Annexin A1 (ANXA1)

Annexin A1 is the protein product of the **ANXA1 gene**. The terms **Annexin A1** and **ANXA1** are often used interchangeably in scientific literature.

Gene and Protein

- **Gene symbol**: ANXA1
- **Protein name**: Annexin A1
- **Location**: Chromosome 9q21
- **Family**: Annexin superfamily (calcium-dependent phospholipid-binding proteins)

Functions

Annexin A1 is involved in:

- Resolution of inflammation
- Inhibition of neutrophil transmigration
- Promotion of apoptotic cell clearance by macrophages
- Glucocorticoid-mediated immune modulation

Role in Cancer

Annexin A1 plays a dual role, depending on the cancer type:

- **Tumor suppressor** in some cancers (e.g. breast, prostate)
- **Tumor promoter** in others (e.g. glioma, pancreatic cancer)

ANXA1 in Glioma

Recent studies show that in glioma, ANXA1:

- Is upregulated in a **methionine metabolism-dependent** manner
- Drives macrophages toward an **immunosuppressive phenotype**
- Promotes immune evasion and tumor progression

In a Translational research with bulk RNA sequencing analysis, scRNA-seq, and in vitro validation Hong Hu *et al.* from the Harbin Medical University published in the **Journal:** Discover Oncology to elucidate how methionine metabolism contributes to the immunosuppressive tumor microenvironment in gliomas, with a focus on macrophage polarization mediated by ANXA1. Elevated methionine metabolism in glioma cells correlates with higher WHO tumor grade and an immunosuppressive microenvironment. High methionine metabolic activity fosters M2 macrophage polarization via ANXA1, which is downregulated upon methionine deprivation [1].

Critical Review

This study leverages multi-omics datasets, particularly MMA-scoring and scRNA-seq, to draw a novel link between methionine metabolism and the immune suppressive phenotype in gliomas, focusing on macrophage polarization. The authors make a credible case for metabolic reprogramming as a driver of glioma malignancy. However, there are caveats:

- **Strengths:** The integration of bulk and single-cell RNA-seq enhances resolution, and the use of in vitro validation lends support to mechanistic claims. The correlation between MMA-scores and glioma grade is statistically compelling.

- **Limitations:** Despite the innovative premise, the study relies heavily on correlative data. Functional validation, particularly in vivo or using clinical samples, is lacking. The assertion that ANXA1-mediated macrophage polarization is solely Met-dependent needs further biochemical interrogation. Furthermore, patient sample heterogeneity and potential confounders are not adequately addressed.

- **Mechanistic Gap:** While ANXA1 expression is shown to respond to Met availability, its downstream effects on macrophage behavior are inferred rather than mechanistically dissected.

- **Clinical Implications:** The study's translational relevance is speculative. No clinical outcome data (e.g., survival stratified by MMA-score) are presented, and therapeutic exploitation remains conceptual.

Final Verdict: Ambitious and methodologically diverse, but insufficiently validated for clinical translation.

Takeaway for the Practicing Neurosurgeon: While methionine metabolism may signal tumor aggressiveness and immune evasion, it is not yet a practical biomarker or therapeutic target without deeper functional validation.

Bottom Line: Promising hypothesis linking glioma metabolism to immune suppression via ANXA1; more robust causal evidence is needed before clinical application.

Rating: 6.5/10

Title: Glioma promotes macrophage immunosuppressive phenotype through ANXA1 in a methionine metabolism-dependent manner **Citation:** Hu H *et al.* Discover Oncology. 2025 Jul 6;16(1):1269. doi:10.1007/s12672-025-03112-y **Publication Date:** July 6, 2025 **Corresponding Author Email:** liuhuaileinsdm@hrbmu.edu.cn

Summary

Annexin A1 = ANXA1 They refer to the same biological entity:

- **ANXA1** → gene name
- **Annexin A1** → protein name

Both are essential to understanding the molecular basis of glioma immune escape.

annexin ANXA1 glioma methionine immunosuppression

Annexin A1, also known as lipocortin I, is a protein that is encoded by the ANXA1 gene in humans.

Also known as lipocortin I, is a protein that is encoded by the ANXA1 gene in humans [2)]

Flores et al. hypothesized that FPR2 activation by FPR2 agonist Annexin A1 (AnxA1) will enhance hematoma resolution via the upregulation of the CD36 signaling pathway, thereby improving short- and long-term neurological outcomes. Bacterial collagenase (0.3 U) was infused intraparenchymally into the right hemispheric ganglionic eminence in P7 rat pups to induce GMH. AnxA1 and FPR2 Inhibitor (Boc2) were given at 1-h post-GMH via intranasal administration. FPR2 CRISPR was given 48-h prior to GMH induction. Short-term neurological deficits were assessed using negative geotaxis test. Hematoma volume was assessed using hemoglobin assay. Protein expression was assessed using western blots. Long-term neurocognitive deficits and motor coordination were assessed using Morris water maze, rotarod, and foot fault tests. We have demonstrated that AnxA1 treatment enhances hematoma resolution and improved short and long-term outcomes. Lastly, FPR2 agonist AnxA1 treatment resulted in the upregulation of the FPR2/p-ERK(1/2)/DUSP1/CD36 signaling pathway [3)]

1)
Hu H, Huang Y, Li J, Liu R, Li H, Cai M, Chen H, Wang N, Yang S, Wang K, Teng L, Liu H. Glioma promotes macrophage immunosuppressive phenotype through ANXA1 in a methionine metabolism-dependent manner. Discov Oncol. 2025 Jul 6;16(1):1269. doi: 10.1007/s12672-025-03112-y. PMID: 40618309.
2)
Lin Z, Wen M, Yu E, Lin X, Wang H, Chen J, Yao C, Zhang H, Ru J, Wang K, Zhang Y, Huang L, Zhuge Q, Yang S. ANXA1 as a Prognostic and Immune Microenvironmental Marker for Gliomas Based on Transcriptomic Analysis and Experimental Validation. Front Cell Dev Biol. 2021 Aug 4;9:659080. doi: 10.3389/fcell.2021.659080. PMID: 34422796; PMCID: PMC8371204.
3)
Flores JJ, Ding Y, Sherchan P, Zhang JH, Tang J. Annexin A1 upregulates hematoma resolution via the FPR2/p-ERK(1/2)/DUSP1/CD36 signaling pathway after germinal matrix hemorrhage. Exp Neurol. 2023 Jan;359:114257. doi: 10.1016/j.expneurol.2022.114257. Epub 2022 Oct 21. PMID: 36279933.