Sociedad Argentina de Microbiología General

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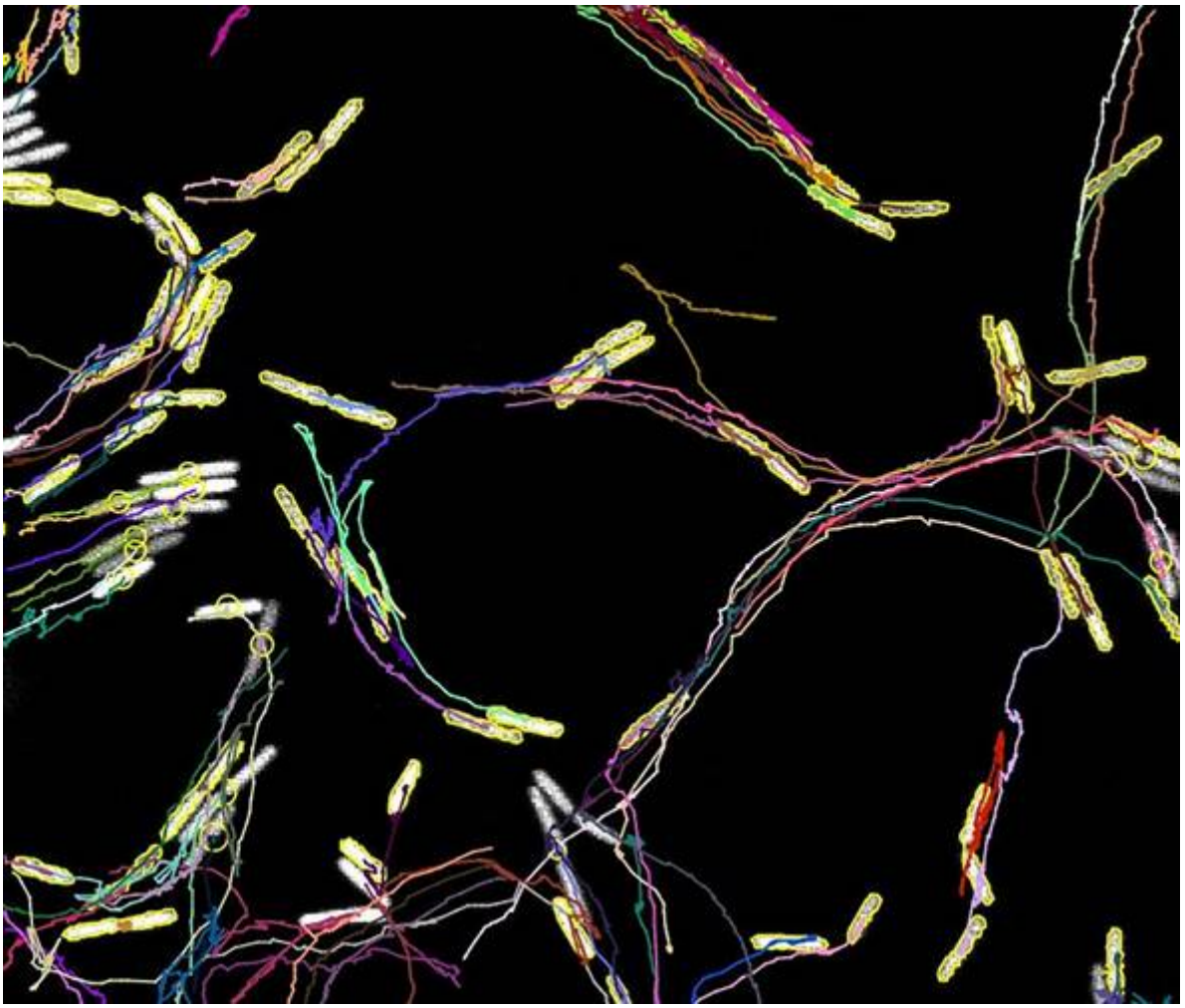

Foto: Se hace camino al andar. Celeste Dea. 1er puesto. Concurso fotográfico SAMIGE 20 años.

EVOLUTION OF A HYPERMUTATOR LINEAGE OF Pseudomonas aeruginosa IN A CF PATIENT: IMPACT OF CFTR MODULATORS

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Cystic fibrosis (CF) is a genetic disorder caused by mutations in the CFTR gene, primarily affecting the lungs and leading to chronic inflammation and persistent infections. *Pseudomonas aeruginosa* is a common pathogen in CF, and the impact of CFTR modulators on its evolution remains uncertain. In a previous study, we analyzed a mutator lineage of *P. aeruginosa* from a CF patient over 30 years of infection, revealing how clones evolved through mutations in resistance genes under antibiotic pressure. This study investigates how CFTR modulator treatments, combined with antibiotics, influenced genetic variations in key resistance genes and the bacterial population's adaptive evolution. Using whole-genome sequencing of clones isolated before and after CFTR modulator treatment, we constructed a phylogenetic tree and performed polymorphism analyses of the *blaPDC* and ftsI ?-lactam resistance genes, as well as the mutS gene. The phylogenetic analysis suggests adaptive evolution of *P. aeruginosa* in response to CFTR modulator therapy, with increased clonality observed during Orkambi treatment. This diversification likely stems from subpopulations optimizing for antibiotic resistance, while others adapt to the altered lung physiology induced by the modulators. Significant shifts in the number and diversity of isolates were observed before and after CFTR modulator therapy. Allelic prevalence analysis revealed shifts in dominant variants of *blaPDC* and ftsI pre- and post-therapy. Ancient subpopulations may persist, undergo extinction, or evolve despite treatment, leading to a mixture of lineages post-therapy. Our findings suggest that CFTR modulators do not exert uniform selective pressure across all bacterial subpopulations, and the emergence of mutations in key resistance and DNA repair genes indicates that these therapies may contribute to maintaining the most resistant strains. This insight is crucial for understanding the evolution of chronic infection in CF patients.

Palabras clave: Cystic fibrosis - CFTR modulator - P. aeruginosa - ?-lactam resistance