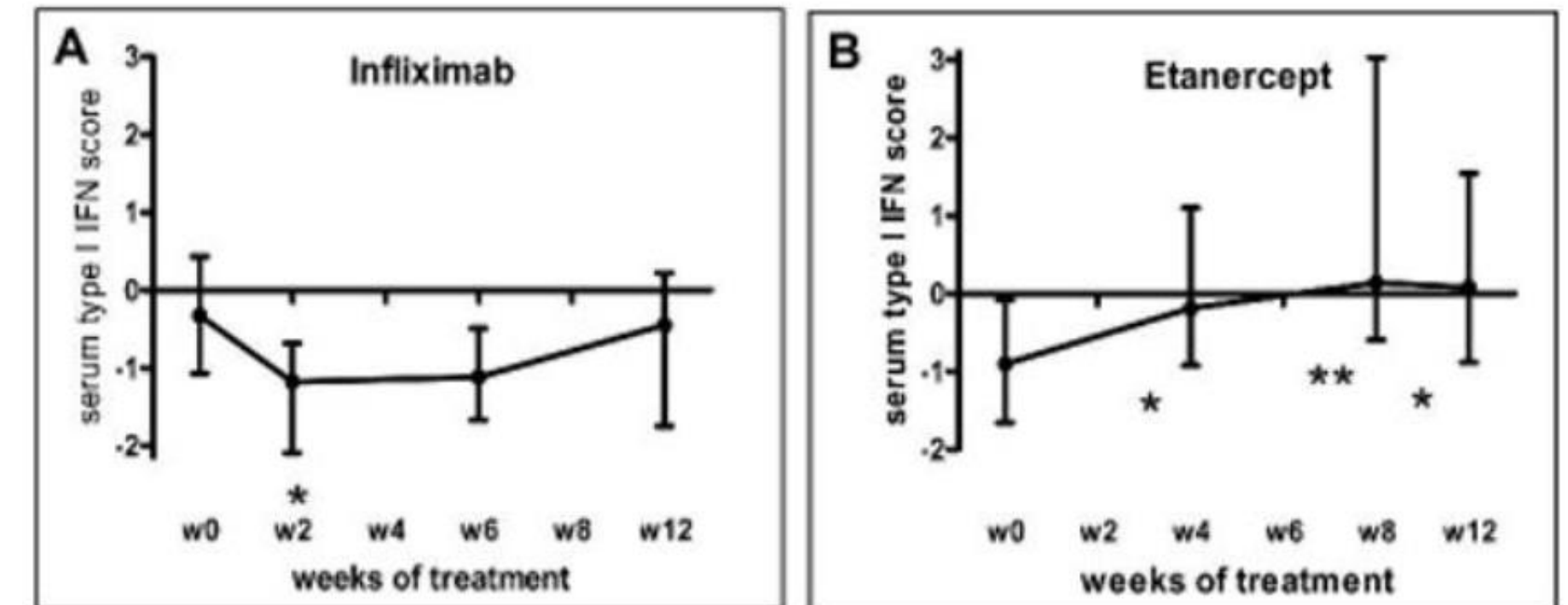
Associations between type I IFN expression and clinical characteristics

Disease Features	Type-I Interferon score		
	Presence	absence	
Demographics	mean ± SD		p-value
Female gender	-0.30 ± 7.20	-0.82 ± 6.82	992
Smoking	0.25 ± 8.10	-1.05 ± 6.15	831
	R		p-value
Age	0,057		0,689
BMI	-0,43		0,012
Disease duration	0,145		0,306
Ever present	mean ± SD		p-value
Enthesitis	-2.48 ± 4.41	0.55 ± 7.90	0,083
Dactylitis	1.36 ± 9.25	-1.25 ± 6.83	0,592
Nail disease	0.28 ± 8.33	-1.86 ± 3.49	0,902
Axial disease*	-1.34 ± 4.91	0.34 ± 8.61	0,898
Uveitis	14.00 ± 12.74	-1.39 ± 5.59	0.02
IBD	-2.21 ± 2.78	-0.36 ± 7.23	987

Disease Features	Presence	absence	p-value
	mean ± SD		
Current [†]	mean ± SD		p-value
Enthesitis	-2.56 ± 4.89	-0.01 ± 7.37	0,147
Dactylitis	1.43 ± 5.73	-0.66 ± 7.11	0,311
Nail disease	0.03 ± 7.58	-1.07 ± 6.41	0,660
BSA=0	-2.44 ± 3.90	2.88 ± 9.62	0.05
MDA	-0.16 ± 5.81	-0.81 ± 8.04	0,264
	R		p-value
DAPSA	0,092		0,524
BSA	0,268		0,05
ESR	0,163		0,263
CRP	-0,09		0,534
DNA damage (OTM)	-0,04		0,791
Current Treatment	mean ± SD		p-value
Steroids	-2.36 ± 6.05	0.33 ± 7.30	0,104
cDMARDs	-0.91 ± 6.24	-0.08 ± 7.78	0,552
Apremilast	-0.32 ± 7.14	-3.47 ± 2.87	0,455
TNFi	-0.18 ± 6.26	-0.77 ± 7.67	0,388
IL-23/17 inhibitors	1.20 ± 10.65	-0.76 ± 6.38	0,793

IFN-I downregulation Is it really a paradox?

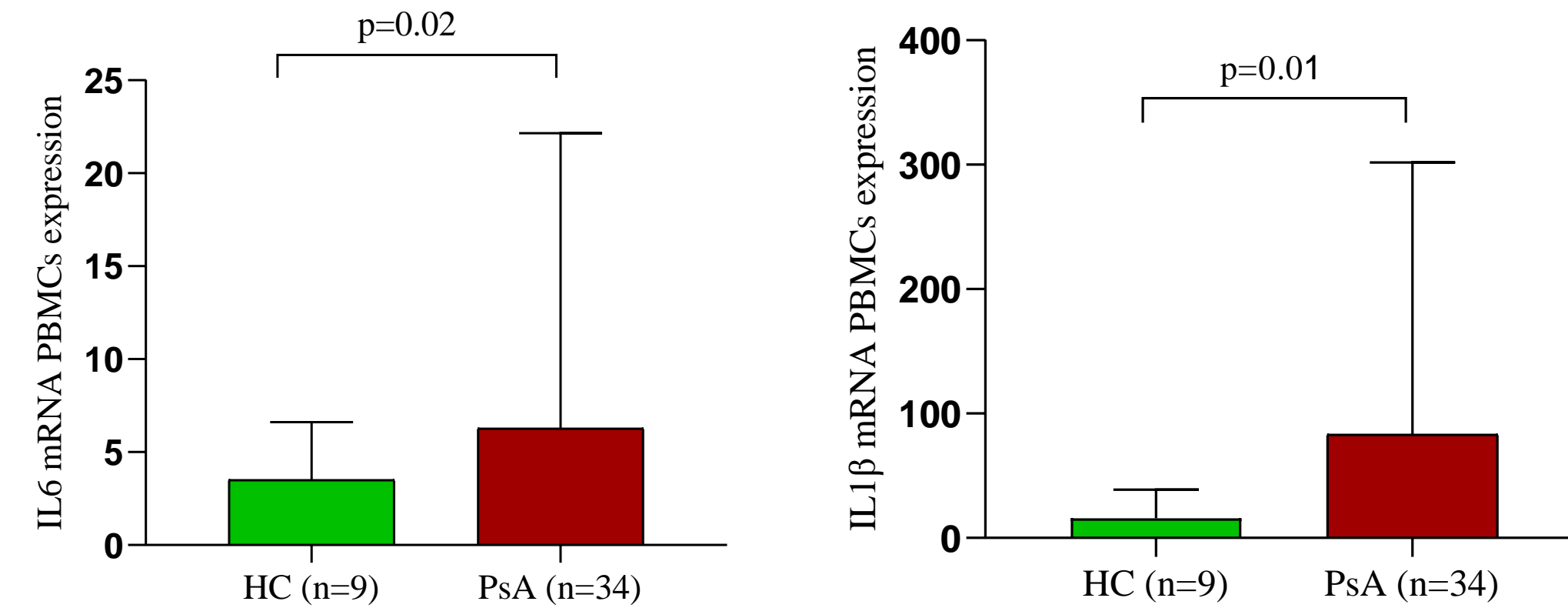
- Down-regulation of IFN-I has been described in the past in SpA patients
- B-27 Tg rats (Vs controls)
 - DC: Downregulation of INF-related genes



IFN-I downregulation

Any explanation?

- In a subgroup of patients (n=34)
 - Expression of the genes encoding for TNF, Interleukin (IL)-1, IL-6, IL-23 and IL-17 was also examined via qRT-PCR
 - PsA Vs Healthy
 - \uparrow IL-1 and IL-6
- Within PsA patients
 - decreased IFN-I scores
 - High IL-1 Vs low IL-1 (-2.35 ± 5.85 vs 0.98 ± 7.11 , $p=0.028$)
 - TNF/IL-23 high Vs TNF/IL-23 (-3.34 ± 2.89 Vs 1.42 ± 7.98 , $p=0.022$)



> *Immunity*. 2011 Feb 25;34(2):213-23. doi: 10.1016/j.immuni.2011.02.006.

Type I interferon inhibits interleukin-1 production and inflammasome activation

Greta Guarda ¹, Marion Braun, Francesco Staehli, Aubry Tardivel, Chantal Mattmann, Irmgard Förster, Matthias Farlik, Thomas Decker, Renaud A Du Pasquier, Pedro Romero, Jürg Tschopp

Limitations - Plans of action

- Cohort consists of patients under immunomodulatory medication —> enrollment of treatment-naive patients.
- Larger validation studies needed

Conclusion

- Increased DNA damage in PSA patients - higher DNA damage in high CRP subgroup
- Type I IFN down-regulation
 - intrinsic feature of SpA/PsA
 - Modulated by other cytokines
- Further studies warranted



Thank you for your attention