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Spotlight

Unravelling evolution one nucleotide at a time

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With the goal to design bacterial genomes with desired functions, Siv Andersson aims to comprehend how bacteria evolved together with their hosts.

Evolving to the surrounding

Throughout her journey of becoming a microbiology researcher, Siv Andersson would change course every four or five years. 'I usually just turn around, see what's available and run off into the direction that looks most exciting, interesting, and challenging'. Every few years, important life decisions impacted her career and somehow paved her journey into academic research. After postdocs at the Laboratory of Molecular Biology in Cambridge and Columbia Medical School in New York, she became an Associate Professor at Uppsala University in 1997, where she had finished her Ph.D. Dissertation. In 2000, she became full Professor for Molecular Evolution and was Head of the Department of Evolution, Genomics, and Systematics at the Evolutionary Biology Centre from 2003 to 2009.

Now being more open for long-term goals, Siv investigates how bacteria evolved throughout time; she even looked at time ranges of several million years. Siv and her group explored how two lineages of the bacterium *Buchnera aphidicola* adapted to their specific hosts, the pea aphid and the wheat aphid (Tamas et al. 2002). This endosymbiosis was established ~150 million years ago, and the two lineages diverged ~50–70 million years ago. Interestingly—and completely unexpectedly—they found that even though both lineages were living as endosymbionts with their respective hosts for such a long time, their gene contents barely differ. 'When we looked at the gene maps and saw they were identical; we were just silent. And then the Ph.D. student started panicking because he thought the samples had been mixed up and the same bacterium had been sequenced twice.' Later, they found that indeed a high degree of divergence was apparent at the nucleotide sequence level. Yet, no inversions, translocations, duplications, or gene acquisitions seemed to have happened throughout this extensive time period. With both endosymbionts having lost the genetic elements for a recombination machinery, their genome size and flexibility were reduced, which instead increased genome stability and left them with the same genomic architecture.

As the next step, Siv aimed to understand the mechanisms of how *B. aphidicola* adapted to its aphid host (Tamas et al. 2008). This endosymbiont has one of the smallest and most A-T-rich bacterial genomes and some of its transcripts with poly(A) sequences contain frameshift mutations resulting in non-functional gene products. Yet, as Siv and her group found, transcriptional slippage of the polymerase can rescue these mutations and—against the odds—lead to functional gene products. Even though a seemingly inefficient mode of information processing, regulation mechanisms like these could be helpful in designing synthetic genomes.

Solving problems and accomplishing challenging tasks

Just as *B. aphidicola* overcame its genomic challenges, Siv loves solving problems 'which is what we as researchers are doing. I like things I don't understand or that are like a mystery to me.' And solving her research questions brought her several prizes and awards over the years. For example, she received two prizes from the Swedish Royal Academy of Sciences, the Gold Medal from the Royal Society of Sciences at Lund and was elected Fellow of the Swedish Royal Academy of Sciences, the Swedish Royal Academy of Engineering Sciences, European Molecular Biology Organization, and latest of the European Academy of Microbiology.

To achieve all of this, Siv understands that she needs a team 'in which members have a lot of different skills and by working well together, we can really accomplish something that neither can do on their own'. She especially enjoys the close relationships with her Ph.D. students towards the end of their projects. This is an intense time 'when it becomes very hectic but now the Ph.D. student is also very focused and we both have a tight schedule.'

So, from her own experience, Siv knows that the research journey is barely ever easy and straight forward; sometimes the most potent sceptics are the ones close to us. This was also the case when the team determined the genome sequence of the epidemic typhus pathogen *Rickettsia prowazekii*. 'I think I'm most proud of that paper because it was not easy and so many researchers in my local environment said 'it's impossible' and told me that I would end my career in science with this project'. By publishing the genome sequence of *R. prowazekii* (Andersson et al. 1998), Siv explored the relation between this intracellular parasite and the mitochondrion. Her study suggested that aerobic respiration in eukaryotes derived from an ancestor of this group of bacteria. To everyone's surprise the small *Rickettsia* genome contains a high fraction of pseudogenes, and comparative analyses revealed the

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molecular process by which bacterial genes are degraded and discarded; a huge step forward in our understanding of bacterial evolution.

Compartmentalizing tasks and functions

Yet, bacteria-derived mitochondria are not the only cellular compartments that Siv is interested in. Even though bacterial cells generally do not contain internal compartments, there are exceptions, like bacteria of the *Planctomycetes* phylum that contain a proteinaceous cell wall and an invaginated inner membrane (Mahajan et al. 2020). In *Tuwongella immobilis*, Siv and her team visualised a complex tunnel system made by the invaginations thus resulting in an increased periplasmic space (Seeger et al. 2021). While the function of this extended compartment is not fully understood yet, it is hypothesised that the bacterium uses the periplasm for storage and degradation of imported macromolecules. 'Understanding the evolution of these bacterial cells may tell us something about the process by which internal membrane systems other than mitochondria originated in eukaryotes'.

And according to Siv, organising and compartmentalising is what researchers ought to do better—especially when it comes to judging their value and their work. 'We should never let the results of a project determine who we are or how we think about ourselves. We have to remember to judge and admire the work and not the person.' Sometimes people mix up the two and take scientific criticism very personally or treat others like a hero because of their work. However, to the next generation of microbiology researchers, she advises 'to be yourself, trust your instincts, and do what feels right for you'.

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