Finding the right target for treating Alzheimer disease

Picking a therapeutic target is not always easy.

The process may be relatively easy for the few diseases in which an etiologic agent fulfills Koch's postulates. Otherwise, potential targets for therapeutic intervention are selected via several approaches.

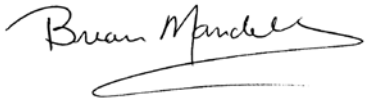
Observational studies may suggest risk factors, and a number of molecular techniques may be used to identify specific cell types, up-regulated genes, or overexpressed potential critical mediators within diseased tissues. The latter approach was used, in part, in the successful development of therapies for rheumatoid arthritis that block tumor necrosis factor (TNF) and interleukin 6 (IL-6).

Once a potential target is found, molecular biologists using current tools of drug development—gene chip analysis, molecular modeling, proteomic scanning, and hybridoma-based synthesis—can produce a small molecule or biologic product to block the effect or expression of nearly any molecule or pathway (although a successful therapy cannot always be developed easily).

But sometimes, potential markers of disease pathogenesis are actually embers of the pathologic process rather than flames driving the disease.

For example, consider tuberculosis. Granulomas are typical of *Mycobacterium tuberculosis* infection. Suppose we didn't know about mycobacteria but assumed instead it was the granuloma per se that was the actual agent of disease. It might then be reasonable to try to treat tuberculosis with the anti-TNF agents, since they can prevent the development of mature granulomas. But that approach would lead to uncontrolled *M tuberculosis* infection, not resolution of clinical tuberculosis.

Although not entirely analogous to an infectious disease, Alzheimer disease is another case in point. On page 689 in this issue of the *Journal*, Dr. David S. Geldmacher discusses how the amyloid plaques of Alzheimer disease may be the footprint but not the actual cause of the disorder. This hypothesis would explain the failure of attempts at treating Alzheimer disease by attacking this presumed pathogenic target and, if true, would require starting anew to find the right target.



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