Identification of a U/Zn/Cu responsive global regulatory two-component system in *Caulobacter crescentus*

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Project Goals: Depleted uranium is a widespread environmental contaminant that poses a major threat to human health. In contrast to humans and animals where a trace amount of uranium can cause damage to kidneys, liver and heart, it is well known that some bacteria can tolerate high levels of uranium and influence its mobility and bioavailability in the environment. As a non-pathogenic bacterium, *Caulobacter crescentus* is an attractive bioremediation candidate due to its high tolerance to heavy metals, and its ability to mineralize uranium. Our goal is to decipher the physiological basis for U response and tolerance in *C. crescentus,* and provide insight into the effect of aerobic bacteria on U biogeochemistry and assess the utility of them in biomineralization applications.

Despite the well-known toxicity of uranium (U) to bacteria, little is known about how cells sense and respond to U. The recent finding of a U-specific stress response in *Caulobacter crescentus* has provided a foundation for studying the mechanisms of U-perception in bacteria. To gain insight into this process, we used a forward genetic screen to identify the regulatory components governing expression of the *urcA* promoter (P_{urcA}) that is strongly induced by U. This approach unearthed a previously uncharacterized two-component system, UzcRS, which is responsible for U-dependent activation of P_{urcA}. UzcRS is also highly responsive to zinc and copper, revealing a broader specificity than previously thought. Using ChIP-seq, we found that UzcR binds extensively throughout the genome in a metal-dependent manner and recognizes a non-canonical DNA binding site. Coupling the genome-wide occupancy data with RNA-seq analysis revealed that UzcR is a global regulator of transcription, predominately activating genes encoding proteins that are localized to the cell envelope; these include metallopeptidases, multidrug resistant efflux (MDR) pumps, TonB-dependent receptors and many proteins of unknown function. Collectively, our data suggest that UzcRS couples detection of U, Zn and Cu with a novel extracytoplasmic stress response.

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