Challenging the conventional view of zinc in biology and establishing zinc as a regulator of the transcriptional and metabolic program in cells

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Zinc is absolutely essential to all forms of life. It is a crucial building block of cells and has been implicated in many fundamental functions, such as DNA synthesis, transcription, metabolism, and apoptosis. For organisms, zinc is required for growth, development and immune function, and perturbation of zinc is associated with numerous pathologies. Given the centrality of zinc in cell biology and human health, it is astounding that at the most fundamental level we still don't understand how zinc status and availability impact basic cellular functions, and the proteins that sense changes in zinc in order to regulate cellular processes remain a mystery. The traditional model of zinc in biology asserts that the ~ 2000 proteins that comprise the zinc proteome bind zinc constitutively. This Pioneer Project will explore a fundamentally different model where zinc acts as a cellular signal and direct regulator of transcription and metabolic processes by titrating occupancy of the zinc proteome. The central premise is that in a low zinc state the vast repertoire of zinc binding proteins will only be partially saturated with zinc, giving rise to reduced output from zinc-dependent transcription factors and enzymes. When zinc levels increase, the fractional saturation of zinc binding proteins will increase, leading to increased output. The consequence of this model is that regulation of zinc dictates occupancy of the zinc proteome, providing a link between dynamic metal regulation and a wide swath of cellular signaling responses. Thus, changes in zinc status – either dynamically during physiological signaling, or permanently as a consequence of disease – could fine-tune the activity of hundreds of zinc-dependent proteins, establishing zinc as a major regulator of cellular function. This challenges the conventional view that zinc is constitutively and stably bound to the proteins and enzymes that constitute the zinc proteome, and establishes a new paradigm for understanding the impact of metal homeostasis on physiology and health. To test this hypothesis, we will 1) Develop methodology for defining zinc occupancy of the proteome and how it changes with: (i) systematic perturbation of metal availability, (ii) zinc dynamics induced by calcium signaling, and (iii) different disease states; 2) Define the downstream consequences of partial occupancy on both the transcriptional and metabolic program of cells; and 3) Define the consequences of altered zinc homeostasis in cellular models of disease.