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Biochemical principles enabling metabolic cooperativity and phenotypic heterogeneity at the single cell level

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Abstract

All biosynthetically active cells release metabolites, in part due to membrane leakage and cell lysis, but also in part due to overflow metabolism and ATP-dependent membrane export. At the same time, cells are adapted to sense and take up extracellular nutrients when available, to preserve metabolic efficiency, biomass, and ultimately, to minimize the number of biochemical reactions that have to operate within a cell in parallel. Within colonies, biofilms or tissues, the co-occurrence of metabolite export and import enables the sharing of metabolites as well as metabolic specialization of single cells. In this review we discuss emerging biochemical concepts that give reasoning for why cells overproduce and release metabolites, and how these form the foundation for cooperative metabolite exchange activity between cells. We place particular emphasis on discussing the role of overflow metabolism in cells that exhibit either the Warburg or Crabtree effect. Furthermore, we discuss the profound physiological changes that cells undergo when their metabolism switches from metabolite synthesis to uptake, providing an explanation why metabolic specialization results in non-genotypic heterogeneity at the single cell level.

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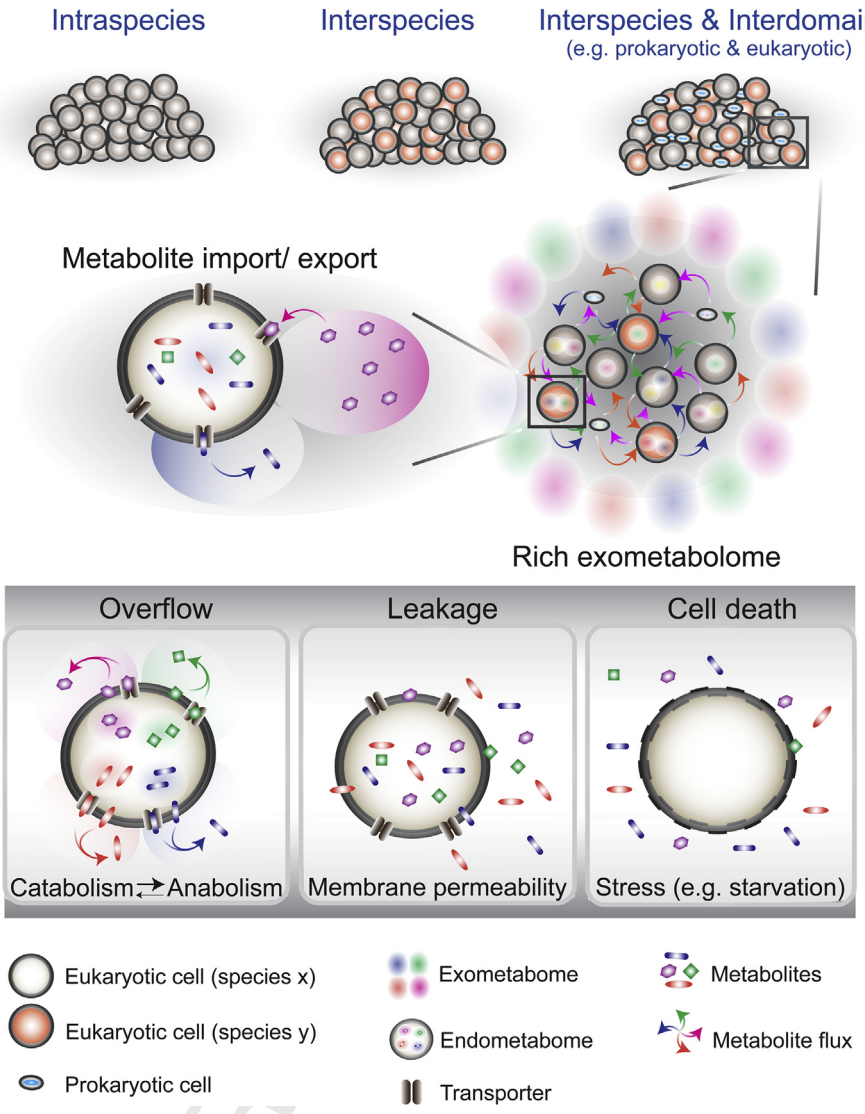
Introduction

To be competitive in their environment, cells from all kingdoms of life have evolved a series of mechanisms to sense nutrients, and uptake the metabolites needed for their growth and survival [1–4]. Metabolite uptake saves energy, carbon and nitrogen, and is further beneficial by reducing the number of biochemical reactions that need to run in parallel, increasing metabolic efficiency [5].

At the same time, biosynthetically active cells are known to release a complex spectrum of metabolites [6–10], and within communities, such as colonies, biofilms and tissues, these metabolites can enrich the extracellular space (Figure 1). The export of metabolites coupled with the preference for cellular import, upon reaching a critical concentration, subsequently allows for the exchange of metabolites between cells and within microbial communities, this metabolite exchange permits the survival of otherwise unculturable cells (auxotrophs). The extent of this metabolite exchange in microbial environments is demonstrated by currents estimates, that up to 90% of bacterial species are not metabolically viable outside a community environment [11–15]. Further, it is becoming increasingly clear that metabolite export and import are equally important as well for cells that do not completely depend on metabolite sharing for growth (prototrophs), and that a broad spectrum of metabolites are involved in these exchange events (Figure 2) [10]. Finally, when individual cells switch from biosynthesis to the uptake of a metabolite their physiology shows to be fundamentally altered [16,17]. In this review we discuss these exchange interactions, from the point of view that they do not solely emerge to confer a selective advantage in the ecological and evolutionary sense, but also as a consequence of basic biochemical properties that underlie the function of the metabolic network.

Figure 1



Sources of extracellular metabolites cellular communities, tissues and biofilms. Biosynthetically active cells release a complex spectrum of metabolites, resulting in an extracellular space rich in products of metabolism. This rich exometabolome allows for the exchange of metabolites between single cells via export/import processes and enables survival of otherwise unculturable auxotrophs, but also changes the physiology of prototrophs that reconfigure their metabolism to exploit the available nutrients. Sources of extracellular metabolites include overflow metabolism, ATP-dependent export, membrane leakage and cell death. A main driver is the topological structure of the metabolic network leading to flux-coupling, imbalances of anabolic over catabolic reactions, and non-enzymatic chemistry that requires metabolite repair through export (inset left). Membrane leakage and non-selective transport processes are other important source of extracellular metabolites (middle), as it is cell death (inset right).

Basic requirements for a metabolite exchange interaction to emerge

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In order for metabolite exchange to be of biological relevance, a few basic conditions need to be fulfilled. First, cells have to export metabolites at a rate where relevant extracellular concentrations can be achieved in the given community, tissue or environment. The rate of accumulation is constrained by the environment and cell density of the community or tissue: but equally what a 'relevant' concentration is depends on the molecule's chemical nature (i.e. reactivity), cost of biosynthesis (i.e. the 'expensiveness' of a metabolite), and the essentialness of its function. The extracellular presence of highly costly metabolites, like thiamine (vitamin B_1), can be physiologically relevant at sub-micromolar concentrations, while much higher concentrations are involved when cells share abundant cellular metabolites, like amino acids, nucleotides or polyamines [18–20]. Related to this is the second requirement, that neighbouring cells need to sense and uptake a particular metabolite. Indeed such mechanisms that meet these conditions exist for a broad range of metabolites, released by both eukaryotic and prokaryotic cells [6,21,22].