Research Advances in Systemic Lupus Erythematosus

Robert P. Kimberly, MD

Systemic lupus erythematosus is an autoimmune disease with a significant genetic component to susceptibility. Some environmental risks are known, and identification of specific genetic factors promises to define new molecular targets for therapy. Broad immunosuppression will be replaced by early, selective, and individualized intervention. Mortality rates will decline, and insights into therapy may apply to other autoimmune conditions.

Major Clinical and Research Advances

Clinical management of SLE is based on use of nonsteroidal anti-inflammatory drugs (NSAIDs), the addition of hydroxychloroquine and other agents originally developed as antimalarials, targeted and judicious use of glucocorticoids, including large intravenous doses, and aggressive use of other immunosuppressive agents, such as cyclophosphamide. Vigorous management of comorbid conditions, including joint damage, techniques will be developed for resurfacing joints with autologously generated cartilage.

REFERENCES


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etnic susceptibility factors is critical for understanding SLE.

**Cutting-Edge Research**

Substantial investigative efforts are focused on studying SLE multiplex families and affected sibling pairs to establish regions of linkage in the genome with the SLE phenotype. Identification of candidate genes associated with disease susceptibility, severity, and response to therapy is progressing in parallel, and elucidation of gene expression profiles in immune cells may identify targets for intervention and guide the discovery of new candidate genes.

Although apoptosis per se does not appear to be grossly defective in SLE, the processing of apoptotic cells and debris contribute to immune dysregulation. Apoptotic material may alter the local tissue environment and the presentation of self as antigenic. Therefore, the determinants of tolerance and the pathways that circumvent tolerance are central to the lupus diathesis.

**Critical Efforts, Discoveries, and Tools**

The Human Genome Project will provide the framework for understanding the basis of individual genetic susceptibility to and severity of SLE. The strong heritability, measured by the risk of disease among siblings, and the convergence of several investigative groups on specific genetic regions of interest underscore the promise of this approach. Nonetheless, the task of unveling this complex, and perhaps heterogeneous, disease is daunting. Effective collaborations with large cohorts of both simplex and multiplex families will be essential. Appropriate understanding of “phenotype” and access to state-of-the-art informatics tools are essential for this undertaking.

The ability to take the discoveries from genetics, functional genomics, and pathoph ysiology to the bedside will require appropriate clinical tools to evaluate efficacy and outcomes. Many of these tools are at hand, and they must be woven into an overall effort addressing new therapies.

**Forecast for Research Advances**

The next 25 years will contain remarkable progress in the understanding and management of SLE. Identification of susceptibility genes and their contribution to disease pathways will provide insight into the understanding of environmental triggers. Assessment of individual genetic “portfolios” with gene array technology, combined with advances in knowledge about exogenous stimuli, will facilitate prevention of SLE. New markers of immune activation and deviation will enable early therapeutic intervention. Biotechnology will provide more effective means of immunomodulation, perhaps through antigen-specific tolerance induction, selective deletion of activated immune cells, or interruption of inflammatory cascades. Glucocorticoid use will decline and alkylating agents will no longer be part of the therapeutic armamentarium. Early, effective interventions will reduce morbidity, which will be attenuated further by aggressive management of the causes of morbidity.

Gene therapy for such a complex genetic disease will be used first for drug delivery, not germ line modification. Discoveries in one autoimmune disease will have lessons and applications for other diseases. More targeted therapies will replace broad, nonspecific immunosuppression for most treatment.

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**REFERENCES**


<table>
<thead>
<tr>
<th>Research Opportunities and Forecast: Lupus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Key Research Opportunities</strong></td>
</tr>
<tr>
<td>Identify Genes That Affect Susceptibility and Disease Severity</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Identify Gene Expression “Signatures” for Early Immune Activation</td>
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<tr>
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<tr>
<td></td>
</tr>
<tr>
<td>Identify Novel Receptors Involved in Activation or Apoptosis</td>
</tr>
<tr>
<td>Identify Receptors Involved in Removal of Apoptotic Material</td>
</tr>
<tr>
<td>Identify Mechanisms Affecting Immune System Gene Expression</td>
</tr>
<tr>
<td>Develop Gene Transfer Vectors for Consistent Expression of Deficient Genes</td>
</tr>
</tbody>
</table>

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