CRISPR still needs microbiologists

Although the spotlight on CRISPR–Cas systems has shone on their immense potential as genome-editing tools, the field's origins are rooted in the microbiology of phage–bacterium interactions. Furthering our understanding of these processes can uncover more systems and generate new reagents with revolutionary properties.

There is no denying CRISPR's rise to fame, with the topic now being featured not only on science news portals, but also in mainstream media outlets on an almost weekly basis. CRISPR has even appeared as a critical plot component of recent Hollywood blockbusters such as *Rampage*, where exposure to the genome-editing agent is responsible for the mutations behind the emergence of city-destroying giant wolves, crocodiles and apes. In light of such widespread exposure, the general public is now growing more cognisant of the huge potential of the technology for genome editing, the ethical debates revolving around the possible use of CRISPR to modify germline cells, and the ongoing legal disputes regarding patents. Yet, most people are probably still unaware of what the acronym actually stands for (clustered regularly interspaced short palindromic repeats), that genome editing does not really require the CRISPR repeats but rather relies mostly on the use of CRISPR-associated (Cas) proteins (such as Cas9), or that the history behind these discoveries is intimately linked to the study of the interactions of bacteria and archaea with the viruses that infect them.

CRISPR–Cas tools are by no means the first to emerge from this area of microbiology. The study of phages and their targets has contributed uniquely to the development of molecular biology, helping to demonstrate that genes are made of DNA; leading to the discovery of restriction enzymes and other essential tools that paved the way for molecular cloning and genome sequencing (including T4 DNA ligase); and more recently revealing the existence of CRISPR–Cas systems[1]. This history perfectly illustrates how the study of basic microbiological processes can widely impact other fields and highlights the importance of curiosity and serendipity — as most of these studies did not set out to find new molecular tools — as the foundations for the development of applications with potential to revolutionize human activities, from agriculture to medicine. Basic research efforts by microbiologists worldwide were essential not only to discover these systems, but also to elucidate the molecular mechanisms by which they operate and to adapt molecules originally involved in microbial defence against invaders into broadly used tools that work in other organisms.

In light of the explosion of CRISPR–Cas papers published over the last decade, it would be easy to think that we now have a complete understanding of exactly how they function, yet many different aspects of their workings are still unclear. For example, the vast majority of CRISPR spacers found in bacteria and archaeal genomes are still of unknown origin, it's unclear why many microorganisms don't encode any CRISPR–Cas genes, and the evolutionary origins of these systems remain enigmatic. Furthermore, although functions beyond serving as adaptive immune systems in microorganisms have been postulated[2] and a few demonstrated[3], such new roles in bacteria and archaea physiology, and in modulating the composition of complex microbial communities and their ecological roles, have so far remained largely unexplored. In addition, given the incredible diversity of CRISPR–Cas systems (including 2 different classes, 5 types and at least 16 subtypes)[4], coupled with continuous efforts to characterize even more microbial genomes that keep revealing new systems and variations[5], there is ample ground to now interrogate what these CRISPR systems do and how they do it, particularly in their native organisms. Such studies are not only important to further our understanding of the basic biology behind CRISPR–Cas, but also have the potential to reveal new molecules with improved features and that could expand the arsenal of CRISPR-based tools and applications. The study of related systems, such as viral-encoded proteins that inactivate CRISPR–Cas systems (termed anti-CRISPRs), also presents a similar setting in which furthering our understanding of fascinating biological processes can be coupled to the discovery of new reagents with potentially disruptive applications, including by identifying proteins that could be used to regulate the activity of Cas9 and other genome-editing enzymes[6].

The continued study of prokaryotic mechanisms of defence against invaders has revealed even more ways through which bacteria and archaea fight their viruses that could, in the future, also be explored for yet-unpredictable uses. Such systems include BREX (bacteriophage exclusion)[7], DISARM (defence island system associated with restriction–modification)[8] and any of the recently identified anti-phage defence islands named after protective deities derived from various mythologies[9], although these are almost certainly just the 'tip of the iceberg' given the vast uncharacterized genomic space in the unsequenced microbial majority.

However, the road from basic discovery to biotechnological blockbuster isn't easy to plan, design or construct, and it will require at least two key ingredients: people and financing. Microbiologists have and will certainly continue to play a crucial role in the process, particularly those doing basic research including phage and archaea virus discovery; genome discovery and analyses to identify and characterize existing and novel systems; and cellular and molecular biology aimed at deciphering the mechanisms and functions of these systems. These are vast areas of research built on the shoulders of many individuals whose praise is often forgotten, but the work of such unsung heroes is paramount for the accolades garnered by the few (https://go.nature.com/2ryVfC3). Financially, this also means that stable funding is required to support the base of the pyramid of discovery, so that new applications emerge at its tip. One interesting possibility is that whichever academic institutions end up winning the ongoing legal disputes over CRISPR patents could reinvest a significant proportion of the profits from licensing deals into basic discovery efforts, to further discovery of what could be the 'next CRISPR', and to support the training and careers of the next generation of microbiologists. ❐

Published online: 24 May 2018
https://doi.org/10.1038/s41564-018-0175-x

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