PublisherInfo		
PublisherName	:	BioMed Central
PublisherLocation	:	London
PublisherImprintName	:	BioMed Central

An Ig-binding peptide prevents SLE in MRL/lpr mice

ArticleInfo		
ArticleID	:	152
ArticleDOI	:	10.1186/ar-2000-66844
ArticleCitationID	:	66844
ArticleSequenceNumber	:	109
ArticleCategory	:	Paper Report
ArticleFirstPage	:	1
ArticleLastPage	:	3
ArticleHistory	:	RegistrationDate : 2000–9–18 OnlineDate : 2000–9–18
ArticleCopyright	:	Current Science Ltd2000
ArticleGrants	:	
ArticleContext	:	130753311

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Keywords

Autoantibody, autoimmune disease, combinatorial chemistry, Fc?R inhibition, immune complex, systemic lupus erythematosus

Context

SLE is characterized by B cell over-reactivity and dysregulation of autoantibody production. Pathogenic autoantibodies against a variety of cellular self-proteins, including DNA, histone, the Sm/RNP nuclear RNA proteins, and certain cytoplasmic complexes, mediate tissue inflammation and destruction in SLE. Autoantibodies, either alone or when bound with their cognate antigen to form immune complexes, mediate tissue damage. Immune complexes deposit in tissue and interact with Fc?Rs on cells of the mononuclear phagocyte system resulting in inflammation and tissue injury. Fc?R -deficient mice demonstrate significantly reduced autoimmune-mediated tissue damage in disease models of SLE and RA. To use combinatorial chemistry to generate a peptide that binds the constant region of IgG and inhibits its interaction with protein A. To then determine if that peptide can interfere with IgG/Fc?R interaction *in vitro,*. Finally, to determine if this peptide can prevent immune complex deposition *in vivo*, and attenuate tissue injury and increase survival in the MRL/lpr mouse model of SLE.

Significant findings

In vitro analysis of the biological activity of TG19320. Marino *et al* first use *in vitro* assays to evaluate the biological activity of TG19320 relative to monomeric TG19320 and the control scrambled peptide. They demonstrate that TG19320, but not the monopeptide or scrambled peptide controls, bind IgG using ELISA. They also demonstrate that TG19320, but not the controls, inhibits binding to Fc?R in several complementary assays.

In vivo evaluation of the impact of TG19320 on murine SLE in MRL/lpr mice. The authors then evaluated TG19320 in MRL/lpr mice. They observed that TG19320 had little effect on anti-DNA serum autoantibody titers, but a much more dramatic effect on reducing proteinuria and increasing survival. They demonstrate a dose-dependent survival effect at 40 weeks with control peptide treatment resulting

in 10% survival, 6 mg/kg TG19320 resulting in 50% survival, 15 mg/kg TG19320 resulting in 70% survival, and 30 mg/kg TG19320 in 80% survival. Similar results were presented in the NZB x NZW murine lupus model.

Comments

These data further highlight the importance of the role of autoantibody and/or immune complex stimulation of Fc?R in mediating tissue injury in systemic lupus erythematosus (SLE), a disease characterized by the presence of circulating immune complexes. Development of therapeutics that inhibit autoantibody and immune complex binding and signaling through Fc?R represents an exciting potential therapeutic strategy for many human autoimmune diseases such as SLE, for which no effective treatments currently exist. If proven safe and efficacious, this would be a powerful method to generically inhibit down-stream Fc?R-mediated tissue injury. Future studies should also address three important questions. First, which Fc receptors are important in this model, given that ligation of some Fc receptors (eg CD16 on natural killer cells) leads to activation, while ligation of other Fc receptors (eg Fc?RII-B1 on B cells) inhibits stimulation? Second, does this compound add efficacy (or perhaps have an adverse effect) on diseases such as rheumatoid arthritis (RA), which is not characterized by the presence of circulating immune complexes? And third, what happens to the circulating immune complexes in treated mice?

Methods

Tripeptides were generated using solid-phase combinatorial peptide synthesis. ELISA was used to screen the tripeptides for ability to bind IgG and FcR. Peptides binding FcR were then tested for ability to inhibit Fc?R-mediated aggregation of sheep red blood cells coated with IgG. The active tripeptide, TG19320, was then synthesized with amino acids in the D configuration (to make the peptides resistant to proteolytic cleavage), as a tetrameric tripeptide in which four copies of the tripeptide are inserted on to a lysine/glycine core. The Ig Fc TG19320 tetrameric tripeptide was delivered to MRL/lpr mice two times per week, from week 7 to 20, to evaluate its efficacy in female MRL/lpr mice. Control treatments included a tetrameric tripeptide of scrambled amino acids derived from TG19320, and a monomeric form of TG19320. Treated mice were followed for survival, development of proteinuria, and histologic evidence of kidney damage.

References

1. Marino M, Ruvo M, De Falco S, Fassina G: Prevention of systemic lupus erythematosus in MRL/lpr mice by administration of an immunoglobulin-binding peptide. Nat Biotechnol. 2000, 18: 735-739.