SII-4-6

Physical Evidence for Communication between the Receiver and Output Domains of the Enhancer-Binding Protein NtrC upon Phosphorylation

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The bacterial enhancer-binding protein nitrogen regulatory protein C (NtrC) activates transcription by the σ^{54}-holoenzyme form of RNA polymerase in a reaction that depends upon hydrolysis of ATP. Phosphorylation of an aspartate residue in the N-terminal receiver domain of NtrC induces oligomerization of the protein and activates the ATPase activity. To study communication between the receiver domain of NtrC, which is known to act positively, and its output domain, we isolated mutant forms of the protein carrying single cysteine residues and derivatized them with a sulfhydryl-specific nitroxide reagent for electron paramagnetic resonance spectroscopic studies of nitroxide mobility. The single cysteines were placed at four positions at which we had obtained constitutive amino acid substitutions, those that yield activity in the absence of phosphorylation. In only one case, derivatized C86 in a-helix 4 of the receiver domain, did the mobility of the side chain change dramatically upon phosphorylation. Importantly, derivatized NtrCD86C (NtrCD86C*) maintained essentially normal capacity to oligomerize, hydrolyze ATP, and activate transcription. Additional experiments indicated that the spectral change observed upon phosphorylation of NtrCD86C* was due to interdomain interactions rather than to a conformational change within the N-terminal domain itself and that formation of active oligomeric forms of NtrC was neither sufficient nor required for these interdomain interactions. The interdomain interactions occurred within a dimer but did not appear to occur within a monomer.

SIII-1-1

Present and Future Market Potentialof Antibacterial Drugs

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Almost 300 antibacterial products are available on the world Market, but successful treatment of bacterial disease is becoming increasingly problematic as the number of elderly and immunocompromised patients increases, the pathogens encounter change and resistance to current agents becomes more widespread. The annual world market for this field has been estimated at $22 billion and is one of the top therapeutic categories in terms of pharmaceutical sales, exceeded only by the cardiovascular, alimentary/metabolic and CNS sectors. From the various classes of antibacterial agents, the market potential for the major antibiotic classes such as β-lactams (penicillins, cephalosporins, carbapenems), macrolides, aminoglycosides, quinolones will be discussed in this seminar as well as some problem pathogens to be overcome in the future.