S100A9 Identifies Distinct Circulating Myeloid Cell Subsets in Metastatic Prostate Cancer

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BACKGROUND

S100A9 is a calcium-binding protein involved in inflammation and immune regulation, predominantly expressed in granulocytes and immunosuppressive monocytes. Its role in the systemic immune landscape of metastatic prostate cancer (mPCa) remains unclear.

OBJECTIVE

This prospective observational study aimed to characterize S100A9 expression in circulating myeloid cells from patients with mPCa using liquid biopsy and to explore treatment- associated changes.

METHODOLOGY

Peripheral blood samples were collected from patients with mPCa (castration-sensitive and castration-resistant) and healthy donors (controls) enrolled between January 2024 and June 2026 at the Instituto de Oncología Ángel H. Roffo (Argentina). Serum, plasma, and leukocyte fractions were processed and stored in the institutional biobank. Flow cytometry was used to quantify S100A9-expressing monocytes (S100A9$^+$CD14$^+$) and granulocytes (S100A9$^+$CD15$^+$). Patient samples were obtained at baseline and at the first response evaluation (~12 weeks).

SAMPLING SCHEDULE

WORKFLOW

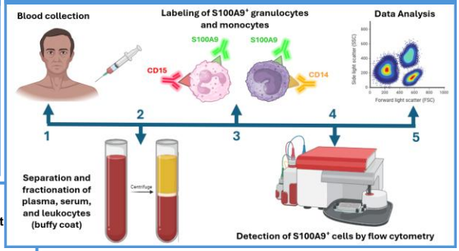

Figure 1: S100A9$^+$ Monocytes in Circulating Leucocytes

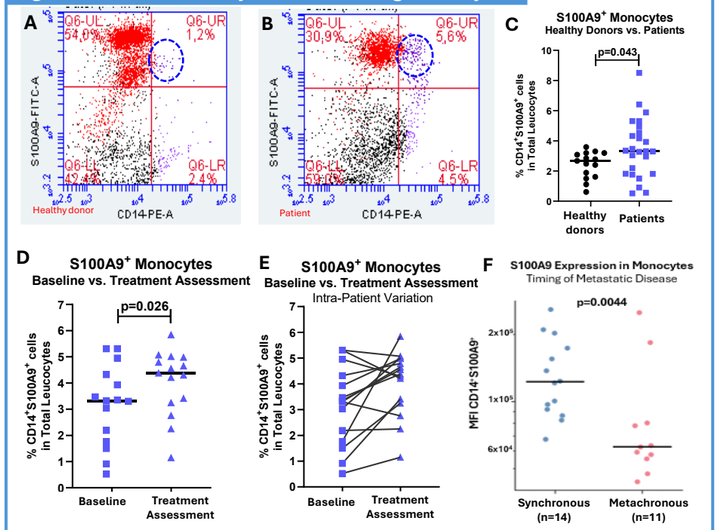

Fig. 1. A–B) CD14 and S100A9 expression dot plots from a representative healthy donor and a patient. **C–E)** Total percentage of S100A9$^+$ granulocytes among circulating leukocytes. **C)** Healthy donors vs. patients. **D–E)** Patient´s samples at baseline and treatment assessment. **F)** Median fluorescence intensity (MFI) of S100A9 in monocytes from patients with synchronous or metachronous metastases.

Figure 2: S100A9$^+$ Granulocytes in Circulating Leucocytes

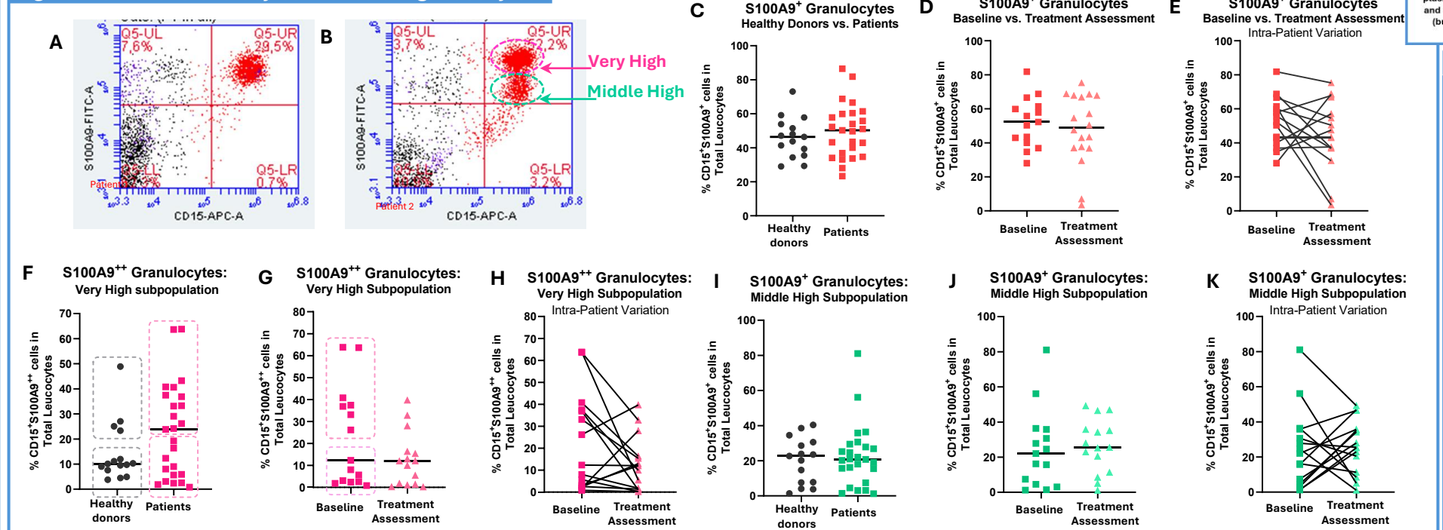

Fig. 2. A–B) CD15 and S100A9 expression dot plots from two different patients. Patient 2 **(B)** showed two distinct granulocyte populations with differential S100A9 expression: one with Very High S100A9 expression (**pink circle**) and the other with Middle High S100A9 expression (**green circle**). **C–E)** Total percentage of S100A9$^+$ granulocytes among circulating leukocytes. **C)** Healthy donors vs. patients. **D–E)** Patient samples atbaseline and treatment assessment. **F–H)** Percentage of Very High S100A9^{++} granulocytes among circulating leukocytes. The dotted rectangle identifies distinct patient groups. **F)** Healthy donors vs. patients. **G–H)** Patient samples at baseline and treatment assessment. **I–K)** Percentage of Middle High S100A9$^+$ granulocytes among circulating leukocytes. **I)** Healthy donors vs. patients. **J–K)** Patient samples at baseline and treatment assessment.

Table 1: Patients Characteristics

Variables	Value (n=25)
Age, years – median (IQR)	72 (65 -74)
Stage at diagnosis – n (%)	
I	2 (8)
II	7 (28)
III	2 (8)
IV	14 (56)
Gleason score – n (%) (initial biopsy)	
≥ 8	19 (76)
< 8	6 (24)
Castration status – n (%)	
Resistant	5 (20)
Sensitive	15 (80)
Radical prostatectomy – n (%)	
Yes	5 (20)
No	20 (80)
Treatment types – n (%)	
Doublet	15 (60)
Triplet	10 (40)

CONCLUSION

Circulating S100A9$^+$ monocytes were significantly increased in patients with mPCa and further expanded after treatment, suggesting treatment-associated modulation of the myeloid compartment. S100A9 expression was also higher in patients monocytes with synchronous metastases than in those with metachronous metastases. We identified previously unrecognized granulocyte subpopulations with distinct S100A9 expression profiles, supporting functional heterogeneity within circulating myeloid cells. These findings highlight a potential immunomodulatory role of S100A9 in the systemic response to therapy. Longitudinal studies in a larger cohort are ongoing to determine the prognostic and predictive value of these immune subsets populations in mPCa.