Sociedad Argentina de Microbiología General

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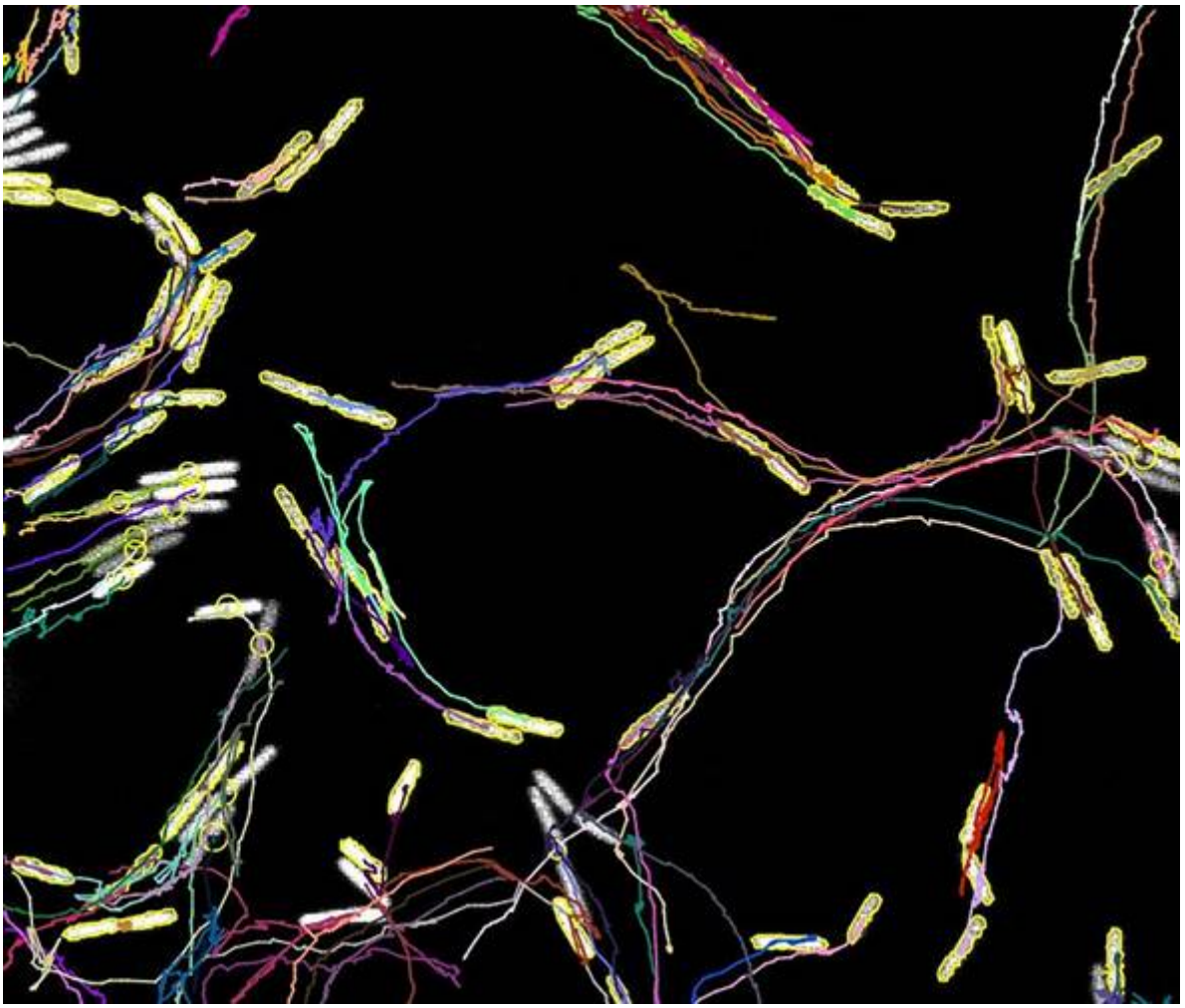

Foto: Se hace camino al andar. Celeste Dea. 1er puesto. Concurso fotográfico SAMIGE 20 años.

EVOLUTION, FUNCTIONAL DIVERSIFICATION, AND DNA BINDING OF METALLOREGULATORS: USING THE ArsR FAMILY AS A CASE STUDY

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Metallostasis refers to the cellular processes that balance the concentrations of metal and metalloid ions within a cell. It ensures an adequate supply of ions for cellular functions while preventing their accumulation to toxic levels. Several metals and metalloids are essential for cell survival because they serve as enzymatic cofactors or participate in protein folding, acting as stabilizing elements for protein structure. Approximately 40% of a typical proteome consists of metalloproteins. Metal/metalloid-inducible transcription factors (mTFs), also known as metalloregulators, regulate the expression of genes that maintain metallostasis. They do this through an allosteric mechanism of metal ion (or other inducer) sensing, allowing the activation of pathways for metal uptake or expulsion to the medium. Around a dozen families of metalloregulators are known in bacteria, but only a few have been characterized at the structural and functional levels. As a result, the diversity of molecules these metalloregulators can sense, and the processes that some of them regulate, remain unknown. The biotechnological application of mTFs has been demonstrated in the development of biosensors based on in vitro transcription systems, due to their specificity in binding to a wide range of inducers and their affinity for DNA-binding operators. Our objective was to provide a large-scale description of the main bacterial metalloregulator families. To achieve this, we used sequence data available in UniProt and grouped putatively isofunctional proteins by constructing sequence similarity networks (SSNs) for each family. Through specific cluster analysis, we identified key residues involved in coordinating different metal/metalloid ions and the binding of non-metallic inducers. We further tested the predictive value of our analysis by focusing on the molecular and functional evolution of the ArsR family, which is likely the most diverse of all the metalloregulatory families. We studied the phylogenetic relationships between ArsR clusters using structural and sequence data, which allowed us to identify "isofunctional" clusters capable of sensing metals, metalloids, reactive sulfur species (RSS), reactive oxygen species (ROS), and other small molecules. Also, we found a moderate degree of syntenic conservation within some ArsR gene clusters and examined the distribution of orthologous groups across different bacterial lineages. Finally, we used deep learning-based methods to predict and evaluate binding affinities

between proteins and target DNA with AlphaFold3 and DeepPBS. In this way, we identified key residues participating in the binding interface between the YgaV regulator (RSS cluster) and various DNA operators. These results represent the first large-scale study of the functional and structural diversity of different metalloregulator families, where we describe the functional and evolutionary diversity of regulators in the ArsR family.

Palabras clave: Transcriptional factor, Metalloregulators, Sequence Similarity Network, Evolution of protein families, DNA-binding proteins