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IgE-gene regulation by triplex-forming oligonucleotides

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Keywords

B cells, IgE, IL-4, triplex-forming oligonucleotides

Context

Allergic diseases, such as asthma, are characterized by increased synthesis of IgE specific for common allergens. Cross-linking IgE with an allergen results in rapid release of a variety of proinflammatory mediators and induces airway cell activation. Production of IgE results from reciprocal activation of T and B cells. In response to T-cell-derived IL-4, resting B cells undergo isotype switching and IgE gene transcription is induced. Thus, the prevention of IgE production represents an attractive therapeutic target in asthma.

The promoter region for IgE contains binding elements for the transcription factors signal transducer and activator of transcription (STAT) 6, nuclear factor (NF)-?B/Rel, PU.1, and C/EBP. STAT6 appears to be the pivotal transcription factor responsible for mediating IL-4-induced activation of IgE transcription. Because the STAT6 binding site and the composite PU.1/NF-?B1 element in the IgE germline promoter are composed of a DNA polypurine stretch, the authors examined the possibility that 2'-aminoethoxy-modified triplex-forming oligonucleotides (TFOs) complementary to this region could be used to form inhibitory DNA triplex structures.

Significant findings

TFOs formed DNA triple-helix structures and inhibited the interaction of STAT6, NF-?B, and PU.1 in a dose-dependent fashion with high specificity and selectivity. In addition, the IL-4-induced activity of the IgE germline promoter was blocked. These data support the concept of specific modulation of gene expression by DNA triplex formation induced with chemically modified oligonucleotides.

Comments

Recently acquired knowledge of normal and 'disease' gene DNA sequences has provided an opportunity for the highly rational design of therapeutic agents that act at the DNA level through sequence-specific interactions. Among the ligands capable of binding DNA in a precise, sequence-specific manner are TFOs. In this study, the authors have shown that TFOs can perturb transcription factor binding and thus effectively inhibit IL-4-induced IgE promoter activity in B cells. Although further studies are required to examine the effectiveness of these oligonucleotides on IgE production *in vitro* and *in vivo*, this study shows that gene targeting agents, such as TFOs, represent new opportunities for rational drug development in asthma and allergy.

Methods

Transient transfection, electrophoretic mobility shift assay, oligonucleotide synthesis

Additional information

References

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