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Opinion Article

DNA Ligase as a Potential Target for Novel Antibacterial Agents

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DESCRIPTION

DNA ligase is an enzyme that catalyzes the formation of phosphodiester bonds between the 5' end of one DNA (Deoxyribonucleic Acid) strand and the 3' end of another DNA strand, thereby joining two DNA fragments into a continuous molecule. DNA ligase is essential for DNA replication, repair and recombination in all living organisms. However, there are different types of DNA ligases that use different cofactors and have different substrate specificities. In eukaryotes and some viruses, DNA ligase uses ATP as a cofactor, while in bacteria and some other viruses; DNA ligase uses NAD^+ as a cofactor. This difference provides an opportunity to develop selective inhibitors of bacterial NAD^+-dependent DNA Ligase (LigA) as novel antibacterial agents.

Structure and mechanism of bacterial DNA ligase

Bacterial DNA ligase has a modular structure consisting of three domains: an N-terminal Adenylation Domain (AdD), a central Oligonucleotide-Binding Domain (OBD) and a C-terminal DNA-Binding Domain (DBD). The AdD contains the active site where NAD^+ is bound and cleaved to form a covalent enzyme-adenylate intermediate. The OBD is involved in the recognition and binding of nicked DNA substrates. The DBD is responsible for the alignment and juxtaposition of the 5' and 3' ends of the DNA strands to be ligated.

The mechanism of bacterial DNA ligase involves four steps: (1) adenylylation of a lysine residue in the AdD by NAD^+, releasing Nicotinamide Mononucleotide (NMN) and pyrophosphate; (2) transfer of the AMP moiety from the enzyme-adenylate to the 5' phosphate of the donor DNA strand, forming a DNA-adenylate intermediate; (3) nucleophilic attack of the 3' hydroxyl of the acceptor DNA strand on the DNA-adenylate, forming a phosphodiester bond and releasing AMP (Adenosine Monophosphate); and (4) dissociation of the ligated DNA product from the enzyme. The structure and mechanism of bacterial DNA ligase are distinct from those of eukaryotic and viral ATP-dependent DNA ligases, which use ATP (Adenosine Triphosphate) as a cofactor and have different domain architectures and substrate specificities. These differences provide opportunities for designing selective inhibitors that target bacterial DNA ligase without affecting human or viral DNA ligases.

LigA is an attractive target for antibacterial drug discovery for several reasons. First, LigA is essential for bacterial survival and viability, as it is required for the completion of DNA replication and the repair of DNA damage. Second, LigA is conserved among various bacterial species, including many pathogenic and drug-resistant strains. Third, LigA has no human homologs, which reduces the risk of toxicity and off-target effects. Fourth, LigA has a unique structure and mechanism that can be exploited for inhibitor design and optimization.

Several classes of LigA inhibitors have been discovered by different approaches, such as High-Throughput Screening (HTS), structure-based design and fragment-based screening. Some of these inhibitors have shown potent and selective inhibition of LigA *in vitro* and *in vivo*, as well as antibacterial activity against various Gram-positive and Gram-negative bacteria. However, none of these inhibitors have reached clinical trials yet, and there are still challenges and limitations to overcome. For instance, some inhibitors have poor solubility, stability or bioavailability; some inhibitors have narrow spectrum of activity or low potency against certain bacteria; some inhibitors have high cytotoxicity or undesirable pharmacokinetic properties. Therefore, further research and development are needed to identify and optimize more effective and safe LigA inhibitors that can overcome the current challenges of antibacterial drug resistance. LigA remains a promising target for novel antibacterial agents that can potentially treat a wide range of bacterial infections.

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