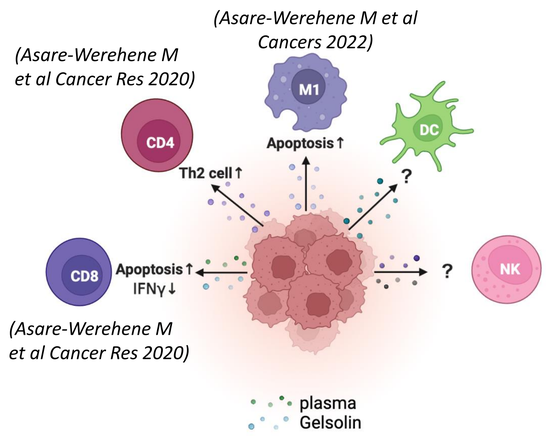
The role of plasma Gelsolin in regulating CD8+ cell and NK cell Function in Ovarian Cancer Chemoresistance

Toshimichi Onuma[1,3], Meshach Asare-Werehene[1,2], Yuko Fujita[3], Yoshio Yoshida[3], Benjamin K. Tsang[1,2]

1. Department of Obstetrics & Gynecology, University of Ottawa
2. Chronic Disease Program, Ottawa Hospital Research Institute
3. Department of Obstetrics and Gynecology, Faculty of Medical Sciences, University of Fukui

Introduction

- Ovarian cancer (OVCA) has the poorest prognosis in gynecologic cancer. Resistance to chemotherapy is a major issue that must be overcome. Plasma Gelsolin (GSN) contributes to chemotherapy resistance of ovarian cancer. Immune cells need to be functional for chemotherapy to be effective.
- Chemoresistant cell-derived plasma GSN induced immune cell dysfunction which leads to poor prognosis.



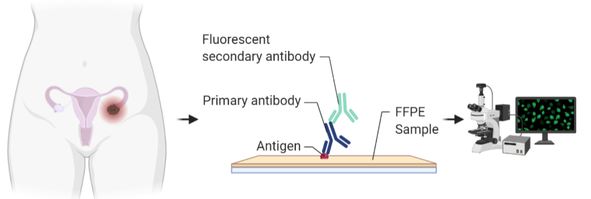
Immunosuppressive effect of Plasma Gelsolin for immune cells in Tumor microenvironment of OVCA

Objective

To investigate the prognostic effect of GSN on CD8+ and NK cells in OVCA chemoresistance.

Methods

- **Immunofluorescence (IF) staining analysis for GSN, CD8, and NCR1 expression**



Primary debulking surgery for OVCA | **Stain GSN, CD8, NCR1, and keratin K8/K18** | **Measure mean fluorescent intensity**

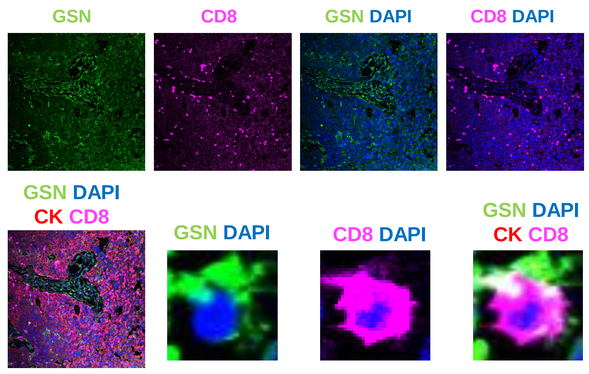
- **mRNA coexpression analysis using ovarian cancer public datasets-**The Ovarian serous carcinoma datasets derived from The Cancer Genome Atlas were used to analyze GSN and markers for T- or NK- cell exhaustion (PD-1,TIM-3, LAG-3, TIGIT, and CTLA-4)

Patient characteristics

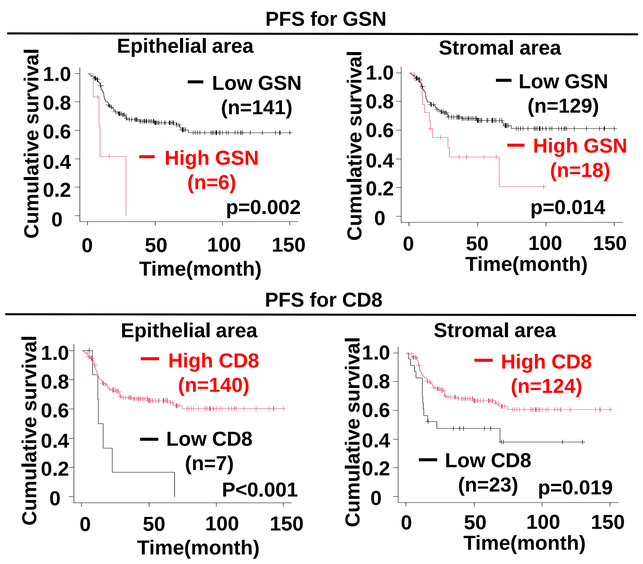
n	147
age(mean)±SD year	57.0±12.2
Stage n(%)	
I	74(50.3)
II	16(10.9)
III	41(27.9)
IV	16(10.9)
Histology n(%)	
High grade Serous carcinoma	70(47.6)
Endometrioid carcinoma	21(14.3)
Clear carcinoma	40(27.2)
Mucinous carcinoma	16(10.9)
Optimal surgery n(%)	101(68.7)
PFS (median) month	37
Recurrence (%)	53(36.1)

Result

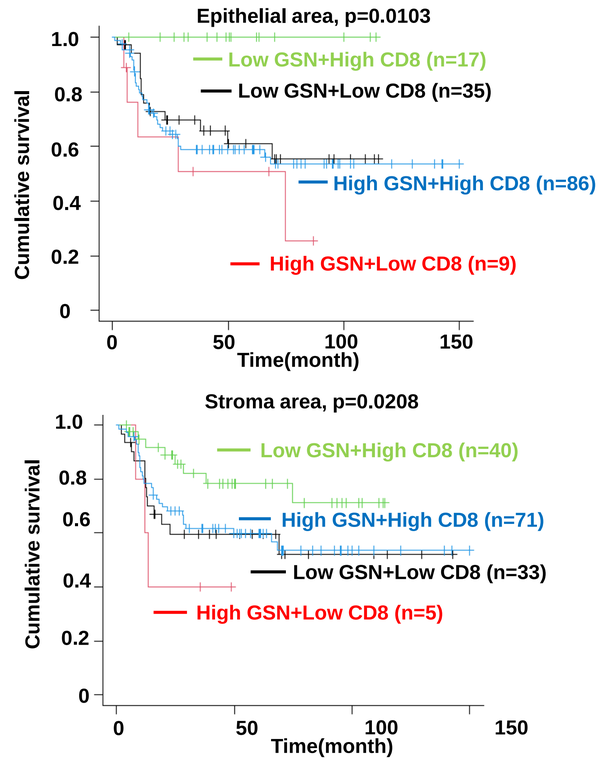
CD8+ cell was co-expressed with GSN



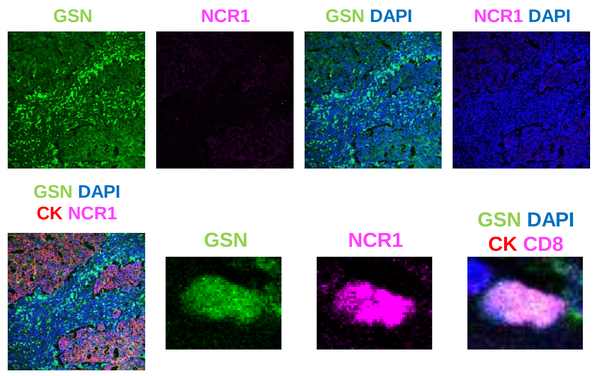
Low GSN and high CD8 expression was associated with a better PFS



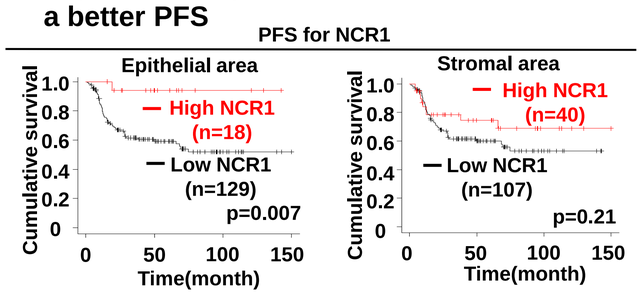
The positive prognostic effect of high CD8 expression was suppressed in high GSN expression.



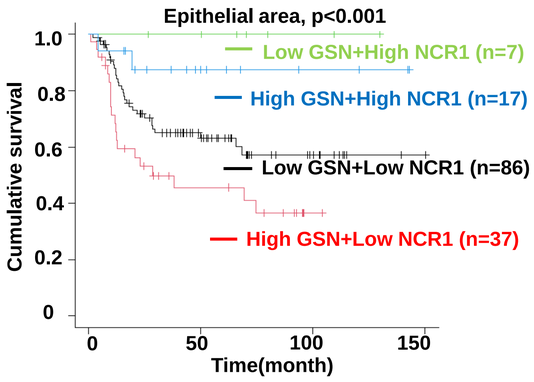
NCR1+ cell was co-expressed with GSN



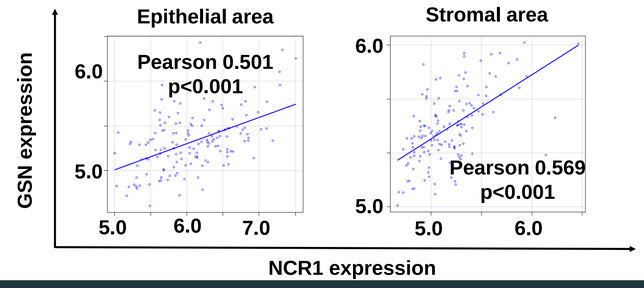
High NCR1 expression was associated with a better PFS



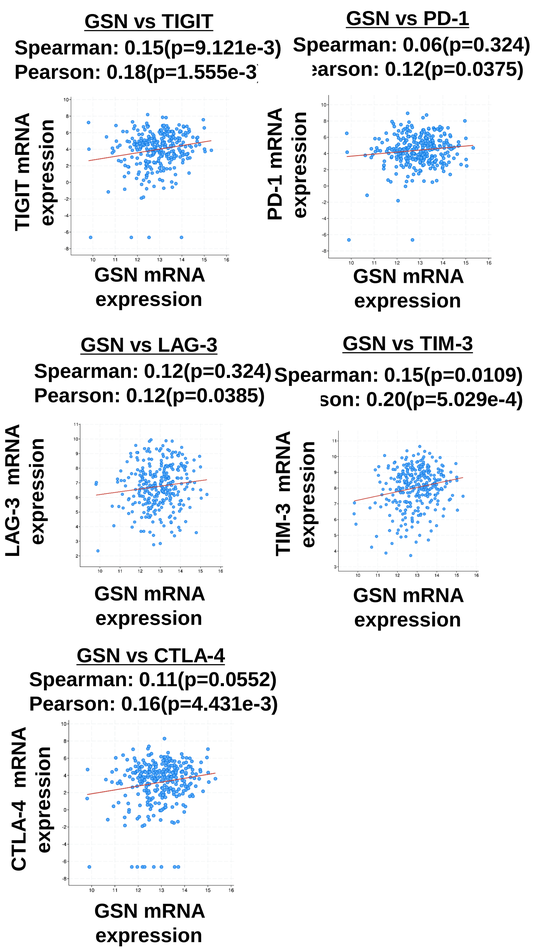
The positive prognostic effect of high NCR1 expression was suppressed in high GSN expression.



The NCR1 expression was positively correlated with GSN expression in IF



The GSN was associated with T- and NK- cell exhaustion markers



Summary

- The positive prognostic effect of CD8 and NCR1 was suppressed by GSN in Japanese ovarian cancer patients.
- T and NK cell might be dysfunctional in the presence of high plasma GSN.
- The NCR1 was positively correlated with GSN. However, The GSN was associated with NK cell exhaustion markers.
- Plasma GSN might act as a chemoattractant as well as on macrophage and cause NK cells dysfunction or apoptosis in TME *(Asare-Werehene M et al Cancers 2022)*.

Conclusion

- The GSN had an immunosuppressive effect that caused a poor prognosis in OVCA.
- Treatments targeting plasma GSN might improve immune dysfunction like an immune checkpoint inhibitor

Work in Progress

We are doing experiment using NK92MI to analyze the effects of GSN on NK cell function.

Acknowledgments

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