THE EFFECT OF HUMORAL IMMUNITY ON URIC ACID CRYSTALS

Umarova Z.B.
Faculty of Medical Pedagogy and Treatment, General Medicine program, Group 213
Hamzayeva N.R.
Department of Medical and Biological Chemistry, Medical Biology, PhD, Biophysics and Medical Informatics, Tashkent State Medical University
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Abstract:

In 2023, approximately 305 million people worldwide were affected by hyperuricemia, a metabolic condition characterized by elevated levels of uric acid in the blood. Despite its high prevalence, only about 10–36% of individuals with hyperuricemia eventually develop gout, indicating that additional pathogenic factors contribute to disease progression. Gout is an inflammatory arthritis caused by the deposition of monosodium urate crystals in joint tissues, leading to recurrent episodes of severe pain and inflammation.

Recent studies suggest that the immune system, particularly humoral immunity, may play a significant role in the initiation and progression of gout. Components of humoral immunity, including antibodies, complement proteins, and immune complexes, may influence the formation, deposition, and inflammatory response to urate crystals within the joints. However, the precise mechanisms by which humoral immune responses contribute to urate crystal formation and joint inflammation remain incompletely understood.

The objective of this research is to investigate the role of humoral immunity in the development of urate crystal deposition in joints among patients with hyperuricemia. By elucidating these immunological mechanisms, this study aims to improve understanding of gout pathogenesis and potentially identify novel targets for early diagnosis, prevention, and therapeutic tervention.

Main objects:

muMT mice, control IgM antibody, CD62L (PE) antibody, CD11b (FITC) antibody, IgM fragmentation kit, SIINFEKL peptide, ^{51}Cr label, ELISA kit for complement C3, reagents for measuring myeloperoxidase, dendritic cell cultures, cell lines, cytokine panels.

Methods:

In the study, uric acid crystallization was assessed in vitro in the presence of IgM antibodies. In vivo, antibodies were administered to mice, and uric acid levels, inflammation (myeloperoxidase), complement C3, and neutrophil activity were measured.

Results:

To determine the role of B cells in the immunostimulatory effect of uric acid, muMT mice (lacking mature B cells) and wild-type (B6) mice were immunized with ovalbumin-coated latex particles and monosodium urate (MSU) crystals or soluble uric acid. In B6 mice, MSU or uric acid significantly enhanced the CTL response, whereas in muMT mice CTL activity was almost absent. This result indicates that the immunostimulatory effect of uric acid depends on B cells and likely on antibodies. Antibodies that bind MSU are present. B6 and Balb/c mice were immunized with preformed

MSU crystals, and high titers of MSU-binding IgM antibodies were detected in their serum (by FACS). Of the monoclonal antibodies obtained, 85% were IgM kappa and specifically bound

MSU crystals. Low titers of such antibodies were also detected in non-immunized mice. This indicates that the B-cell response to MSU binding is T-cell independent and dominated by IgM antibodies.

UBA antibodies enhance uric acid crystallization. In vitro, when supersaturated uric acid solutions were incubated with UBAs (UBA 11 or UBA E6), the rate of MSU crystal formation was significantly higher than with the control protein (OVA). The $F(ab)_2$ fragment bound MSU crystals but did not induce crystallization, indicating that the pentameric structure of IgM is essential for crystal formation.

UBAs restore uric acid–mediated immune effects in B-cell–deficient mice. When UBAs were administered to muMT mice, serum uric acid levels decreased, while myeloperoxidase and C3 levels increased and CD62L expression decreased, indicating activation of inflammation. At the same time, CTL activity in muMT mice was restored to the level observed in wildtype (B6) mice, demonstrating that UBAs restore the endogenous adjuvant effect of uric acid.

Conclusion:

This study demonstrates that IgM antibodies (UBAs) play a critical role in uric acid crystallization and in the immunostimulatory and pro-inflammatory effects of monosodium urate (MSU) crystals. In B-cell–deficient mice, the addition of UBAs restores the immuneactivating effect of uric acid, increases inflammatory markers (myeloperoxidase, C3), and reestablishes the CTL response. Moreover, MSU-binding IgM antibodies accelerate crystal formation, thereby intensifying inflammatory processes. The findings suggest that the formation of endogenous MSU crystals and their immunological effects are closely linked to IgM antibodies.

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