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Mini Review

Staphylococcus aureus metabolic response to changing environmental conditions – A metabolomics perspective

Manuel Liebeke[a,*], Michael Lalk[b]

[a] Biomolecular Medicine, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, London SW7 2AZ, UK
[b] Institute of Biochemistry, Ernst-Moritz-Arndt-University of Greifswald, 17487 Greifswald, Germany

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ABSTRACT

Microorganisms preserve their metabolic function against a wide range of external perturbations including biotic or abiotic factors by utilizing cellular adaptations to maintain cell homeostasis. Functional genomics aims to detect such adaptive alterations on the level of transcriptome, proteome and metabolome to understand system wide changes and to identify interactions between the different levels of biochemical organization. Microbial metabolomics measures metabolites, the direct biochemical response to the environment, and is pivotal to the understanding of the variability and dynamics of bacterial cell metabolism. Metabolomics can measure many different types of compounds including primary metabolites, secondary metabolites, second messengers, quorum sensing compounds and others, which all contribute to the complex bacterial response to an environmental change. Recent data confirmed that many metabolic processes in pathogenic bacteria are linked to virulence and invasive capabilities. Deciphering bacterial metabolism in response to specific environmental conditions and in specific genetic backgrounds will help map the complex network between the metabolome and the other "-omes". Here, we will review a selection of case studies for the pathogenic Gram-positive bacterium *Staphylococcus aureus* and summarize the current state of metabolomics literature covering staphylococci metabolism under different physiological states.

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Introduction

Pathogenic bacteria are a major cause of infections such as cholera, sepsis, typhoid fever and tuberculosis leading to serious human disease and even death. Some organisms, such as staphylococci, represent a class of commensal bacteria with huge potential for human burden. The fast development of multi-resistance against antibiotics makes these bacteria so called "super bugs" (Payne, 2008). Staphylococcal strains have recently been shown to increase their repertoire of virulence factors, make these bacteria even more harmful to humans (Li et al., 2009). Also, changes in environmental conditions have been shown to modulate virulence factor expression (Chan and Foster, 1998). Current data implicates a direct link between the metabolic activity, virulence, survival, and persistence of several organisms (Somerville and Proctor, 2009; Eisenreich et al., 2010). It is therefore of enormous importance to human health to decipher the metabolism of pathogenic bacteria and obtain a systems-wide view of the metabolite landscape during different environmental conditions.

The complexity of biological systems poses a great scientific challenge for a comprehensive and integrative understanding of how signaling components contribute to overall cellular function. In recent years, advances in global genome, transcriptome, and proteome analysis have provided insight into the gene-centered aspects of biological complexity. A direct link between such compositional data and the dynamic metabolic and physiological behavior of cellular systems has not yet been identified. Downstream products of transcripts and proteins are mainly metabolites, as well as small non-coding RNAs and structural proteins without enzymatic function. These molecules are the metabolome of an organism and make up the 'ome' with greatest plasticity (Fiehn, 2002; Dumas, 2012). The metabolome is defined as the quantitative complement of low-molecular-weight metabolites (>1500 Da) present in an organism under a given set of physiological conditions (Oliver et al., 1998; Fiehn, 2002) (for related terms and definitions, see Table 1). Quantitative understanding of microbial metabolism and its regulation requires knowledge of both extracellular and intracellular metabolite levels. This study of metabolic flux and interconnection between bacteria and the environment is particularly important for *in vitro* culture systems and the more complex bacteria–host systems.

Recent developments in analytical chemistry have made it possible to measure very low abundant metabolic changes by

* Corresponding author. Tel.: +49 421 2028 825.
E-mail addresses: m.liebeke@imperial.ac.uk, mliebeke@mpi-bremen.de (M. Liebeke).

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Table 1
Terms and definitions in metabolomics.

Metabolome	The quantitative complement of all low-molecular weight compounds (metabolites <1500 Da) present in a biological sample. - metabolites from cell surroundings (e.g. growth medium) = **exometabolome** - metabolites from cell extracts = **endometabolome**
Metabolomics	The comprehensive analysis (identification and quantification) of all measurable metabolites in cells, tissues or organisms under a given set of conditions
Metabonomics	Quantitative measurement of the dynamic multiparametric metabolic response of living systems to pathophysiological stimuli or genetic modifications (Nicholson et al., 1999)
Targeted metabolomics	Quantification of a highly related subset of predefined metabolites following appropriate sample preparation
Nontargeted metabolomics	Relative quantification of a complete set of both known and unknown metabolites in a biological sample, in an unbiased way and without the need for prior information of metabolite identities
Metabolic profiling	Quantification of a specific group of metabolites (e.g. nucleotides) for discrimination of samples from different biological origins or status. Sample preparation and metabolite extraction are selective to the particular class of metabolites
Metabolic footprinting	Untargeted profiling of growth culture supernatant
Metabolic fingerprinting	Untargeted profiling of cell extracts

using highly sensitive mass spectrometry approaches. Microbial metabolomics makes use of many different techniques to analyze the metabolome in a comprehensive way (e.g. nuclear magnetic resonance spectroscopy NMR; gas- or liquid chromatography coupled to mass spectrometry analyzer – GC–MS, LC–MS), which are reviewed elsewhere (Kuehnbaum and Britz-McKibbin, 2013). Recent efforts to understand the metabolic adaption of pathogenic bacteria resulted in many new associations between metabolism and pathogenicity (Somerville and Proctor, 2009; Joshi et al., 2011; Nuxoll et al., 2012). Similarly, recent studies have induced changes in *S. aureus* physiology by gene knock out studies and utilized metabolomics to identify downstream metabolites relevant for virulence and pathogenicity. This review will focus on specific applications of metabolomics for the elucidation of the metabolome of the Gram-positive bacterium *Staphylococcus aureus* in response to different aspects of environmental conditions and genetic manipulation relevant for pathogenicity.

Constitution of a bacterial metabolome

The composition of the metabolome can vary considerably among a diversity of organisms. 200,000 primary and secondary metabolites have been reported to be present in Fiehn (2002) and Mungur et al. (2005). To date, only 600 metabolites have been estimated in the less complex eukaryotic *Saccharomyces cerevisiae* metabolome (Forster et al., 2003). Still an open question for microbial metabolome analysis is: "How large is a bacterial metabolome?" More than 20 genome-scale models of bacterial metabolism predict an average of 600 metabolites for diverse bacterial species (Durot et al., 2009). Importantly, the genome annotations and model characteristics of the metabolome prediction differs between calculations, e.g. the Gram-positive bacterium *Bacillus subtilis* have a predicted range of metabolites from 988 to 1138 (Oh et al., 2007; Henry et al., 2009), whereas only 537 compounds were predicted after manual curation for analytically accessible metabolites (van der Werf et al., 2007). *In silico* calculations for the Gram-negative organism *Escherichia coli* predicted 1039 compounds (Feist et al., 2007) and only 694 metabolites after correction (van der Werf et al., 2007). Genome-scale metabolic networks for *S. aureus* posses over 700 metabolic reactions and estimated 422, 571 and 712 metabolites in three different calculations (Becker and Palsson, 2005; Heinemann et al., 2005; Liang et al., 2011). Recently, a genome-scale comparison of 13 *S. aureus* strains suggested a larger number of metabolic reactions (~1250) and metabolites (~1400) based on new reconstruction methodologies and the use of comprehensive whole-genome data (Lee et al., 2009). Based on these studies, *S. aureus* is predicted to be one of the most complex microorganisms in terms of estimated metabolite numbers so far, accompanied by *Klebsiella pneumonia* with 1658 metabolites (Feist et al., 2009). In contrast, the bacteria with very small genomes like *Mycoplasma pneumonia* or *Mycoplasma genitalium* are predicted to produce only 150 and 270 metabolites, respectively (Suthers et al., 2009; Maier et al., 2013). Yet the field still relies on mathematical predictions, as full metabolome annotation is still hindered by analytical drawbacks.

To correctly assign metabolite diversity and abundances in an organism, one has to consider the environmental conditions at the time of sampling. It is possible that environmentally dependent pathways (e.g. non-expressed genes) are responsible for the difference between estimated and detected metabolite numbers. Yet analytical capabilities like lack of comparable standard compounds, limits of detection still make measurement of quantitative metabolite distribution difficult. Quantitative metabolite data from a systems-wide view are rare but present for some bacteria (van der Werf et al., 2007; Bennett et al., 2009; Liang et al., 2011; Maier et al., 2013). These comprehensive quantitative data show that for *E. coli* and *S. aureus* under glucose-rich conditions in exponential growth phase, that glutamate is the main metabolite in *E. coli*: 96 mmol L^{-1} cell and *S. aureus*: 160 mmol L^{-1} (*S. aureus* data in (Liebeke et al., 2011) is given as μmol g^{-1} cell dry weight, we calculated these values back to concentration v/v and this equals approx. to 1/3 μmol mL^{-1} or mmol L^{-1}) whereas nucleosides and cofactors are the less abundant measured metabolites (*E. coli*$_{\text{Adenosine}}$: 1.3×10^{-7} mol L^{-1} cell) (Bennett et al., 2009). This highlights a five concentrations magnitudes between main metabolites and less abundantly detected ones. The complexity and varying distribution of the bacterial metabolome therefore requires a sensitive and broad analytical method. A variety of analytical methods and examples of quantitative microbial metabolomics were previously (Mashego et al., 2007; Merlo et al., 2011).

Metabolome sampling

The goal of microbial metabolomics is not only to generate data, but to translate metabolomic data into biologically meaningful information. Thus it is essential to provide representative snapshots of a bacterial metabolome. In particular a metabolomic dataset has to accurately present metabolite composition (Bolten et al., 2007). Concerning this demand, the metabolome analysis of a microorganism is much more challenging than that of proteomes and transcriptomes as the turnover of analytes is strikingly different. Proteins and mRNA levels change within minutes or even hours but in enzymatic active solutions metabolites showed turnovers in the range of milliseconds and seconds. Therefore, accurate determination of intracellular metabolite levels requires well-validated procedures for sampling and sample handling. The first steps of sample treatment, like rapid sampling, quenching of metabolic activity, separation of extracellular medium (if possible) and metabolite extraction were shown as most crucial steps in microbial metabolomics and lead to the development of a

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