An Intergrated Approsch for Matching Metals and Metallodrugs to Proteins

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The effect of metals in biology effects is double-edged. Metal ions operate, on one hand, as cofactors for around 40% enzymes, on the other hand, they also exhibit toxic effects. Some metal ions, although being not essential, have been widely used in human healthcare as either therapeutic agents or diagnosis agents. To understand the molecular mechanism of a metallodrug, it is crucial to match metals to proteins at a proteome-wide scale [1,2]. We used an integrated approach consisting of gel electrophoresis and inductively coupled plasma mass spectrometry, LA-ICP-MS, IMAC and bioinformatic approach to identify metal-associated proteins using bismuth antiulcer drug as an example [3,4]. Using continuous-flow gel electrophoresis in combination with ICP-MS, we developed a comprehensive and robust strategy to readily identify metal-associated proteins as well as to quantify the metals for fast metallome/proteome-wide profiling of metal-binding proteins.

At the same time, we have developed a tunable fluorescent method to visualize metal-binding proteins and histidine-rich proteins directly in cells. To match metals to proteins, we also established a bioinformatic method which allows potential metal-binding proteins both sequentially and spaciously to be searched [5-7]. Surprisingly, histidine-rich proteins and motifs (HRMs) are commonly found in proteins. We systematically analyzed the proteomes of 675 prokaryotes including 50 archaea and 625 bacteria for HRMs, and show that HRMs are extensively distributed in prokaryotic proteomes, with the majority (62%) of histidine-rich proteins (HRPs) being involved in metal homeostasis. Importantly, the occurrence of histidine-rich proteins (motifs) in the proteomes of prokaryotes is related to their habitats.

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