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The Mutacins of *Streptococcus mutans*: Regulation and Ecology

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SUMMARY

Streptococcus mutans is generally recognized as a causative agent of human dental caries. The production of mutacins (bacteriocins) by *S. mutans* is considered to be an important factor in the colonization and establishment of *S. mutans* in the dental biofilm. Two types of mutacins have been characterized: the lantibiotics and the non-lantibiotics. The lantibiotics generally have a wider spectrum of activity than the non-lantibiotics, which make them attractive targets for development into new antimicrobial modalities. The non-lantibiotics are much more prevalent among strains of *S. mutans* and play a significant role in both community and population level interactions in the dental biofilm. These interactions are directly mediated through the ComCDE two-component system and the newly characterized LytTR Regulation Systems HdrRM and BrsRM. These systems coordinate natural competence development and mutacin production as a means to acquire transforming DNA either by killing closely related streptococcal species in the vicinity of *S. mutans*, or through an altruistic suicide mechanism among a subpopulation of competent cells within the *S. mutans* community. As more *S. mutans* strains are sequenced, it is anticipated that additional mutacins with novel functions will be discovered, which may yield further insights into the ecological role of mutacins within the oral biofilm.

Keywords

mutacin; *Streptococcus mutans*; bacteriocin

INTRODUCTION

Streptococcus mutans is a gram-positive, facultative anaerobic bacterium that inhabits the human oral cavity and is commonly recognized as a primary pathogen in dental caries. One of its principal virulence factors is the production of bacteriocins (peptide antibiotics) referred to as mutacins (Hamada & Ooshima, 1975a). In fact, *S. mutans* is one of the most prolific producers of bacteriocins within the entire *Streptococcus* genus. For example, the sequenced reference strain UA159 was originally considered to be a *mutacin-negative* wild type. However, since the time of its sequencing, this strain has been shown to actively produce three separate bacteriocins and it likely encodes *at least* several more! Hence, it is fair to say that it is probably difficult, if not impossible, to identify a true mutacin-negative wild type strain of *S. mutans*. This suggests that mutacin production likely plays a fundamental role in the survival of the species. Mutacins may help *S. mutans* to compete with other streptococci in early dental biofilms and allow it to establish or sustain colonization of the tooth surface (Kuramitsu *et al.*, 2007). On the other hand, because the oral cavity is one of the primary portals of entry for human pathogens, it is conceivable that the production of mutacins could even play an important role in protecting the host from

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many harmful infections, similar to observations made with other oral streptococci [for reviews, see (Burton *et al.*, 2011, Tagg, 2004, Tagg & Dierksen, 2003)]. In the following review, we examine the current state of mutacin research and give particular attention to mutacin gene regulation and the potential roles of mutacins in *S. mutans* ecology, as these details have yet to be compiled in a review format.

History of mutacins

The term “mutacin” was first coined by Hamada and Ooshima (Hamada & Ooshima, 1975b) and it refers specifically to the bacteriocins produced by *S. mutans*. Multiple examples of mutacins from both of the major classes of bacteriocins (the lantibiotics and non-lantibiotics) have been characterized to date (Table 1). The lantibiotic mutacins tend to have a wide spectrum of activity against gram-positive bacteria, including non-producing strains of *S. mutans*, whereas the non-lantibiotic mutacins have thus far proven to be primarily active against closely related species. The mutacin repertoire of individual strains of *S. mutans* also tends to be highly strain-specific. For this reason, mutacin types had been previously used as an epidemiological tool to track the transmission of *S. mutans* before the dawn of the molecular age (Baca *et al.*, 1990, Davey & Rogers, 1984, Rogers, 1980).

Lantibiotic mutacins

The currently characterized lantibiotic mutacins include mutacin I (Qi *et al.*, 2000), mutacin II (Novak *et al.*, 1994), mutacin III/mutacin 1140 (these two mutacins have identical sequences. See Hillman *et al.*, 1998, Qi *et al.*, 1999b), mutacin B-NY266 (Mota-Meira *et al.*, 1997), mutacin K8 (Robson *et al.*, 2007), and mutacin Smb (Yonezawa & Kuramitsu, 2005). The term “lantibiotic” refers to the characteristic dehydrated amino acids and intramolecular thioether bonds that create lanthionine and methyllanthionine residues within the bacteriocin molecule (Jung, 1991). These unusual structures result from extensive post-translational modifications of the prepeptide and are crucial for the inhibitory activity of the bacteriocin. They also confer tremendous stability to the peptide making them highly resistant to inactivation under a wide range of environmental extremes. Lantibiotics (also referred to as Class I bacteriocins) may consist of a single peptide, such as mutacins I, II, III, 1140, B-NY266, and K8, or two peptides such as mutacin Smb. Based upon their tertiary structures, lantibiotics are classified either as Type A (linear) or Type B (globular) (Jung, 1991). All characterized lantibiotic mutacins belong to the Type A class, which kills susceptible cells primarily through membrane pore formation. Recent studies have demonstrated that some Type A lantibiotics, such as nisin as well as mutacin 1140, use lipid II as docking molecules for pore formation (Hasper *et al.*, 2006). Consequently, this also results in the simultaneous inhibition of cell wall synthesis, likely compounding the bacteriocidal activity. This mode of action may explain why lantibiotics have such a wide spectrum of activity against gram-positive bacteria. Genes for the lantibiotic precursor, the modification of the prepeptide, transport/processing of the propeptide, and immunity against self-toxicity are encoded within the same gene cluster (Fig. 1) and transcribed in a coordinated fashion. The production of lantibiotics requires multiple dedicated enzymes and occurs through conserved mechanisms that have been reviewed previously. Interested readers are directed to these excellent reviews for additional information (Bierbaum & Sahl, 2009, Guder *et al.*, 2000, Kupke & Gotz, 1996, Sahl *et al.*, 1995, Willey & van der Donk, 2007).

Non-lantibiotic mutacins

In contrast to the lantibiotic mutacins, which are produced by only a small minority of isolates (Bekal-Si Ali *et al.*, 2002, Kamiya *et al.*, 2005), the non-lantibiotic mutacin genes are present in every *S. mutans* strain analyzed thus far. Typically, individual strains encode multiple non-lantibiotic mutacin genes. Unlike the lantibiotics, the non-lantibiotic mutacins are not post-translationally modified and their antimicrobial spectra are much narrower than

that of the lantibiotic mutacins. For example, mutacin IV is active against numerous non-mutans streptococcal species, but is inactive against the mutans streptococci, staphylococci, or enterococci (Qi *et al.*, 2001). Currently, four non-lantibiotic mutacins have been characterized (mutacins IV, V, VI, and mutacin N) (Balakrishnan *et al.*, 2000, Hale *et al.*, 2005b, Qi et al., 2001, Xie *et al.*, 2010), but *S. mutans* likely encodes many additional uncharacterized non-lantibiotic mutacin-like peptides. One of the characteristic features that are often used to identify potential mutacins from genome data is the presence of a conserved peptide leader region that terminates in a double-glycine (GG) motif. The leader peptide targets the prepeptide to a membrane bound ABC transporter apparatus, which is responsible for both secreting the peptide and cleaving the leader sequence at the GG processing site (Nes *et al.*, 1996). Similar machinery is also used for the secretion of a variety of peptide pheromones, such as the *S. mutans* competence-inducing peptide ComC (Petersen & Scheie, 2000). Unlike the lantibiotic mutacins, genes for the production of the non-lantibiotic mutacins (the prepeptide, ABC transporter, and immunity) may not be localized within the same gene cluster. Also, one ABC transporter may be responsible for the production of multiple non-lantibiotic mutacins (Hale *et al.*, 2005a) (Fig. 3). Intoxication by non-lantibiotic bacteriocins is generally considered to result due to the dissipation of the proton motif force via pore formation (Hechard & Sahl, 2002). For Class IIa bacteriocins, the mannose specific PTS has been shown to function as a receptor required for bacteriocin susceptibility (Nes *et al.*, 2007). The relative susceptibility can even be further subdivided based upon the particular phylogeny of mannose PTS (Kjos *et al.*, 2009). Assuming other non-lantibiotics also utilize particular protein receptors, this may account for their relatively narrow spectrum of activity.

REGULATORY SYSTEMS CONTROLLING MUTACIN GENE EXPRESSION

Mutacins are regulated by multiple genetic and environmental factors that frequently overlap. For this reason, we discuss the regulation of mutacin gene expression based upon the different categories of regulation. A summary of the mutacin regulatory interaction network is provided in Fig. 3.

Regulation by Rgg-like regulators (MutR)

Of the mutacin gene clusters characterized to date, the mutacin I, II, and III loci have each been shown to encode homologous Rgg-family transcription regulators referred to as *mutR* (Fig. 1) (Chen *et al.*, 1999, Qi et al., 1999b, Qi et al., 2001). Though the entire mutacin 1140 locus has yet to be sequenced, a partial open reading frame annotated as ORF X was identified in the beginning of the published sequence (Hillman et al., 1998). A BLASTN search of this sequence yields a match with 100% identity to the latter portion of the *mutR* open reading frame of mutacin III (unpublished results), which indicates that mutacin 1140 is highly likely to encode *mutR* as well. In addition, for each of these mutacin loci, the location of *mutR* is conserved as the first gene in the cluster (Fig. 1). From studies of mutacins I and II, it is known that MutR is an essential activator of mutacin operon gene expression. In a *mutR* background, mutacin activity is undetectable by the deferred antagonism assay, while transcription of the downstream mutacin operon is severely reduced (Kreth *et al.*, 2004, Qi *et al.*, 1999a). Studies of the mutacin II operon promoter region have identified three inverted repeat sequences (IR I-III) and three direct repeats (DR I-III) that may play a role in regulating the expression of the operon via MutR (Qi *et al.*, 1999a). Of particular note, IR II and III are located upstream of the −35 site (Fig. 2) and bear some similarities to regulatory elements found in the promoter region of the staphylococcal lantibiotic epidermin (Qi *et al.*, 1999a). In *S. epidermidis*, these repeats are bound by the epidermin operon activator protein EpiQ (Peschel *et al.*, 1993). In the mutacin I and III operons, direct repeat sequences can also be found in similar locations as mutacin II (Fig. 2). Interestingly, for mutacins I and III, the putative -35 sequences overlap with the direct repeat

sequences, which is inconsistent with the role of MutR as a transcription activator. Thus, additional biochemical studies will be required to fully address the role of MutR for these mutacins. Furthermore, studies of *mutR* transcription in mutacin II (Qi *et al.*, 1999a) and mutacin I (Merritt and Qi unpublished) have determined that *mutR* expression is relatively invariant, whereas the mutacin operon is subject to extreme changes in gene expression (Kreth *et al.*, 2005b, Merritt *et al.*, 2005). This suggests that mutacin operon gene expression is highly unlikely to be controlled at the level of *mutR* transcription and additional uncharacterized regulatory elements are likely to play a major role in mutacin operon regulation.

Regulation by two-component signal transduction systems

Two component signal transduction systems are commonly utilized by bacteria to regulate both non-lantibiotic and lantibiotic bacteriocin gene expression (Eijsink *et al.*, 2002, Kleerebezem, 2004). In *S. mutans*, the ComCDE two-component signal transduction system plays a direct role in the regulation of a variety of mostly non-lantibiotic bacteriocins, while the ScnRK-like sensory system (SMU.1814 – SMU.1815, also referred to as MukRK) probably serves an analogous function for the lantibiotic mutacin K8 (Fig. 1).

The *S. mutans* ComCDE two-component regulatory system responds to cell density and certain environmental stresses by excreting a peptide signal molecule called CSP (encoded by the *comC* gene) (Li *et al.*, 2001, Perry *et al.*, 2009). When the optimal CSP concentration has accumulated in the environment, it will induce the autophosphorylation of the ComD sensor kinase and the subsequent phosphotransfer to the ComE response regulator (Cheng *et al.*, 1997, Havarstein *et al.*, 1996, Pestova *et al.*, 1996). Phosphorylated ComE will then activate gene expression from its target bacteriocin promoters, which results in greatly increased bacteriocin production (Kreth *et al.*, 2005a, Kreth *et al.*, 2006, Perry et al., 2009, van der Ploeg, 2005, Yonezawa & Kuramitsu, 2005). Both *in silico* analyses and *in vitro* DNA binding studies have identified conserved direct repeat regulatory elements in the promoters of the bacteriocin genes controlled by the ComCDE system (Fig. 2). These repeats match to the proposed consensus pattern recognized by members of the LytTR family of transcription regulators and serve as the binding site for ComE (Hung *et al.*, 2011, Kreth *et al.*, 2007, Nikolskaya & Galperin, 2002, van der Ploeg, 2005). Accordingly, ComE is also a member of the LytTR family. For each of the bacteriocins regulated by ComE, the LytTR consensus direct repeats were shown to occur just upstream of weak −35 sequences, which indicates a role for ComE in the transcription activation of these genes (Kreth et al., 2007, van der Ploeg, 2005, Xie et al., 2010). Likewise, most members of the LytTR family are also known to function as transcription activators (Galperin, 2008).

The entire lantibiotic mutacin K8 locus is highly homologous to that of the lantibiotic SA-FF22 of *Streptococcus pyogenes*. In the SA-FF22 locus, the ScnR response regulator is essential for the production of SA-FF22 (Hynes & Ferretti, 1995) and the mutacin K8 locus encodes a similar ScnRK-like two-component system referred to as MukRK (Fig. 1) (Robson et al., 2007). However, it has not been tested experimentally whether this two-component system is also essential for mutacin K8 production. Interestingly, the genes encoding the MukRK sensory system and the MukFEG immunity proteins are clustered in many *S. mutans* strains that do not encode the structural genes for mutacin K8, such as the sequenced reference strain UA159. Given that *S. pyogenes* strains containing the SA-FF22 locus exhibit immunity to mutacin K8 (Robson et al., 2007), it would be interesting to determine whether mutacin K8 non-producer strains such as UA159 have retained the *mukRK* and *mukFEG* genes in order to detect and prevent the toxicity associated with mutacin K8 production from other strains. This may also give further insight into the regulation of the mutacin K8 locus.

Regulation by LytTR Regulatory Systems

Recently, a newly described class of gene regulatory system in *S. mutans* was shown to play a direct role in the regulation of the same bacteriocin genes controlled by the ComCDE system (Table 1) (Okinaga *et al.*, 2010a, Xie et al., 2010). Interestingly, these systems (referred to as LytTR Regulatory Systems) do not require ComCDE to exert their effect (Okinaga et al., 2010a, Okinaga *et al.*, 2010b). Therefore, they appear to form fully independent, parallel regulatory pathways for mutacin gene expression (Fig. 3). So far, the HdrRM and BrsRM LytTR Regulatory Systems of *S. mutans* are the only characterized examples of LytTR Regulatory Systems, but numerous uncharacterized homologous systems can be found widely distributed throughout the phylum Firmicutes (unpublished). A LytTR Regulatory System consists of a membrane bound inhibitor protein (M) that antagonizes the activity of an associated LytTR family transcription regulator (R). The genes encoding both proteins are cotranscribed (Merritt *et al.*, 2007). Currently, it is unknown which cellular or environmental signals activate LytTR Regulatory Systems, but they can be constitutively activated by simply mutating the membrane bound inhibitor protein. Consequently, a mutation of *hdrM* or *brsM* results in a constitutively active HdrR or BrsR, respectively. Activated HdrR and BrsR transcription regulator proteins will then cause greatly increased mutacin gene expression and mutacin production (Okinaga et al., 2010a, Xie et al., 2010). Given that both HdrR and BrsR are members of the LytTR family, it is also not surprising that they too interact with the same direct repeat sequences bound by ComE (Fig. 2). Mutagenesis of these repeats negates the increased bacteriocin expression phenotypes of an *hdrM* or *brsM* mutation, while BrsR DNA binding studies have confirmed that the LytTR consensus repeats are essential for a stable protein-DNA interaction (Okinaga et al., 2010a, Xie et al., 2010). Multiple lines of evidence indicate that both HdrR and BrsR function as transcription activators utilized to compensate for the weak −35 sequences found within the mutacin promoters.

ENVIRONMENTAL INFLUENCE UPON MUTACIN PRODUCTION

Mutacin production is highly influenced by environmental conditions. It has yet to be demonstrated how these environmental factors are able to influence mutacin gene expression, but it is assumed that they must control the activity of the aforementioned mutacin regulatory systems. Interestingly, mutacins share a large degree of overlap in the environmental cues that positively or negatively influence their gene expression, even though they are directly controlled by a wide variety of separate regulatory systems. Overall, the two most influential environmental factors are cell density and nutrition. In the following sections, we describe the current knowledge regarding the role of these two environmental factors on mutacin production. These factors are also incorporated into the mutacin regulatory network illustrated in Fig. 3.

The role of cell density

A variety of environmental factors have been shown to influence the production of mutacins, primarily through altered transcription of mutacin structural genes or operons. By far, the most potent inducer of mutacin transcription seems to be related to cell density, particularly conditions of extreme high cell density. Studies of the non-lantibiotic mutacin IV and the lantibiotic mutacin I have demonstrated that the relatively weak transcription of both of these mutacins in liquid culture can be pushed considerably higher if the cells are centrifuged and incubated as a cell pellet (Kreth et al., 2005b, Kreth et al., 2005a, Merritt et al., 2005). A similar result can also be obtained by spotting planktonic cells onto agar plates and incubating for 1 – 3 hrs (unpublished), while mutacin transcription can be increased even further still if the cells are allowed to develop into colonies on a plate (Kreth *et al.*, 2005b). Thus, there is a direct correlation between the level of mutacin transcription and

increasing cell density. Though, mutacin transcription at any growth stage in batch culture is generally low relative to the level of mutacin gene expression on a plate. Ecologically, this type of extreme high cell density regulation is well suited for mutacins, since bacteriocins are both energetically expensive to produce and are only effective when there is a high density of producer cells. For example, most bacteriocins function in the nanomolar range (Sang & Blecha, 2008). In batch culture or during growth in saliva, excreted mutacins would be quickly diluted, resulting in the loss of their inhibitory activity. In contrast, plate colonies or oral biofilm communities routinely yield cell densities up to 1000-fold higher than batch cultures (Evaldson *et al.*, 1982). Under these conditions, considerably smaller quantities of metabolic resources are required to maintain an inhibitory local concentration of mutacin. In addition, the physiochemical properties of an agar plate or a biofilm likely reduce the diffusion rate of bacteriocins away from the producer cells (Chan *et al.*, 2004). This should further concentrate the mutacins as they are excreted and improve the range at which they are effective. Consequently, it appears that the regulatory machinery controlling mutacin transcription has evolved a mechanism to promote mutacin production in the environment that provides the greatest benefit to the producer. How mutacin transcription is coordinated with conditions of extreme high cell density remains a significant open question.

Nutrient availability and mutacin production

Despite the strong influence of cell density upon mutacin transcription, other factors such as nutrient composition can play a major role in determining whether particular mutacins are produced. For mutacin I, the addition of ~5 mM phosphate to the growth medium significantly delayed the temporal pattern of mutacin production, whereas production was permanently inhibited at concentrations >10 mM (Nguyen *et al.*, 2009). This effect was demonstrated to occur as a result of significantly decreased mutacin operon transcription. However, it has yet to be determined whether phosphate has any influence upon the production or activity of the mutacin I transcription activator MutR. In general, easily fermentable carbohydrate sources and yeast extract stimulate the production of numerous mutacins (Delisle, 1975, Nicolas *et al.*, 2004, Nicolas *et al.*, 2006, Qi et al., 1999a). In some cases, this effect is maximized only when these nutrients are supplied in limiting quantities (Qi & Kreth, 2010). Studies of mutacin I have demonstrated that diluted growth medium results in much greater mutacin operon transcription and mutacin production than a more concentrated growth medium supplemented with additional carbohydrate (Kreth *et al.*, 2005b). These studies have led to the suggestion that mutacin production is optimal when the cells are subjected to mild stress.

ECOLOGICAL ROLE OF MUTACIN

Mutacins play an interesting role in the ecology of dental plaque. The frequent co-occurrence of mutacin loci and transposase genes (Fig. 1) implicates horizontal gene transfer as the primary driving force dictating the highly strain-specific repertoire of mutacin genes in *S. mutans* isolates. It also attests to the selective advantage mutacins provide to the producer. As studies probe deeper into mutacin regulation and function, mounting evidence suggests that they serve multiple functions both on the population and the community levels. The simplest and probably most obvious of these is their role in community level interactions. Many early colonizing species vie with *S. mutans* for a limited supply of available ecological niches. This naturally creates a scenario that is ripe for competitive behaviors among the organisms. Compared with *S. mutans*, many competitor species such as *S. sanguinis* colonize available tooth surfaces earlier, grow faster, and are more resistance to oxygen and oxidative stress (Kreth *et al.*, 2009). Without some counterbalancing competitive advantage, *S. mutans* would have little chance of survival. Despite the greater aciduricity and acidogenicity of *S. mutans*, *in vitro* competition studies with *S. sanguinis* clearly demonstrate that bacteriocin activity from mutacins I and IV is required for *S.*

mutans to maintain its dominance within dual species biofilms (Kreth *et al.*, 2005b). Similarly, *in vivo* studies of humans infected with a non-acidogenic/non-cariogenic mutacin 1140 producer strain indicate that its increased mutacin production is sufficient to support reliable colonization and persistence within new hosts (Hillman, 2002). Presumably, the broad-spectrum inhibitory activity of mutacin 1140 and related lantibiotics plays a significant role in increasing the colonization potential of the producers. Though, surprisingly, studies indicate that only a minority of *S. mutans* strains actually harbor these lantibiotic clusters (Kamiya et al., 2005, Bekal-Si Ali et al., 2002), whereas most strains encode multiple non-lantibiotic mutacins that exhibit very narrow activity spectra (Kamiya *et al.*, 2008).

Thus, the ecological function of these narrow-spectrum mutacins is perhaps more complex. For example, a large number of these mutacins are coordinately regulated with the development of genetic competence (Kreth et al., 2006, van der Ploeg, 2005), while no such coordination exists for the wide-spectrum mutacins I, II, III, and 1140. A comparison of the oral bacterial species susceptible to the competence-coordinated mutacins IV, V, VI, and Smb reveals a strong bias for organisms closely related to *S. mutans*, such as the “mitis” streptococci (Qi et al., 2001, Hale et al., 2005b, Xie et al., 2010, Paul & Slade, 1975). In a highly diverse biofilm, why might such a bias exist? Indeed, some of these organisms, such as *S. sanguinis*, are numerically more abundant and colonize the tooth surface before *S. mutans*, but the same could be said for various *Actinomyces* species. Yet, actinomycetes are infrequent targets of mutacin activity. This discrepancy may be partially explained by the fact that actinomycete genomes exhibit weak homology with *S. mutans. In vitro* co-culture studies of *S. mutans* and *S. gordonii* have demonstrated that the induction of the competence system can result in the interspecies transfer of transforming DNA from *S. gordonii* to *S. mutans* (Kreth *et al.*, 2005a). Furthermore, this phenomenon was stimulated by the ability to produce the competence-coordinated bacteriocin mutacin IV. In contrast, the competence-independent lantibtiotic mutacin I played little or no role in this process. This has led to the hypothesis that competence-coordinated bacteriocins serve a dual purpose. The first function is to attack competitor species to either invade occupied niches or to protect niches already occupied by *S. mutans*. The second function is to provide transforming DNA from closely related organisms that could be used for genome repair and/or the acquisition of novel fitness-enhancing traits. Liberated DNA from distantly related species would be highly unlikely to recombine with the *S. mutans* chromosome. Consequently, there is probably little selective advantage to acquire such DNA. By selecting which organisms are targeted for attack, *S. mutans* can maximize the potential utility of the released DNA. Further support for this notion may be found among the competence-coordinated bacteriocin gene sequences. As previously discussed, the promoters of these bacteriocins all share highly conserved regulatory elements (Fig. 2) that are essential for induction by the ComCDE system or LytTR Regulatory Systems. In addition to mutacin regulation, the ComCDE and LytTR Regulatory Systems also have the ability to simultaneously induce competence development through the competence-specific sigma factor ComX (Okinaga et al., 2010a, Aspiras *et al.*, 2004). In this way, these systems serve as the principal intermediaries to coordinate mutacin expression and competence development (Fig. 3). Despite the extensive homology found within the promoter regions of the competence-coordinated mutacins (Fig. 2), their structural genes exhibit considerable diversity, even encoding bacteriocins of multiple classes. This suggests that the selective pressure to maintain a regulatory connection with the competence system is quite strict, whereas the mutacin open reading frames seem to have much greater flexibility to evolve. One can speculate that this flexibility within the coding portion of the genes serves to prevent target organisms from developing resistance to these bacteriocins (Kjos *et al.*, 2011).

In addition to community level interactions, recent studies are beginning to offer insight into a previously unexplored aspect of mutacin production: the role of competence-coordinated mutacins in population level interactions. Studies of the ComCDE two-component system and LytTR Regulatory Systems have demonstrated that the competence-coordinated bacteriocins mutacin IV and V each have the potential to kill the producer strains in a process that resembles a suicide-like pathway (Perry et al., 2009, Xie et al., 2010). In the case of mutacin V, this process appears to occur intracellularly (Perry et al., 2009), which implicates a unique killing mechanism. Presumably, such activity serves an altruistic function that benefits the *S. mutans* population during conditions of severe stress. This ability would not be surprising given that analogous altruistic behaviors are a common feature of microbial communities (Thomas & Hancock, 2009, Rice & Bayles, 2003). However, the use of bacteriocins for this purpose appears to be a novel strategy that could potentially form the basis for a new chapter in mutacin research.

FUTURE PERSPECTIVES

With the advent of more affordable next-generation sequencing technologies, it seems inevitable that the pan-genome of *S. mutans* will be assembled. At this stage, the true breadth of the mutacin repertoire will be revealed. This should offer many interesting opportunities for future mutacin research. Current studies have largely focused on two mutacin categories: the wide-spectrum lantibiotics and the competence-coordinated mutacins. However, even with the limited genome sequence information that is currently available, one can identify additional uncharacterized mutacin-like genes that do no fit into either of these categories. Perhaps these genes share some features that could place them into a third category of mutacin. For the mutacins already characterized, many significant questions remain regarding their role in oral biofilm ecology. If the competence-independent lantibiotic mutacins, such as mutacins I, II, and III are such efficient weapons, why are they only encoded by a small subset of *S. mutans* isolates? What is the selective advantage for strains such as UA159 to encode the immunity genes for particular mutacins, but not the structural genes? There is even some indication that mutacins may have additional functions in *S. mutans* biology. In addition to their potential role in cellular suicide, mutacins also play a role in the proper development of genetic competence. Noticeably lower transformation frequencies are observed when mutations are introduced into the genes encoding mutacin V and mutacin VI (Dufour *et al.*, 2011, Perry et al., 2009). Clearly, the connections between competence development and mutacin production are intimately interwoven in *S. mutans*. Lastly, there is a longstanding interest to commercialize the wide-spectrum lantibiotic mutacins. They hold great promise as therapeutics for Gram-positive infections, particularly with the increasing threat of vancomycin resistant enterococci (VRE), methicillin resistant *Staphylococcus aureus* (MRSA), or perhaps even the newly emerging strains of vancomycin-resistant *S. aureus* (VRSA). Unfortunately, the complex chemistry that gives these mutacins their potent activity, also makes them difficult (i.e. expensive) to synthesize chemically. Therefore, if the commercial potential of these bacteriocins is ever going to be realized, either new breakthroughs will be required for chemical synthesis or novel strategies will need to be devised to greatly increase the yield of mutacins produced in batch cultures. As previously described, mutacin transcription is heavily dependent upon extreme high cell density growth conditions, but such an environment is currently impractical to replicate using industrial-scale fermentors. In addition to the wide-spectrum mutacins, the numerous narrow-spectrum mutacins may hold commercial potential as well. For example, we have found penicillin resistant *S. pneumoniae* to be highly sensitive to mutacin VI (unpublished results). Therefore, it may be feasible to use this mutacin to treat pneumococcal otitis media cases in order to reserve the use of beta-lactams or other wide-spectrum antibiotics for more serious infections. Targeted mutacin activity would also have the advantage of being minimally disruptive to the human flora, unlike the vast majority of commonly used

antibiotics. With the continued discovery and characterization of new mutacins, it is becoming increasingly evident that there is a potential wealth of useful antimicrobial compounds located right beneath our noses.

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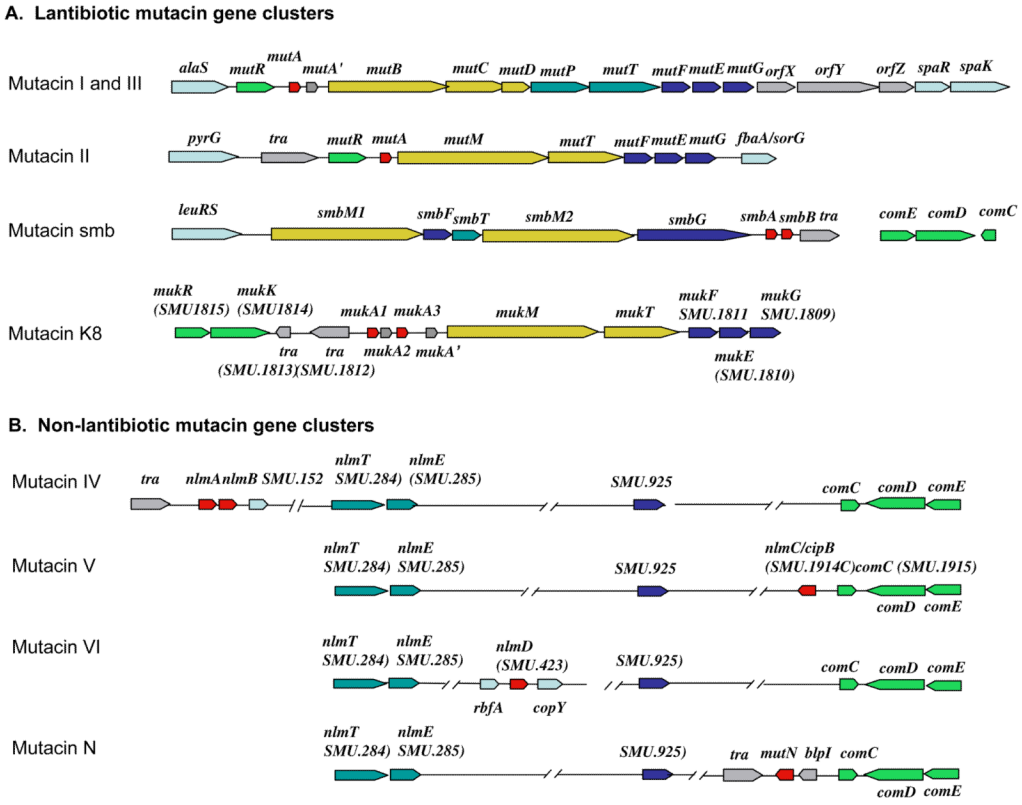

Fig. 1.

Gene clusters of characterized lantibiotic mutacins. Green: mutacin transcription regulators; red: structural genes for the prepro-mutacin peptides; yellow: modification enzymes for the prepeptide; dark green: transportation and processing enzymes for the propeptide; dark blue: immunity proteins; gray: transposases or other genes not required for mutacin production; light blue: flanking genes outside the locus.

Fig. 2A

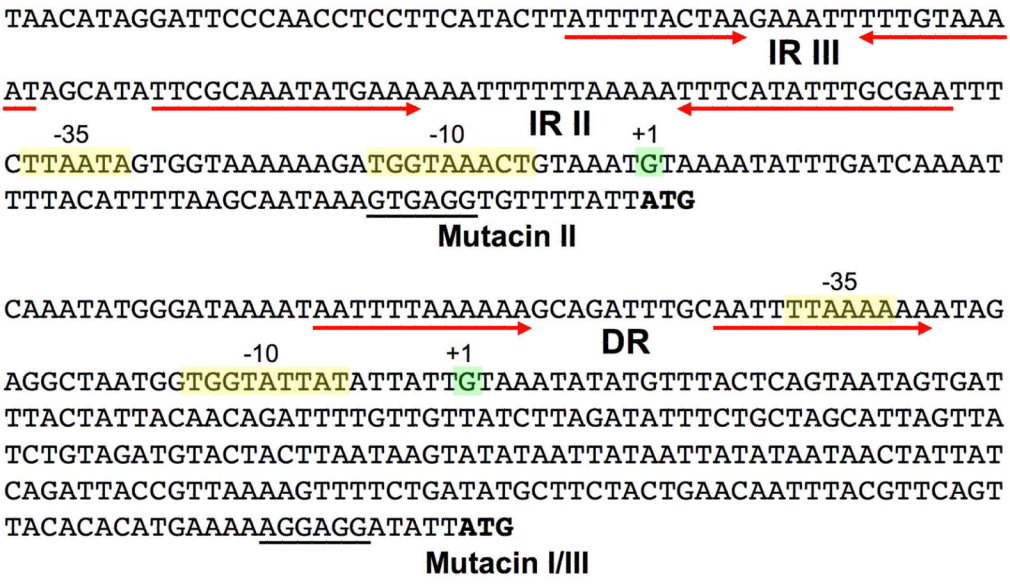

Fig. 2B

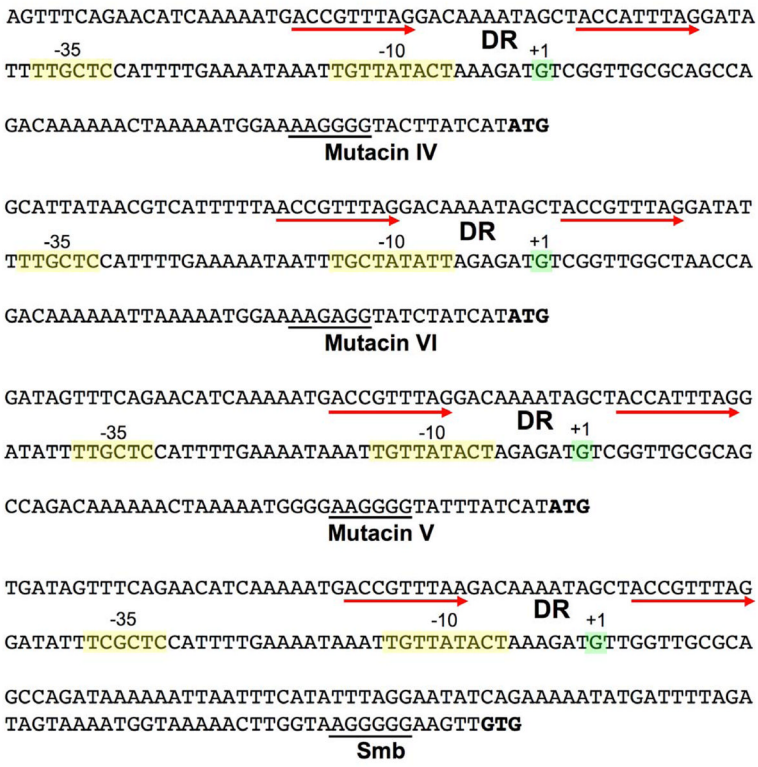

Fig. 2.

Comparison of the promoter regions for mutacin genes. A) The promoter regions upstream of the mutacin structural genes are shown for mutacins I, II, and III. The initiation codons are listed in bold and the ribosome binding sites are underlined. The transcription start sites

are highlighted in green, while the −10 and −35 sequences are highlighted in yellow. Both inverted repeat (IR) and direct repeat sequences (DR) are marked with red arrows. B) Sequences of the upstream intergenic regions of mutacins IV, VI, V, and the Smb operon. The direct repeat sequences for mutacins IV and VI were confirmed as BrsR binding sites in strain UA140, while the mutacin V direct repeats were shown to be bound by ComE in strain UA159. The transcription start sites for mutacins IV and VI were identified by rapid amplification of cDNA ends (RACE) PCR, while those of mutacin V and the Smb operon are inferred based upon their sequence similarity to mutacins IV and VI.

Fig. 3.

Summary of the regulation and ecology of mutacins. Components belonging to individual regulatory or genetic pathways are grouped by color. Colored line arrows indicate transcription regulation, whereas striped block arrows indicate post-transcriptional regulation. Of the extrinsic factors regulating mutacins, cell density is the predominant stimulus. It directly or indirectly affects the expression of the ComCDE system, the HdrRM and possibly BrsRM LytTR Regulatory Systems, as well as uncharacterized factor(s) controlling the expression of the lantibiotic mutacins I, II, and III. CSP is the signal directly sensed by the ComCDE system and MukA' has been suggested to be the signal sensed by the MukRK sensory system. Nutrient composition also impacts the regulation of the lantibiotic mutacins through an uncharacterized mechanism. The ComCDE, HdrRM, and BrsRM regulatory systems are all autoinducing and activate the expression of the competence coordinated bacteriocins mutacins IV, V, and VI. These mutacins kill related oral species containing homologous chromosomes. The DNA released from intoxicated cells can be imported into the mutacin producer strain through the competence system. The competence system is itself induced by the ComCDE and HdrRM systems. Hence, these two systems can coordinate the production of particular mutacins with the development of natural genetic competence. The lantibiotic bacteriocins mutacins I, II, and III are regulated primarily by cell density and nutrients through an unknown mechanism. The mutacin operon transcription activator MutR is responsible for ensuring the transcription of the mutacin structural gene as well as all of the machinery required to posttranslationally modify and excrete the peptide and to provide immunity against self-intoxication. These lantibiotics kill most Gram-positive organisms due to interactions with the conserved lipid II molecule. The lantibiotic mutacin K8 locus also encodes similar machinery as mutacins I, II, and III. However, the K8 locus also encodes the MukRK sensory system that is presumably essential for inducing the expression of the *muk* genes. The K8 inhibitory spectrum does not appear to be as broad as mutacins I, II, and III and it is unknown which, if any, molecules are used as mutacin K8 receptors.

Table 1

Characterized mutacins

Name	Mature peptide Sequence	Producer strains	Regulator
	Lantibiotics*		
Mutacin I	FS**S**LSL**CS**LG**C**TGVKNP**S**FN**SYCC**	UA140, CH43	MutR
Mutacin II	NRWWQGVVP**T**V**S**YE**C**RMN**S**WQHVF**TCC**	T8	MutR
Mutacin III/1140	FK**S**WSL**CT**PG**C**ARTG**S**FN**SYCC**	UA787, JH1140	MutR
Mutacin B-NY266	FK**S**WSF**CT**PG**C**AKTG**S**FN**SYCC**	NY266	
Mutacin Smb	STPACAIGVVGITVAVTGISTACTSRCINK (SmbA) GTTVVNSTFSIVLGNKGYICTVTVECMRNCSK (SmbB)	GS5	ComE, HdrR?, BrsR?
Mutacin K8	MGKGAVGTISHECRYNSWAFLATCCS	K8	MukR?
	Non-lantibiotics		
Mutacin IV	KVSGGEAVAAIGICATASAAIGGLAGATLVTPYCVGTWGLIRSH (NlmA) DKQAADTFLSACGGAASGFTYCASNGVWHPYILAGCAGVGAVGSVVFPH (NlmB)	UA140, UA159, 25175, L13	ComE, HdrR, BrsR
Mutacin V	GRGWNCAAGIALGAGQGYMATAGGTAF LGPYAIGTGAFGAIAGGIGGALNSCG	UA159, UA140	ComE, HdrR, BrsR
Mutacin VI	GMIRCALGTAGSAGLGFVGGMGAGTVT LPVVGTVSGAALGGWSGAAVGAATFC	UA159	ComE, HdrR, BrsR
Mutacin N	SRQAADTFLSGAYGAAKGVTARASTGVYVVPATLVALGVYGAGLNIAFP	N	ComE?

*Bold letters denote residues involved in thioether linkages in the mature peptide.