

Editorial overview: Causes and biotechnological application of microbial metabolic specialization

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The nature and pervasiveness of metabolic specialization

Metabolic specialization is a general feature of every microbial community. The number of available substrates that are effectively catabolized by any individual cell-type can be limited by intrinsic tradeoffs between the requisite metabolic processes. The consequence is that different specialized cell-types can emerge and co-exist with each other, where each cell-type specializes at catabolizing different subsets of the available substrates. Moreover, the number of biosynthetic building blocks that any individual cell-type can biosynthesize *de novo* can also be limited by intrinsic tradeoffs between the requisite biosynthetic processes. Again, the consequence is that different specialized cell-types can emerge and co-exist with each other via cross-feeding of biosynthetic building blocks, where each cell-type biosynthesizes and provides one or more building blocks required by other cell-types. Such metabolic specialization has profound importance for the assembly and functioning of microbial communities. For example, it can determine the types of interactions that occur within microbial communities, bestow community functionalities and behaviors that are otherwise impermissible, and contribute to the promotion and maintenance of biodiversity within microbial communities. Clearly, a deeper understanding of metabolic specialization is essential for improving our basic understanding of microbial communities.

How pervasive is metabolic specialization within the microbial world? At first glance, one may have doubts. Many typical laboratory microorganisms, such as *E. [scherichia](#) coli* K-12, can catabolize a wide variety of substrates and biosynthesize all of the required building blocks to support their growth, and thus could be defined as effective metabolic generalists. Yet, such laboratory microorganisms appear to be the exception rather than a rule. Recent experimental and bioinformatic analyses, along with support from mathematical simulations, suggest that the majority of microorganisms outside the laboratory have rather restrictive catabolic capabilities and cannot biosynthesize all of the required building blocks to support their growth ([e.g., e.g.](#) many are auxotrophic for one or more co-factors, amino acids, [eteetc.](#)) [1]. Moreover, such metabolic specialization ~~need not~~[does not need to](#) have a genetic basis, as metabolic specialization can occur even within a single genotype. Stochastic phenotypic variants can emerge within clonal populations, where different phenotypic variants catabolize different substrates and/or biosynthesize different biosynthetic building blocks [2-4]. Thus, while the complete extent of metabolic specialization remains unclear, its pervasiveness appears to be far greater than one might have initially expected, and may be the rule rather than the exception within the microbial world.

Causes of metabolic specialization

What are the underlying causes of metabolic specialization? Stated alternatively, what gives rise to tradeoffs between different metabolic processes? There are potentially myriad answers to these questions, but several themes repeatedly emerge. First, because the cell is a finite entity, the cell contains a limited amount of intracellular resources that could be invested into different metabolic processes [5,6]. Such intracellular resources may include building blocks for biosynthesizing enzymes, co-factors for empowering enzymatic activity, or cellular space to contain those enzymes. Under certain conditions, it may be beneficial to invest those intracellular resources into a subset of metabolic processes rather than distribute them across all possible metabolic processes [7]. This would then result in the emergence of a metabolically specialized cell-type. As the environment changes, the cell-type could then dynamically change its distribution of those intracellular resources to achieve a different type of metabolic specialization. Second, all metabolic processes produce intermediates and end-products, and these intermediates and end-products can, in some cases, impose costs and deleterious effects on the cell [6]. Under certain conditions, it may be advantageous to avoid the accumulation of these intermediates and end-products by down-regulating the expression

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of the responsible metabolic processes, consequently resulting in the emergence of a metabolically specialized cell-type. In both cases, genetic mutations may then accumulate such that the cell-types become “locked-into” locked into a particular type of metabolic specialization. Thus, the emergence of metabolic specialization can be viewed as a consequence of basic cellular economics (i.e., i.e. the costs and benefits of different intracellular resource distributions) and evolutionary change.

Measuring and predicting metabolic specialization

How can we empirically measure metabolic specialization? Can we make general predictions regarding which metabolic processes are likely to be performed by the same cell-type and which metabolic processes are likely to be performed by different cell-types? Recent advances in experimental microbiology, such as microfluidic cultivation, now enable us to measure metabolic specialization within individual genotypes and assembled cultures [8]. This allows us to address novel questions in the field. For example, how is the metabolic profile of one cell-type modulated by the presence of a second gene cell-type? These experimental observations, in turn, can help calibrate and improve models that predict the metabolic profiles of individual cell-types under specified environmental conditions and, in turn, the interactions likely to occur between different cell-types [1,7]. For example, theoretical considerations built upon first principles, such as the theory of optimal pathway length, provide predictions about the environmental conditions likely to promote or repress the emergence of metabolic specialization [6].

Biotechnological applications of metabolic specialization

A deeper understanding of metabolic specialization could set the stage for tangible advances in the field of biotechnology [9]. For example, can we predict how best to distribute different metabolic processes across different cell-types to optimize the performance of a desired biotransformation? If we could predict the costs and benefits of dividing metabolic labor at specific breakpoints, then this would provide a foundation for the rational engineering of synthetic microbial communities. Different cell-types could be selected *a priori* and mixed together such that the benefits of distributing metabolic labor are maximized, thus potentially leading to improved process performance. The Eukarya domain already provides us with good examples of how metabolic specialization results in different metabolic routes to the same target compound [10]. By finding the right combination of essential catalytic reactions and associated transport steps between different compartments, the negative impact of stress responses during cultivation might be decreased and thereby target product formation increased.

For many decades, natural microbial communities have been efficiently applied for waste-water treatment or decontamination of polluted soil. When considering more specific metabolic tasks, e.g. for example, elimination of single contaminants in food, so-called bioremediators can be employed [11]. For the design of bioremediators at the cellular and molecular level, mechanistic modelling is a valuable tool which, however, also requires appropriate quantitative data to allow for suitable predictions.

Synthetic microbial communities for the production of small molecules are currently based on straightforward approaches combining specific metabolically specialized “helper” cells that provide access to complex feedstocks or additional precursor molecules to feed the “producer” helper cells that provide access to complex feedstocks or additional precursor molecules to feed the ‘producer’ cells with the essential ingredients for target product synthesis [12]. For the production of complex chemicals, such as natural compounds, multi-chassis and co-culture engineering approaches are currently emerging and can help to effectively minimize the metabolic burden that is inherent to longer biosynthetic routes involving many enzymes, intermediates and cofactors [13,14].

While for such designs the proof-of-concept under classical laboratory-scale conditions was already successful, alternative process control strategies or even new technical solutions are required to enable more complex synthetic consortia as well as robust large-scale bioproduction processes. Here one strategy follows an upgrading of conventional stirred tank reactors by introducing, e.g. for example, additional media supply channels, specific membranes or light fibres, to create defined ecological niches for the co-cultivation of metabolically specialized microorganisms with non-matching abiotic requirements [15]. Another highly sophisticated strategy follows the engineering of spatially linked microbial consortia, where different metabolically specialized cell-types might be arranged in single modules that are connected but independently controlled to ensure optimal growth and production conditions [16].

Finally, in the field of medical biotechnology, technological advancements and engineering of commensal bacteria enable a much better understanding of host-microbiome interactions [17]. By employing this knowledge, alternative therapies for metabolic disorders and cancer are already conceivable. These rely on the synthesis of various molecules ranging from antimicrobial metabolites and peptides to enzymes with specific catalytic or activating functions to provide chemotherapeutic drugs or cytotoxic immune cells.

Conclusions

Our understanding of microbial metabolic specialization is in a period of rapid change. We are now obtaining a deeper and more complete understanding of why and under what conditions metabolic specialization is likely to occur. This basic knowledge, in turn, provides the necessary foundation for applying microbial metabolic specialization in biotechnological processes. For example, can we leverage such knowledge to rationally select collections of metabolic specialists to achieve engineering objectives? How best should we divide metabolic labor to improve the performance of biotechnological processes? We believe that answering these questions using principles of microbial

metabolic specialization could have timely impacts on microbial biotechnology and lead to a paradigm shift in how we design, control, and manipulate microbial communities.

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