The impact of two-component sensorial network in staphylococcal speciation
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Bacteria use two-component systems (TCSs) to sense and respond to their environments. Free-living bacteria usually contain dozens of TCSs, each of them responsible for sensing and responding to a different range of signals. Differences in the content of two-component systems are related with the capacity of the bacteria to colonize different niches or improve the efficiency to grow under the conditions of the existing niche. This review highlights differences in the TCS content between Staphylococcus aureus and Staphylococcus saprophyticus as a case study to exemplify how the ability to sense and respond to the environment is relevant for bacterial capacity to colonize and survive in/on different body surfaces.

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Introduction
Bacterial genomes encode for a variable number of two-component sensor – response regulator pairs. The number of TCSs is proportional to the genome size, the diversity of environments in which organisms live, and the complexity in cellular differentiation [1]. Thus, bacteria with larger genomes, more metabolic versatility, and complex lifestyles are more likely to have a larger number of two-component systems than bacteria inhabiting relatively stable environments [2]. Acquisition of new TCSs occurs through mechanisms of lateral gene transfer or gene duplication and subsequent accumulation of mutations that insulate the new pathways from the existing two-component pathways [3]. In few cases, the newly introduced genes will improve the efficiency to grow under the conditions of the existing niche and consequently will be fixed in the genome. In most of the cases, their presence will interfere with existing TCSs and they will be eliminated from the genome and thus, no longer present in extant species. Comparative analysis of the collection of TCSs present in two closely related bacterial species can be useful to explain why one bacterial species can colonize a wide range of tissues and cause many different types of infections, while the other is far more restricted in its distribution and pathogenicity [1,4].

Staphylococcus aureus is a highly versatile opportunistic pathogen able to adapt to very different types of environments. It can live freely outside the host or exist either as a commensal external colonizer or as a pathogen in both humans and animals [5]. The anterior nares are the main ecological niche for S. aureus [6]. However, multiple other sites in the human body such as the skin, axillae, vagina, and gastrointestinal tract can also be colonized by this bacterium. The core genome of S. aureus contains 16 TCSs (http://mistdb.com, http://www.ncbi.nlm.nih.gov/Complete_Genomes/SignalCensus.html, http://www.p2cs.org) [7,8,9]. Among the sixteen TCSs, only WalRK, is essential for bacterial growth [10]. All the other TCSs are dispensable, and they can be deleted individually [11] or simultaneously in the same strain without affecting cell viability [12]. Using S. aureus mutant strains deprived of its complete non-essential sensorial TCS network, Villanueva et al. [12] showed that complementation with unique TCSs was sufficient to restore the capacity to grow under different environmental conditions such as low pH (GraRS) and low temperature (SrbBA) and to reduce nitrate to nitrite (NreCB) or to resist to Triton X-100 (VraRS), experimentally validating the widely offered idea that TCSs are self-sufficient, autonomous entities able to confer the capacity to sense and respond to a particular environmental condition. This study also showed that sensor histidine kinases exhibit strong preference for their cognate response regulators (RR), though in some cases, cross-regulation between non-cognate sensor-RR pairs can occur in vivo.

The set of 16 TCSs of S. aureus are conserved in other closely related coagulase negative staphylococcal species such as Staphylococcus epidermidis and Staphylococcus haemolyticus (https://mistdb.co) [9]. However, Staphylococcus saprophyticus, a coagulase negative staphylococcus whose genome is just 0.3 Mb smaller than that of S. aureus,
contains only 11 TCSs (Table 1) [13]. This lack of correlation between the genome size and the number of TCSs is very likely due to various environmental factors. S. saprophyticus is a common inhabitant of the urinary tract, perineum, rectum, urethra, cervix, and gastrointestinal tract [14]. It is the second most common cause of community-acquired urinary tract infections (UTI) in young and middle-aged female outpatients, after Escherichia coli, without the involvement of indwelling catheters [15,16]. The narrow niche of tissues that S. saprophyticus colonizes compared to S. aureus is very likely related with the reduced number of TCSs in S. saprophyticus and consequently to the capacity of the bacterium to adapt to the environmental conditions encountered in the different tissues [17]. In this review, we summarize and discuss our current knowledge about the TCSs that are missing in the S. saprophyticus genome compared to S. aureus and the consequences that their lack has for the bacterium.

KdpDE
In general S. aureus can tolerate a high concentration of salt and low water activity for a non-halophilic bacterium [18]. It is assumed that this osmosensitivity supports bacterial growth on a high-salt environment such as the human skin. Potassium is the major monovalent cation in cells and plays an essential role for all living organisms. Within bacterial cells, potassium is required for the maintenance of a constant pH, membrane potential and osmotic pressure. S. aureus maintains high intracellular potassium concentrations of 0.5–1.5 M, even in the absence of a high osmolarity environment, thanks to two specific potassium uptake systems, the inducible Kdp and the constitutively expressed Ktr [19]. The activation of Kdp requires the presence of the functional KdpDE TCS which is induced by high osmolarity and inhibited by cyclic di-AMP [20]. Once activated, the most highly induced genes by the KdpDE TCS are the constituents of the KdpFABC transport machinery involved in uptake of K⁺, as well as genes involved in other compatible solute and sugar uptake; capsule biosynthesis; and amino acid and central metabolism (Figure 1). The KdpFABC system plays a physiological role under very low K⁺ conditions [21]. At high K⁺ concentrations, a lower-affinity and constitutively expressed Ktr ion transporter is responsible for K⁺ transport using energy generated by electrochemical ion gradients [22]. The analysis of mutants in Kdp and Ktr systems revealed that the Ktr system is the major K⁺ uptake system in S. aureus and the function of Kdp is required primarily during times of K⁺ starvation and/or fluctuating ionic conditions. However, acquisition of potassium ions in a potassium-limited environment seems to be important during S. aureus infection [23]. Accordingly, some methicillin resistant S. aureus strains carry a second KdpDE homologous TCS in the SCCmec mobile element [24]. Similarly, a KdpDE paralog has also been described in some types of the arginine catabolic mobile element (ACME) of S. epidermidis [25,26]. In some S. epidermidis strains containing the KdpDE system of the ACME element, the chromosomal KdpDE copy has been lost very likely to avoid cross-talk between both systems. S. saprophyticus has to cope with the highly variable ion content of urine without the contribution of the KdpDE system. In this bacterium, osmotolerance relies on Ktr and other osmoprotectant transport systems (proline/betaine, glycine betaine/choline transporter, proline permease) (Figure 2) [13]. Because urine contains large amounts of potassium, it seems that the Ktr system is sufficient to import enough K⁺ in the absence of the high affinity uptake system. Another interesting peculiarity regarding the cellular osmotic tolerance of S. saprophyticus and not S. aureus is the presence of plasmids carrying the aquaporin gene (aqpZ). Aquaporins are water channels that mediate rapid entry or exit of water in response to changes in osmolality, and consequently, it has been proposed that they may also aid to osmotic balancing [13]. However, this hypothesis remains to be tested.

SaeSR
The staphylococcal accessory element (see) TCS has been previously characterized as a positive regulator of many secreted toxins, exoenzymes, and immunomodulatory proteins involved in staphylococcal pathogenesis (Figure 1). Loss of SaeSR abolishes the secretion of many of these proteins including exotoxins, immune evasion factors, superantigens, adhesins, staphylococcal protein A, and proteases [27]. All these factors have a direct causative link with S. aureus pathogenicity and play a role once bacteria have crossed the epithelial barrier by inhibiting complement activation, neutrophil recruitment, as well as blocking opsonization by immunoglobulins [28,29]. It is therefore not surprising that mutants lacking saeSR result in lower mortality in systemic and intraperitoneal mouse infection models and show reduced ability to adhere to lung epithelial cells [30,31]. S. saprophyticus infections affect almost exclusively the urinary tract, without crossing the epithelial barrier and consequently, most of the typical virulence factors regulated by SaeSR in S. aureus are not needed in S. saprophyticus’ lifestyle. Instead, S. saprophyticus needs to maintain tight adherence to the bladder and ureter epithelium. For that, it produces different types of adhesins such as the highly conserved Aa hemagglutinin, the surface-associated lipase, Ssp, that forms fimbria-like surface appendages, and cell wall-anchored proteins (UafA, UafB, SssF and SdrI) [13,25] (Figure 2). UafA is a chromosome-encoded adhesin that mediates hemagglutination and adherence to human bladder cells. This adhesin is exclusive of S. saprophyticus strains and it is absent in other staphylococci. UafB is a plasmid encoded serine-rich glycoprotein that binds fibronectin, fibrinogen, and human bladder-epithelial cells. SssF is another plasmid-encoded cell-wall-associated serine-aspartate-rich protein that binds collagen and plays a role in acute UTI and...
Table 1

Two-component systems in *S. aureus* and *S. saprophyticus*

| Two-component system | *S. aureus* GenBank accession | *S. saprophyticus* GenBank accession | Function |
|----------------------|-------------------------------|-------------------------------------|----------|
| warRK                | MW0018 SSP0021                | SSP0022                             | Cell wall maintenance, cell viability |
| hptSR                | MW0019 SSP0022                | SSP0017                             | Intracellular survival, uptake of hexose phosphate |
| lytSR                | MW0236 SSP0483                | SSP0484                             | Autolysis, edNA release, biofilm |
| graRS                | MW0621 SSP2061                | SSP2062                             | AMPs resistance, growth at low pH |
| saeSR                | MW0667                        |                                    | Virulence factors regulation (toxins, exoenzymes . . .) |
| tcs7SR               | MW1208 SSP1446                | SSP1547                             | Uncharacterized function |
| arsR                 | MW1304 SSP1323                | SSP1324                             | Pathogenesis mechanisms: autolysis, adhesion, biofilm . . . |
| srrBA                | MW1445 SSP1260                | SSP1261                             | Anaerobic respiration metabolism, growth at low temperature |
| phoRP                | MW1630 SSP1073                | SSP1074                             | Phosphate uptake and homeostasis |
| airsR                | MW1789 SSP0946                | SSP0947                             | Oxidative stress response |
| vraRS                | MW1824 SSP0908                | SSP0909                             | Cell wall-affecting antibiotic resistance, cell wall biosynthesis |
| agrCA                | MW1962 SSP0839                | SSP0840                             | Quorum sensing control of adhesion and virulence factors |
| kdpDE                | MW2002                        | SSP0840                             | Potassium homeostasis regulation |
| hssRS                | MW2282 SSP0540                | SSP0541                             | Heme metabolism regulation |
| nreCB                | MW2313                        | SSP0541                             | Response to low oxygen, nitrate reduction |
| braSR                | MW2544                        | SSP0541                             | Antimicrobial peptide resistance |

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autophosphorylation in the absence of nitrate (via binding to NreB) [36]. Inactivation of NreCB abrogates the ability of *S. aureus* to reduce nitrate, forcing the bacterium to upregulate fermentative pathways for survival [5]. The *nreCB* genes are transcribed together with the nitrate reductase genes (*narGHJI* operon) which is located downstream the genes encoding the nitrite reductase. Also located within the vicinity of *nreCB* is the nitrate transporter encoding gene (*narT*). This genome organization strongly suggests that *nreCB* belongs to a gene cluster that has been acquired by horizontal gene transfer. *S. saprophyticus* cannot use nitrate and nitrite as final oxygen acceptors because of the lack of respiratory nitrate reductase NarGHJI and assimilatory nitrite reductase NirRBD as well as the corresponding NreCB TCS on the genome. An exception to this is *S. saprophyticus* subsp. *bovis*, a regular colonizer of bovine nostrils that contains the NreCB TCS and also the nitrate but not the nitrite reductase genes on what appears to be a transposable element [37]. Another consequence of the nitrate and nitrite reductase activities is the generation of ammonia that allows nitrogen to be converted to an organic form. *S. saprophyticus* produces a potent urease that can obtain ammonia from urea (Figure 2). The urease activity of *S. saprophyticus* is significantly higher than other staphylococcal species and it is required for persistent infection in the urinary tract [38]. Besides, the urease activity is responsible for raising the pH of human urine, which allows precipitation of normally soluble polyvalent ions to carbonate apatite. These compounds aggregate around bacteria and very often are the cause of the formation of urinary stones.

### NreCB

Under conditions of low oxygen tension, *S. aureus* uses nitrate and nitrite as its final oxygen acceptors. NreCB is an oxygen sensing system that activates the expression of the cluster of genes needed for nitrate reduction (*narGHJI*) and nitrite reduction (*nirRBD*) [35,36] (Figure 1). Activation of NreCB is controlled by the nitrate-sensing NreA protein, which inhibits NreB persistent kidney infections [33]. Another specific feature of uropathogenicity found in *S. saprophyticus* is the presence of a D-serine deaminase responsible for degrading high concentrations of D-serine present in the urine [34]. Regulation of the expression of all these colonization factors in *S. saprophyticus* is not integrated under a single TCS. Instead, *S. saprophyticus* has more specific regulatory genes that may act individually for the modulation of such adhesion factors and metabolic enzymes for a prompt and individual response in metabolite-rich urine.

### BraSR

BraSR (bacitracin resistance associated) is associated with resistance to the antimicrobial peptides, nisin and bacitracin [39–42]. BraSR forms a module with the ABC transporter BraDE. The ABC transporter is involved in sensing the signal and participates by mechanisms that still are not completely understood in the phosphotransfer between BraS to BraR [43]. In this system, the ABC transporter and the TCS have an absolute mutual requirement for each other in both sensing and responding [44**]. BraSR also activates the expression of VraDE, which encodes for the cognate ABC transporter associated with GraRS (Figure 1).
of GraRS induces the expression mprF and the dltABCD operon. The dltABCD operon contributes to the net positive surface charge by covalently incorporating d-alanine to the cell wall linked teichoic acids whereas MprF adds positively charged lysine residues to phosphatidyl glycerol within the cell membrane [45]. It is hypothesized that GraRS in S. saprophyticus would also induce the expression of mprF and the dltABCD operon to confer resistance to AMPs (Figure 2). However, this hypothesis has not been experimentally tested.
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Figure 2

Summary of the activity of the TCSs absent in S. saprophyticus. HptSR, SaeSR, KdpDE, NreCB, and BraSR are the five TCSs present in S. aureus but missing in S. saprophyticus. S. aureus colonises different niches to S. saprophyticus and consequently has to adapt to different environmental conditions. The five TCSs specific to S. aureus allow it to sense relevant environmental signals and allow it to respond by activating the expression of different target genes. Thus, S. aureus uses its larger arsenal of TCSs to adapt its physiology to the new environments. The genome of S. saprophyticus encodes genes that may compensate for the loss of genes and pathways regulated by the TCSs absent in this staphylococcal species. HptSR and its function in the uptake of extracellular hexose-6-phosphates is the only TCS-regulated adaptation mechanism for which S. saprophyticus does not encode any alternative.

**HptSR**

HptSR is required to sense extracellular hexose phosphates and to activate the transcription of *uhpT*, a gene located directly downstream *hptSR* that encodes the unique glucose 6-phosphate transporter of *S. aureus* [46] (Figure 1). UhpT is medically relevant because it can mediate the uptake of the antibiotic Fosomycin [47]. *S. aureus* is currently regarded as a facultative intracellular pathogen [48]. Host cell invasion and intracellular survival is mediated by *S. aureus* to infect macrophages, spread to secondary points of infection, evade immune recognition, and avoid exposure to last-resort antibiotics [49,50]. To survive and multiply within host cells, *S. aureus*, as many other intracellular pathogens [51], needs to adapt to the available nutrients and other physiological conditions (pH, temperature, oxygen). Since hexose phosphates are abundant carbon sources within the host cell cytosol, the HptSR system is important for intracellular survival and multiplication of *S. aureus* within host cells (Figure 2). Indeed, *S. aureus* strains deficient in *hptSR* show impaired survival/multiplication within mammalian cell lines [46]. *S. saprophyticus* is an extracellular pathogen that shows strong adhesion to various epithelial cell lines. Internalization of *S. saprophyticus* has been described in human bladder carcinoma cell lines [46], but the relevance of UTI infection has not been documented. Even if *S. saprophyticus* might get internalized by some epithelial cells during its life cycle, the absence of a system to take up hexose phosphates would impair the replication and multiplication of the bacterium in the cell’s cytoplasm. Alternatively, it cannot be excluded that the absence of HptSR might be replaced by a different pathway for the uptake of glucose 6-phosphate or that other nutrients are important for intracellular survival of *S. saprophyticus*. The HptSR system involves four genes that are located together in...
the *S. aureus* genome. Thus, complementation of *S. saprophyticus* with the whole system would be the direct approach to determine whether HptSR is sufficient to confer *S. saprophyticus* the capacity to replicate in the cytosol of the host cell.

### Conclusion and future directions

*S. aureus* and *S. saprophyticus* have been classified as high and medium-pathogenic staphylococci, respectively. Medium-pathogenic staphylococci are more specialized in their infective strategies and cause a narrow spectrum of diseases [52]. The reduced number of TCSs is not by itself the reason for a lower pathogenic capacity because many other medium-pathogenic staphylococci (*S. epidermidis, S. lugdunensis, S. haemolyticus* and *S. pseudointermedius*) have at least the same number of TCSs as *S. aureus*. Instead, the number of TCSs correlates with the presence/absence of those genes encoding for metabolic pathways necessary to adapt bacterial growth to the hostile environment of the host and to harmonize their expression. A question that remains open is whether the common staphylococcal ancestor contained the sixteen TCSs and *S. saprophyticus* suffered genome reduction events during evolution or alternatively, the staphylococcal ancestor contained a lower number of TCSs and *S. saprophyticus*, contrary to other staphylococcal species, did not gain additional TCSs. The mechanisms of TCS acquisition/loss during bacterial evolution have been theoretically predicted but they have not been experimentally addressed. Hence, an effort that considers long-term experiments, in which bacteria gain a selective advantage through the acquisition/loss of a TCS would provide insights into how adaptation to different niches was established over evolutionary time.

### Conflict of interest statement

Nothing declared.

### CRedit authorship contribution statement

**Beatriz Rapun-Araiz**: Data curation, Investigation, Methodology, Writing - review & editing. **Andreas F Haag**: Data curation, Investigation, Methodology, Writing - review & editing. **Cristina Solano**: Funding acquisition, Writing - review & editing. **Iñigo Lasa**: Conceptualization, Data curation, Investigation, Methodology, Funding acquisition, Writing - original draft, Writing - review & editing.

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