Discovery may lead to development of safer immunosuppressants

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Immunosuppressive treatment is necessary to prevent rejection of an organ after transplant and has great potential for treating chronic inflammatory diseases. However, currently available immunosuppressant drugs can pose serious health risks, restricting their long-term use. Now, new research findings may lead to the development of immunosuppressant drugs that have fewer adverse side effects. The study, published by Cell Press in the March 13th issue of the journal *Molecular Cell,* reveals detailed information about how drugs commonly used to prevent transplant rejection interact with their target.

Calcineurin (CN) is a highly conserved protein that plays a multitude of roles in diverse biological processes. Previous work has shown that CN regulates a protein called nuclear factor of activated T cells (NFAT) in mammals and that this regulation involves a docking interaction between CN and NFAT. The CN-NFAT pathway is known to play a critical role in processes such as inflammation, diabetes and cardiac hypertrophy.

CN is the target of the immunosuppressant drugs cyclosporine A (CsA) and FK506 which are used to prevent rejection after a transplant. These drugs have also been used to treat atopic dermatitis, severe asthma, and refractory rheumatoid arthritis. "CsA and FK506 each form complexes with a specific immunophilin binding proteins and it is these complexes, called IS-IP complexes, that inhibit CN activity," says senior study author Dr. Juan Miguel Redondo from the Department of Vascular Biology and Inflammation at the Centro Nacional de Investigaciones Cardiovasculares in Madrid.

Dr. Redondo and colleagues designed a series of experiments to investigate how IS-IP complexes and substrates like NFAT interact with CN. They identified a "pocket" within the CN molecule that mediated binding to NFAT and other substrates. Their analyses also provided insights into the mechanisms by which immunosuppressants inhibit CN. "We showed that IS-IP complexes compete for binding to the same docking surface in CN that mediates interactions with natural substrates, thereby blocking CN signaling," explains Dr. Redondo.

The discovery of a common CN docking pocket for substrates and IS-IP complexes reveals a promising target for development of less toxic immunosuppressive drugs. "Many of the severe side effects of FK506 and CsA, such as neurotoxicity, diabetes, kidney dysfunction and hypertension, are at least partly independent of CN," says Dr. Redondo. "Identifying selective CN inhibitors that avoid these secondary effects is of high interest."

Source: Cell Press (news : web)