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Copper and Bacteria

Evolution, Homeostasis and Toxicity

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Preface

Of the three domains of life, bacteria, archaea, and eukarya, the two prokaryotic domains represent the bulk of the earth's biomass. Prokaryotes live in all possible niches on earth and also colonize all multicellular organisms. The techniques of metagenomics have recently allowed to define microbiomes, the collection of prokaryotic species of a microbiota (a specific niche, such as human skin or the gut). Recent work revealed that human microbiomes are affected by lifestyle, diet, and disease. We are only at the beginning of understanding the intricate human–bacteria interaction and its role in human well-being. Such an understanding requires the investigation of individual microbes to understand their metabolism and their interaction with the surrounding world.

An important facet of all bacterial life is their ability to deal with the toxic, yet essential trace element copper. The study of copper homeostasis in different prokaryotic species over nearly four decades provides an in-depth knowledge of the process. In discussing prokaryotic copper homeostasis, it is important to know that the bacterial world is divided into two groups: Gram-negative and Gram-positive organisms (the latter including all archaea). The distinction is based on a simple staining procedure in which some organisms stain, while others do not. It was devised by the Danish physician Hans Christian Gram in 1884 and has remained a valid criterion to this day (Fig. 1) [1]. Gram-positive organisms only possess a single-cell membrane which is surrounded by a cell wall, and it is the cell wall which absorbs the Gram stain. In Gram-negative bacteria, the cell wall is surrounded by a second membrane, preventing the stain to reach the cell wall. Photosynthetic bacteria can occur to either group. In Gram-negative organisms, the two membranes separated by the periplasmic space call for special transport systems for solutes and biomolecules. For this reason, many membrane- and transport-related systems, including copper homeostasis, differ significantly between Gram-positive and Gram-negative organisms, but they also share some fundamental components.

The investigation of copper homeostasis in bacteria has brought to light proteins with surprising new functions, like copper-pumping ATPases or copper chaperones. The evolutionary conservation of some of these proteins from bacteria to humans

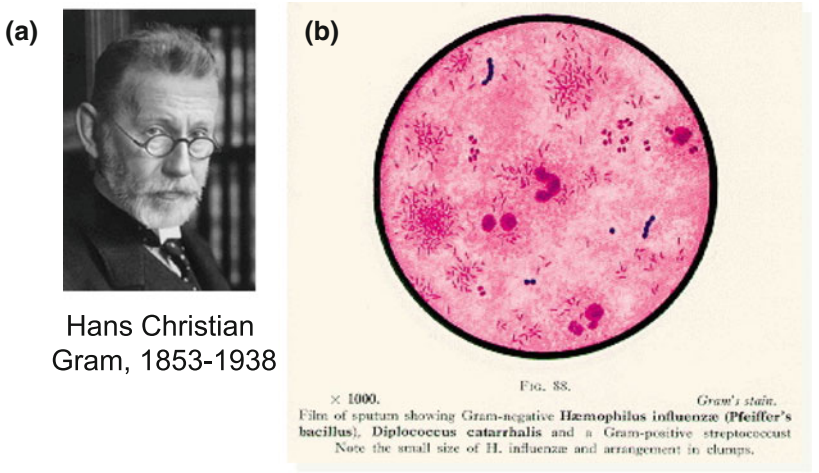

Fig. 1 **a** Hans Christian Gram. **b** Gram staining of a sputum, showing swarms of Gram-negative *Haemophilus influenza*, pairs of Gram-negative *Diplococcus catarrhalis*, and two chains of Gram-positive streptococci. The few large cells are probably yeast. **c** Schematic drawing of the cell membrane-wall structures of Gram-positive and Gram-negative bacteria. Note the thick peptidoglycan cell wall of Gram-positive bacteria

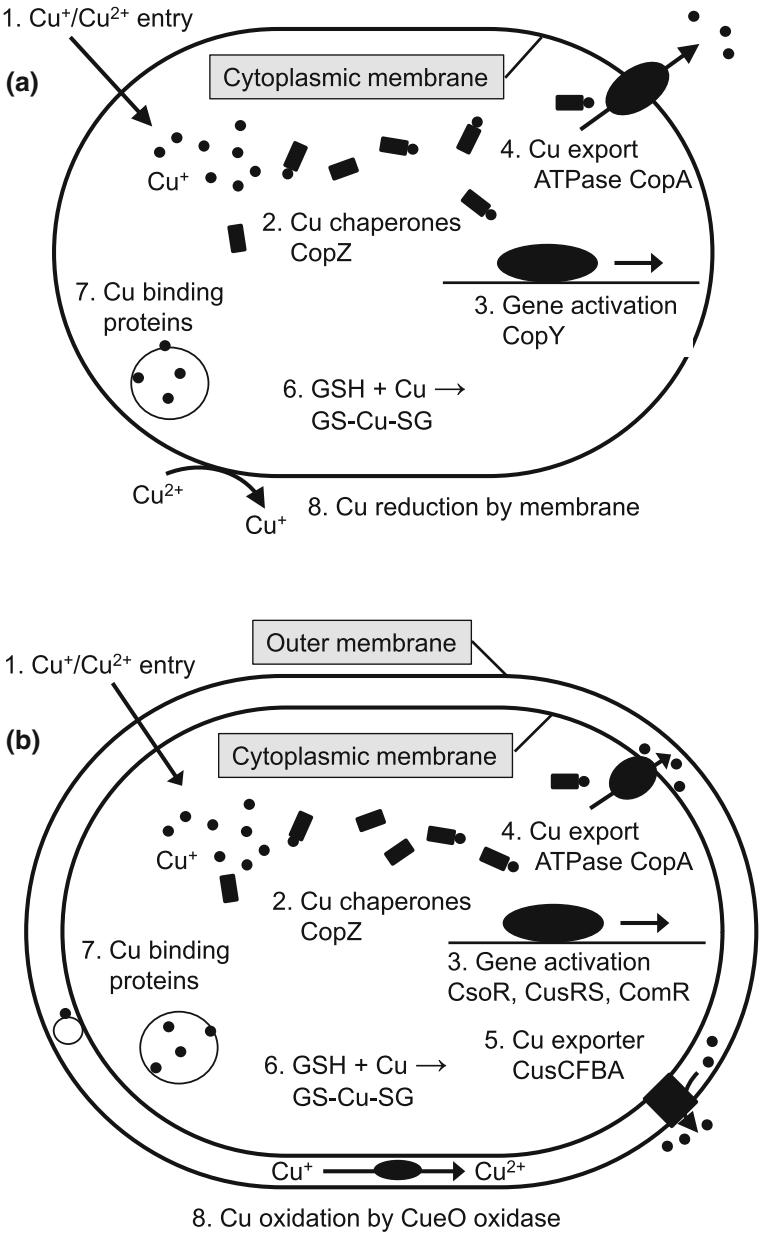

Fig. 2 Key elements of bacterial copper homeostasis. **a** Gram-positive bacterium. **b** Gram-negative bacterium. The main elements of copper homeostasis are: 1, copper entry into bacteria; 2, copper chaperones sequester cytoplasmic copper for detoxification and routing to places of export or regulations; 3, several genes are induced in response to elevated cytoplasmic copper; 4, copper is pumped across the cytoplasmic membrane by copper ATPase, powered by ATP; 5, only in Gram-positive bacteria, a CusCFBA transporter pumps copper across the outer membrane; 6, glutathione (GSH) can bind copper for detoxification; 7, copper-binding proteins buffer excess cytoplasmic copper. All steps are discussed in detail in Chaps. 3 and 4

led to a new understanding of the development of copper resistance, homeostasis, and the use of copper by cells as a modern bioelement. These evolutionary aspects will be discussed. Many examples of gene regulation by copper were characterized in detail, along with the respective genes and operons. Also, copper toxicity was revisited in recent years and new concepts have emerged. Other topics covered in this book include copper reduction by bacteria and the role of chalkophores in copper acquisition by methanotrophs, and the mechanism of copper loading of cuproenzymes. For the metallation of enzymes, I have formulated a new, universal conceptuality that first needs to be tested.

Some proteins involved in copper homeostasis are conserved from bacteria to humans, and it comes as no surprise that there has been extensive interaction, including common meetings, between researchers working on prokaryotic and eukaryotic systems. The focus of this book is laid on fundamental concepts, rather than on summarizing all the available data and historic developments (*Cupriavidus metallidurans* was the topic of a separate monograph of this series). Consequently, eukaryotic work is mentioned when it illustrates fundamental concepts particularly well or when mechanisms and proteins have been better characterized in a eukaryotic system. The copper field has greatly profited from this cross-fertilization and has made copper the trace element which is probably best understood today in terms of homeostasis and toxicity.

For a general overview and to help organize the readers' mind, Figs. 1 and 2 give simplified overviews of copper homeostasis in Gram-positive and Gram-negative bacteria. It is apparent that the two processes are of (i) limited complexity and (ii) very similar in the two bacterial worlds. The major difference is that Gram-positive bacteria require an additional copper transporter, CusCFBA, to transport copper across the outer membrane.

Keywords Copper homeostasis · Antimicrobial copper · Copper ATPases · Gene regulation by copper · Copper chaperones · Copper toxicity

Reference

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About the Author

A native of Zurich, Marc Solioz studied chemistry and engineering in Zurich. He then moved to the USA, where he obtained his Ph.D. in Biochemistry at St. Louis University in 1975. The Ph.D. work focused on genetic transfer in photosynthetic bacteria. During postdoctoral studies at the Biocenter in Basel, he investigated the genetics and biogenesis of mitochondria. This was followed by seven years as an assistant professor at the ETH in Zurich, where he investigated proton transport by cytochrome oxidases and potassium transport by a bacterial K-ATPases.

In 1989, he became professor of biochemistry at the University of Bern. With the discovery of the first copper-pumping ATPase in 1992, his focus shifted to copper and he investigated copper homeostatic mechanisms of Gram-positive bacteria. This also brought about advisory activity on government and industry panels in relation to copper toxicity and human exposure to copper. In 2009, he started to investigate the mechanism whereby metallic copper surfaces kill bacteria.

From 2004 to 2010, he was the chief organizer of the biannual International Copper Meeting. The International Copper Meetings were inaugurated in 1997 by Arturo Leone, University of Salerno, Italy, and Julian Mercer, Murdoch Institute for Research, Melbourne, Australia, and continue to this day. These meetings have become a focal point of copper research and keep drawing copper researchers from all over the world to Italy.

Facing mandatory retirement in 2014, he moved to Tomsk State University, Siberia, where he built up a new laboratory to investigate heavy metal resistance in bacteria. Siberia offered a unique setting to isolate new heavy metal-resistant organisms from deserted mines. The endeavor was funded by a Russian Government Grant for leading scientists. This project terminated in 2016 due to funding restrictions.

Currently, he is active as a science writer and as an independent advisor to the industry. He also runs a small company which produces the antimicrobial CopperPen®.

Abbreviations

[4Fe-4S]	Iron–sulfur clusters
COX	Cytochrome *c* oxidase
CRP	cAMP response protein
EXAFS	Extended X-ray absorption fine structure
GSH	Glutathione (reduced)
GSSG	Glutathione (oxidized dimer)
H_2O_2	Hydrogen peroxide
HMA	Heavy metal-associated (domain)
HSAB	Pearson soft–hard acid–base concept
MBD	Metal-binding domain
Mbt	Methanobactin
MCO	Multicopper oxidase
MFS	Major facilitator superfamily
MMO	Methane monooxygenase
NAD^+	Oxidized nicotinamide adenine dinucleotide
NADH	Reduced nicotinamide adenine dinucleotide
NMR	Nuclear magnetic resonance
NO	Nitrous oxide
Pi	Inorganic phosphate
PKK1	Polyphosphate kinase
pMMO	Particulate (membrane-bound methane monooxygenase)
PPX	Exopolyphosphatase
PSII	Photosystem II
RND	Resistance–nodulation–cell division
ROS	Reactive oxygen species
SOD	Superoxide dismutase
XANES	X-ray absorption near-edge structure
Ybt	Yersiniabactin