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Redox Dependent Gene Regulation by the Arc Two-Component Signal Transduction System

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Adaptation to ever-changing environmental conditions is critical for the survival of all microorganisms in nature. Bacteria modulate their morphology, behavior, metabolism, and gene expression in response to environmental signals, such as respiratory conditions, availability of nutrients, changes in physical conditions, and signaling molecules produced by other cells. These adaptive responses often depend on a homologous family of two-component signal transduction systems that consist of a plasma membrane-associated sensor kinase protein and a cytosolic response regulator. The sensor continuously monitors specific changes in its immediate environment by a signal receptor domain that conducts the stimulus across the membrane to the cytosolic domain, thereby modulating its catalytic activity. The signal is then transmitted to the response regulator, which in general is a transcriptional modulator. In such cases, the process involves an ATP-dependent phosphorylation of a conserved histidine residue in the transmitter domain of the sensor kinase and a subsequent phosphoryl-group transfer to a conserved aspartyl residue on the receiver domain of the response regulator.

The ArcB/A (anoxic redox control) two-component system of *Escherichia coli* regulates the expression of more than 40 operons depending on the redox conditions of growth. This system comprises ArcB as the membrane-associated sensor kinase and ArcA as the cognate response regulator. ArcB is unorthodox in possessing an elaborate cytosolic structure that comprises three catalytic domains: a primary transmitter with a conserved His residue at position 292, a receiver with a conserved Asp at position 576, and a secondary transmitter with a conserved His at position 717. ArcA is a typical response regulator possessing an N-terminus receiver domain with a conserved Asp residue at position 54 and a C-terminus helix-turn-helix DNA binding domain. Under reducing conditions, ArcB autophosphorylates at His292, a reaction which is enhanced by several fermentation metabolites, such as *D*-lactate, pyruvate, and acetate. The phosphoryl group is then sequentially transferred to ArcA via a His292 → Asp576 → His717 → Asp54 phospho-relay. Phosphorylated ArcA (ArcA-P), in turn, represses the expression of many genes involved in respiratory metabolism (e.g., enzymes of electron transport, the tricarboxylic acid cycle, and the glyoxalate shunt)and activates other genes encoding proteins involved in fermentative metabolism (e.g., pyruvate formate lyase, and hydrogenase I). Under oxidizing conditions ArcB dephosphorylates ArcA-P via an Asp54 → His717 → Asp576 reverse phospho-relay.

ArcB is also unorthodox as a sensor kinase in having a very short periplasmic sequence of only about 16 amino acid residues, in contrast to typical sensor kinases that have a substantial periplasmic domain for environmental sensing. Unexpectedly, replacing the various segments of the ArcB membrane region with a counterpart of MalF (a subunit of maltose permease), which does not share any sequence homology with ArcB, was without significant impact on the signal transduction process. From this lack of sequence specificity it was concluded that the region of ArcB delimited by the two transmembrane segments (the sequences of the two transmembrane segments are equally not important for signal reception) does not participate in signal reception but rather serve as an anchor to keep the protein close to the source of the signal Therefore, it was concluded that the ArcB transmembrane domain (amino acids 22-77) does not participate in signal reception but rather serve as an anchor to keep the protein close to the source of the signal. In fact the

oxidized forms of the quinone electron carriers in the cytoplasmic membrane were shown to act as direct negative signals that inhibit autophosphorylation of ArcB during aerobiosis. This finding explains the importance of tethering the sensor kinase to the membrane. Were it not so, the lipophilic quinones located exclusively in the membrane bilayer would be able to silence only a small fraction of the ArcB molecules at any given time, since most of them would be randomly distributed in the cytosol. Thus, the Arc two-component signal transduction system provides a novel link between the electron transport chain and gene expression.