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Peptidoglycan plasticity in bacteria: emerging variability of the murein sacculus and their associated biological functions

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The peptidoglycan (PG) sacculus once thought to be just a reinforcing, static and uniform structure, is fast becoming recognized as a dynamic cell constituent involved in every aspect of bacterial physiology. Recent advances showed that in addition to 'classical' tasks — as an essential element to define bacterial shape, size, division and resistance to osmotic stress — the sacculus plays very important roles in many other fields. The very few chemical and structural changes that were once considered as bizarre, or maybe exotic exceptions, are now universally accepted as fundamental pieces in bacterial cell wall adaptation to different kinds of environmental stresses; immune response; intra-specific and inter-specific signalling and antibiotics, just to mention a few. Most, if not all, of these implications are a consequence of the enormous adaptability of PG metabolism to cope with changing conditions, a characteristic for which the term plasticity is proposed. Here we overview and comment on a number of recent contributions on the cell wall adaptive responses to environmental challenges that has greatly impacted the already high complexity of the PG biology field. These new evidences have revived the interest in PG plasticity as an exciting and trendy topic in current microbiology which considers this variability as the trustworthy picture of bacterial PG in nature.

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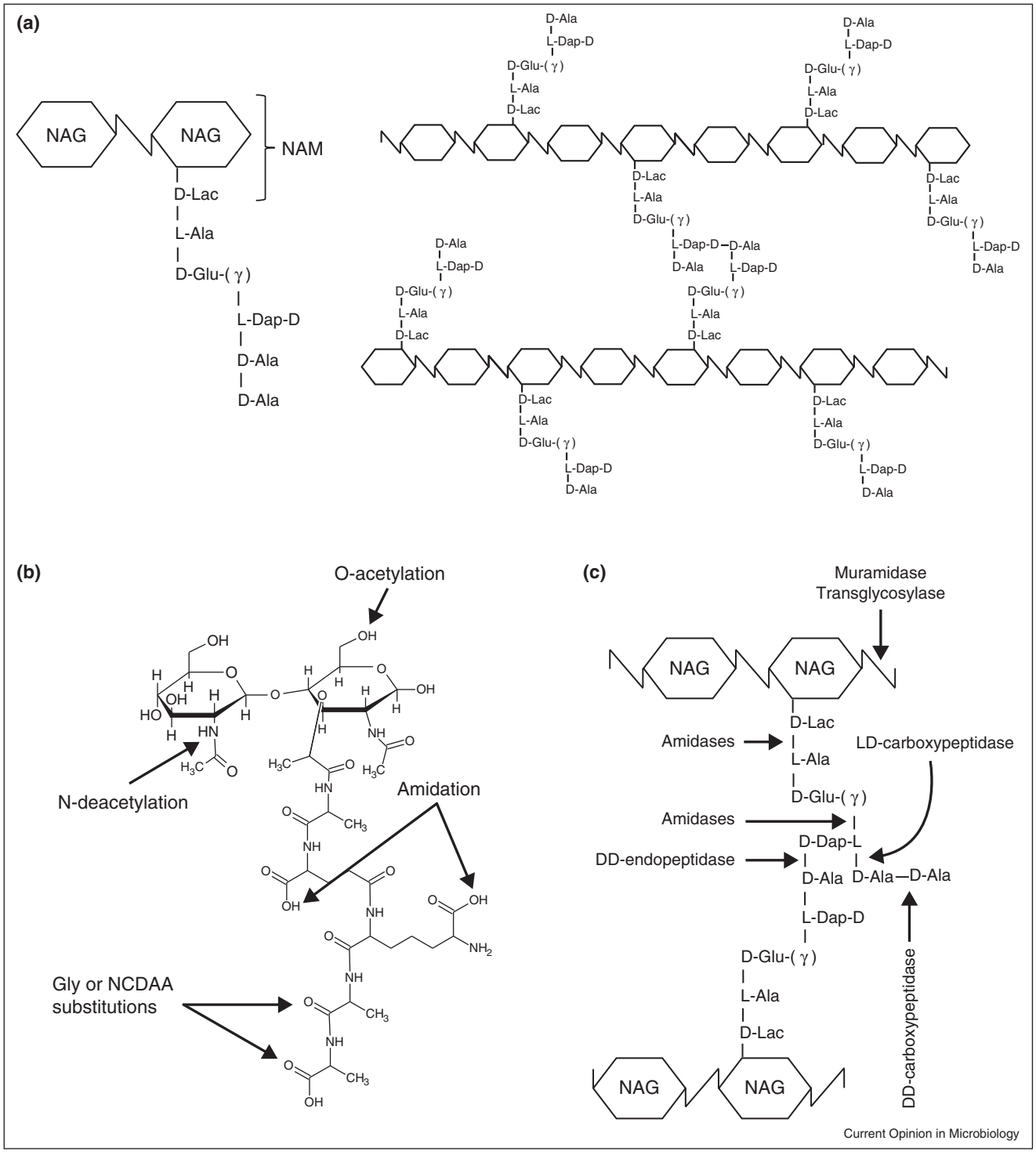
Introduction

One of the defining characteristics of bacteria is the presence of a peptidoglycan (PG) layer or murein sacculus, as a critical component of the cell envelope. PG is a hetero-polymer made up of linear glycan strands cross-linked by peptides in a net-like fashion. Because it is a covalently closed structure and overlays the cytoplasmic membrane, the sacculus works as an exoskeleton conferring physical strength to the envelope, and defining the shape and size of the cell. Furthermore, cell growth is strictly conditioned by a concomitant enlargement of the sacculus. The intricacies of PG biosynthesis and cell wall growth have been recently addressed in a number of excellent reviews which clearly support PG metabolism as a highly complex process second only to protein synthesis [1–8]. Here we will focus on one aspect of cell wall biology which should largely benefit from the mind-set and technical advances of the 'omics' era; PG plasticity. By this term we refer to those modifications of PG which happen in response to environmental alterations. Therefore, plasticity is an adaptive response where a particular character is expressed in response to a stimulus, but the cell (species) is potentially able to do so at any time (Figure 1, Table 1). The idea of the PG sacculus as a dynamic structure subjected to adaptive changes, first proposed in the 1980s [9–13], has permeated the field slowly. However, the recent identification of a number of instances where PG plasticity plays important roles in stress response, virulence and survival is boosting research in this direction. The most recent results are pointing to cell wall metabolism as an important element in the bacterial strategy to adapt to challenging conditions. This in turn is unveiling new potential targets to manipulate bacterial behaviour, and fighting harmful bacteria.endospore differentiation in

PG plasticity and morphogenesis

Bacteria are more often than not under nutritional stress, a condition that triggers specific response mechanisms [14], including severe alterations in shape, size and PG composition [10,12,15]. An extreme case of PG plasticity is endospore differentiation in several species of Gram-positive bacteria, mostly *Bacillus* and *Clostridium*. [16–22]. Other bacterial groups develop metabolically semi-inert, persistence forms in order to adapt to stress conditions [23]. The human gastric pathogen *Helicobacter pylori* is known to undergo a morphological transition to coccoid forms following long term cultivation [24], which entails rearrangements of the sacculus [25]. When compared to PG of spiral cells, the PG of the coccoid forms was richer in disaccharide dipeptide and had a reduced cross-linking. Accumulation of dipeptide muropeptides and development of coccoid forms depends on activation of the amidase AmiA and promote escape from immune system recognition [26] (Figure 1, Table 1).

Figure 1



Relevant aspects of peptidoglycan structure and modification sites. **(a)** The chemical composition of the basic PG subunit (left hand side) and a representation of fragment of macromolecular PG showing the relationship between glycan chains and peptide cross-bridges. **(b)** The chemical groups more often modified in PG as well as the nature of the more frequent modifications. **(c)** Sites of action of the PG hydrolases more often associated to adaptive modifications of the sacculus. In all instance *E. coli* PG structure was used as reference. NAG, N-Acetyl-glucosamine; NAM, N-Acetyl muramic acid; D-Lac, D-lactate; L-Dap-D, meso-diamino pimelic acid.