**From association to function: G Protein Signaling Modulator 3 (GPSM3) polymorphisms in rheumatoid arthritis**

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Background: West Virginia ranks among the worst in the nation for arthritis prevalence, with 25%-33% of WV's population being affected by some form of the autoimmune disease. A particular burden is rheumatoid arthritis (RA), mediated by dysregulation of immune cells including leukocytes. *GPSM3* is a protein with restricted expression solely in leukocytes. Notably, two human *GPSM3* single-nucleotide polymorphisms (SNPs) are associated with a *decreased* likelihood of developing RA, but the mechanism of this association is unknown.

Methods: Volunteers were recruited to donate blood for qRT-PCR analysis of *GPSM3* transcript abundance and promoter-driven luciferase activity *in vitro*.

Results: Blood mRNA from volunteers homozygous for 'protective' *GPSM3* SNPs (n = 11) contained 24% less *GPSM3* transcript than volunteers without the SNPs (n = 58). From *in vitro* reporter gene data, the *GPSM3* SNP rs204989 was associated with decreased promoter activity. Functionally, GPSM3-deficient human neutrophil-like cell lines exhibited disrupted chemotaxis.

Discussion and conclusions: 'Protective' *GPSM3* SNPs cause decreased transcript abundance *in vivo*, likely resulting in decreased GPSM3 protein expression. Therefore, GPSM3 may play a role in the migration of proinflammatory neutrophils to synovial tissues during RA inflammatory bouts -- invasion into synovial tissue is likely decreased when GPSM3 levels are decreased. Having identified that decreased *GPSM3* expression is associated with protection from RA, we are now pursuing strategies to inhibit GPSM3 expression or function as potential new treatment modalities in arthritis pharmacotherapy.

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