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CHAPTER 10

Cyclic Peptides in Neurological Disorders: The Case of Cyclo(His-Pro)

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1 Introduction

Bacterial quorum sensing (QS) is a cell-to-cell communication system based on the production, secretion, and detection of signals, named autoinducers. These signals are generated in response to variations in population level variables such as the density of bacterial population and changes in the makeup of its constituent species, and simultaneously regulate gene expression and coordinate collective behaviors. In this way, diverse bacterial communities acquire the capacity to act as a group and switch on virulence factor production, biofilm formation, and resistance development. Indeed, many microbial processes would be ineffective if performed by a single bacterial cell acting alone (Ng and Bassler, 2009; Bassler and Vogel, 2013; Cornforth et al., 2014; Schluter et al., 2016). QS processes have been found in Gram negative and Gram positive bacteria species, but interestingly, numerous examples of "interkingdom" signals (i.e., signals that cross taxonomic borders, for example between prokaryotic and eukaryotic cells) have also been identified. From the beginning, prokaryotes and eukaryotes survive and coexist by sensing and responding to signals produced and released by the other (Rosier et al., 2016). Once synthesized, the signal, whose concentration is proportional to population density, is secreted. When the levels of signal exceed a threshold value, the signal is detected by a QS receptor that engages a downstream transduction cascade to launch a high cell density gene expression program.

In Gram negative bacteria, AIs molecules are drawn from several chemical classes, such as acyl homoserine lactones (AHLs), alkylquinolones, α-hydroxyketones, and diffusible signal factors (fatty acid-like compounds), synthesized from common metabolites via a single synthase or a series of enzymatic reactions (Hawver et al., 2016; Ryan et al., 2015). AI can freely cross cell membranes, and when their extracellular concentration is sufficiently high, they can diffuse back to act in an autocrine manner on the producing cell by binding cytosolic receptors. The latter act as transcription factors and, upon AI binding, regulate the expression of QS genes.

Quorum Sensing. https://doi.org/10.1016/B978-0-12-814905-8.00010-1

Typically, Gram negative bacteria use QS systems homologous to the luminescence (*Lux*) controlling operon (LuxI/LuxR system) originally identified in the luminescent marine bacterium *Vibrio fischeri*. The LuxI homolog acts as an AI synthase while the LuxR homolog is a cytosolic transcription factor AI receptor which, upon AI binding, acquires transactivating capacity and mediates the transcription of target genes (Hawver et al., 2016; Ryan et al., 2015).

The homologous system in Gram positive bacteria is slightly more complex and is mediated by short oligopeptides. Autoinducer peptides (AIPs) are produced by the AIP synthase, and after proteolytic processing are actively secreted via a transporter, usually an ATP binding cassette transporter. When their extracellular concentration reaches a threshold level, they can be transported back into the cytoplasm, where they are detected by a QS transcription factor. At high cell density, the AIPs, once released into the extracellular space via a transporter, undergo posttranslational modifications and bind to transmembrane receptors, thus triggering a phosphorylation cascade that controls the downstream QS response (Cook and Federle, 2014; Hawver et al., 2016; Monnet et al., 2016). The receptors for Gram positive QS comprise a family with four members—Rap, NprR, PlcR, and PrgX (Rocha-Estrada et al., 2010)—collectively termed *RNPP*. Rap is an aspartyl phosphate phosphatase and transcriptional activator protein, whereas NprR, PlcR, and PrgX are DNA-binding transcription factors. In addition, NprR is a neutral protease regulator, PlcR is a phospholipase C regulator, and PrgX regulates the plasmid conjugative transfer (Rocha-Estrada et al., 2010; Zouhir et al., 2013; Cook and Federle 2014). A third type of molecule, a furanosyl borate diester, also called autoinducer-2 (AI-2), represents a universal signal for interspecies communication (Hense and Schuster, 2015).

Thus while specific details vary, generically, QS systems connect the release of a diffusible messenger molecule to the targeted regulation of a specific and context-appropriate program of gene expression. QS enables cooperative behavior distinct from traditional paracrine signaling, where sender and receiver cells are different; in QS the sender and receiver are frequently one and the same. Moreover, these QS behaviors have characteristic ecological functionalities and evolutionary properties (Diggle et al., 2007). QS systems integrate and process information from the physical environment to optimize their activities at a community level, enabling the cooperative and coordinated behavior of a diverse cell population. Thus QS systems are distributed over a wide taxonomic range, such as fungi, plants (algae), animals, and possibly even viruses, where host cell lysis may depend on the virus concentration (Hallmann, 2011; Hogan, 2006; Moussa et al., 2012; Sprague and Winans, 2006; Weitz et al., 2008).

2 Cyclic Peptides

Many biologically active peptides, consisting of either the canonical 20 amino acids or nonproteogenic amino acids, have been discovered in bacteria (Clardy and Walsh, 2004). These linear or cyclic peptides can be synthesized in the ribosomes and later processed or

produced independently of ribosomes by peptide synthetases (Clardy et al., 2006). Peptides, as well as proteins, are bioactive molecules constituting attractive initial leads for a rational drug design (Tapeinou et al., 2015). Linear peptides, because of their susceptibility to proteolytic degradation, have not historically been molecules of choice for the pharmaceutical industry. However, the introduction of modifications can render these molecules more attractive. Indeed, cyclization leads to increased stability, *N*-methylation can increase membrane permeability and stability, the incorporation of unnatural amino acids increases specificity and stability, PEGylation (i.e., the attachment or amalgamation of polyethylene glycol (PEG) polymer chains) is capable of reducing clearance, and assorted structural constraints (e.g., disulfide bonds), as well as recent progress in "stapled" peptides, improved potency and specificity. These modifications are currently employed as promising new modalities for future therapeutics (Tapeinou et al., 2015; Verdine and Hilinski, 2012). In particular, peptides, once cyclized, have superior binding affinities and reduced entropic cost associated with receptor binding. Indeed, confining a peptide into a cyclic structure reduces the conformational freedom of its parent linear structure and enhances its metabolic stability, bioavailability, and specificity. Naturally occurring cyclic peptides have a wide variety of unusual and potent biological activities: many of these compounds control intra- and interspecies bacterial virulence and bacterial-host interactions, penetrate cells by passive diffusion, and some, like the clinically important drug cyclosporine A, are orally bioavailable (Bockus et al., 2013). Cyclic dipeptides (CDPs), such as enniatins, can be produced by plant pathogens and act as mycotoxins by disturbing the physiological behavior of the host cells. Moreover, they display several other biological effects such as insecticidal, antifungal, and antibacterial activities. Indeed, by exerting a potent cytotoxic effect on human and animal cell lines, they are considered potential anticancer drugs (Prosperini et al., 2017). Hence, cyclic peptides are promising lead compounds for drug development in a wide range of clinical settings and represent attractive biosynthetic targets.

The QS peptides described in the literature are stored in the curated Quorumpeps database (http://quorumpeps.ugent.be), giving details of the peptides and QS processes (receptor, activity, species) in which they are implicated (Wynendaele et al., 2015). The analysis of the 231 QS peptides, listed in Quorumpeps, shows that cyclic peptides occupy a distinct portion of the QS peptide space according to their size distribution, compactness, lipophilicity/hydrophobicity, presence of aromatic amino acids, and sulfur atoms. On the other hand, results of the species distribution indicate that most of the Gram positive bacteria synthesize chemically similar peptides. Notably, cyclic peptides, named θ-defensins, have also been found in leukocytes of rhesus macaques and baboons (Lehrer et al., 2012), where they are involved in defense from a range of viral (HIV-1, HSV, and influenza A viruses, coronavirus severe acute respiratory syndrome) and bacterial pathogens (*Bacillus anthracis* spores), therefore representing interesting potential therapeutic agents.

2.1 Cyclic Dipeptides

CDPs, also known as 2,5-diketopiperazines, are a family of small and biologically active molecules, mostly acting as QS effectors, that contain a family-defining CDP core/scaffold structure (Fig. 1), and are produced by proteobacterial species as well as by humans (Bellezza et al., 2014a,b; Borthwick, 2012; Cornacchia et al., 2012; Minelli et al., 2008; Mishra et al., 2017; Prasad, 1995). CDPs are a class of cyclic organic compounds in which the two nitrogen atoms of a piperazine 6-membered ring form amide linkages. The nomenclature of CDPs is indicated by the three-letter code for each of the two amino acids, plus a prefix to designate the absolute configuration (e.g., cyclo(L-Xaa-L-Yaa)). CDPs can be configured as both cis and trans-isoforms, but cis configurations are predominant (Eguchi and Kakuta, 1974). Various amino acid modifications confer diversified chemical and biological functions. CDPs exhibit better biological activity than their linear counterparts due to their higher stability, protease resistance, and conformational rigidity, all factors that increase their ability to specifically interact with biological targets (Liskamp et al., 2011; Menegatti et al., 2013). They constitute a large class of secondary metabolites produced by bacteria, fungi, plants, and animals (Borthwick, 2012; Giessen and Marahiel, 2014; Huang et al., 2010; Mishra et al., 2017; Prasad, 1995). Indeed, approximately 90% of CDP producers are bacterial (Giessen and Marahiel, 2014). The CDP scaffold can be synthesized either by purely chemically means using different solid phases or under reflux conditions in solution (Borthwick, 2012; Gonzalez et al., 2012) or, more naturally, by biosynthetic enzymes called nonribosomal peptide synthetases (NRPSs) and CDP synthases (CDPSs; Belin et al., 2012; Giessen and Marahiel, 2014). Common chemical synthesis of CDPs includes the condensation of individual amino acids at high temperature. Dipeptides substituted with an amine at one terminus and an ester at the other can also spontaneously cyclize to form a CDP. However, conditions must be optimized in order to force a cyclization reaction and to limit racemization. This is the procedure most commonly used for the chemical synthesis of CDP. Cyclization of amino dipeptide esters can also be carried out under thermal conditions, normally by refluxing them in high boiling solvents such as toluene or xylene for 24 h (Borthwick, 2012). In addition, CDPs are often products of unwanted side reactions or degradation products of oligo- and polypeptides in processed food and beverages (Borthwick and Da Costa, 2017; Prasad, 1995). They are frequently formed during the chemical degradation of products in roasted coffee, stewed

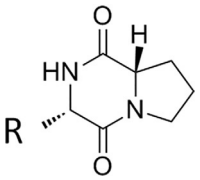

Fig. 1
Family-defining core/scaffold structure of histidine containing cyclic dipeptides.

beef, and beer (Chen et al., 2009; Gautschi et al., 1997; Ginz and Engelhardt, 2000). Nonenzymatic processes can also lead to the formation of functional CDPs in various organisms, as described for cyclo(L-His-L-Pro) (Bellezza et al., 2014a,b; Minelli et al., 2008). In mammals, cyclo(His-Pro) (CHP) is obtained from the action of pyroglutamate aminopeptidase on the thyrotropin-releasing hormone (TRH, pGlu-His-Pro). The resulting dipeptide is then nonenzymatically cyclized to CHP. The proline induces constraints that promote the cis-conformation of the peptide bond between the histidine and the proline, thereby facilitating cyclization, which generates the CDP scaffold.

As for the enzymatic pathways of CDP formation, two unrelated biosynthetic enzyme families catalyze the formation of CDPs: NRPSs and CDPSs. It has been shown that CDP scaffolds can be synthesized by one or more specialized NRPSs, either via specific biosynthetic pathways or via the premature release of dipeptidyl intermediates during the chain elongation process. The NRPS genes for certain peptides are usually organized in one operon in prokaryotes, and in a gene cluster in eukaryotes (Schwarzer et al., 2003). NRPSs are large modular enzymes, which simultaneously act as a template and as biosynthetic machinery. Each module is responsible for the incorporation of one amino acid into the final peptide, and can be further subdivided into the catalytic domains responsible for specific synthetic steps during peptide synthesis (Felnagle et al., 2008). In each module, NRPSs consist of three necessary domains: an adenylation (A) domain; a thiolation (T) domain, posttranslationally modified with a 4′-phosphopantetheinyl (4′-Ppant) arm, also termed the peptidyl carrier protein (PCP) domain; and a condensation (C) domain, separated by short spacer regions of approximately 15 amino acids. The A domain selects, activates, and loads the monomer onto the PCP domain. Here, the thiol group of the 4′-Ppantarm of the T domain mediates the nucleophilic attack of the adenylated amino acid. Subsequent peptide bond formation between two adjacent T-bound aminoacyl intermediates is catalyzed by the C domains (Belin et al., 2012). Another essential NRPS catalytic unit is the thioesterase (TE) domain, which is located in the C-terminus and catalyzes peptide release by either hydrolysis or macrocyclization. In addition, modification domains can be integrated into NRPS modules at different locations to modify the incorporated amino acids. Epimerization and *N*-methyltransferase domains catalyze the generation of D- and methylated amino acids, respectively (Koglin and Walsh, 2009; Strieker et al., 2010). NRPSs rely not only on the 20 canonical amino acids, but also use several different building blocks, including nonproteinogenic amino acids, and this contributes to the structural diversity of nonribosomal peptides and their differential biological activities (Koglin and Walsh, 2009). CDPs, once synthesized by NRPSs, can be further modified by tailoring enzymes, usually encoded by genes clustered with the NRPS genes. The majority of known NRPS-derived CDPs are produced by fungi, whereas few bacteria are recognized as NRPS-derived CDP producers. Many CDPs can be formed by dedicated NRPS pathways, such as brevianamide F, erythrochelin, ergotamine, roquefortine C, acetylaszonalenin, thaxtomin A, gliotoxin, and

sirodesmin PL (Balibar and Walsh, 2006; Correia et al., 2003; García-Estrada et al., 2011; Gardiner et al., 2004; Healy et al., 2002; Maiya et al., 2006; Lazos et al., 2010; Yin et al., 2009). In a few cases, CDPs can be formed by NRPSs during the synthesis of longer peptides, as truncated side products, as in the biosynthesis of cyclo(D-Phe-L-Pro) and cyclomarazine A (Gruenewald et al., 2004; Schultz et al., 2008). Biosynthesis of CDPs can also be CDPS-mediated: CDPS are a family of tRNA-dependent peptide bond-forming enzymes that do not require amino acid charging. CDPSs share a common architecture reminiscent of the catalytic domain of class-Ic amino acid tRNA synthetases (aaRSs), such as TyrRS and TrpRS (Sauguet et al., 2011). Both CDPSs and class-Ic aaRSs comprise well conserved Rossmann-fold domains, structural features associated with binding of nucleotides such as flavin adenine dinucleotide, nicotinamide adenine dinucleotide (NAD^+), and nicotinamide adenine dinucleotide phosphate ($NADP^+$), along with a helical connective polypeptide 1 (CP1) subdomain. However, class-IcaaRSs possess signature motifs involved in ATP binding (HIGH and KMSKS sequences) that are not present in CDPSs. In addition, CDPSs do not possess a distinct tRNA-binding domain, but rather contain a large patch of positively charged residues located in helix α4, which are important for the binding of aminoacyl-tRNA substrates. All these observed differences between CDPSs and their ancestral aaRSs result in unique enzymes for CDP biosynthesis. CDPSs use amino acid tRNAs as substrates to catalyze the formation of CDP peptide bonds (Belin et al., 2012; Giessen and Marahiel, 2012; Giessen et al., 2013; Gondry et al., 2009), diverting two aminoacyl-tRNAs from their essential role in ribosomal protein synthesis for use as substrates and catalyzing the formation of the two peptide bonds required for CDP formation (Lahoud and Hou, 2010). The synthesis process is initiated by the binding of the first aminoacyl substrate, likely involving ionic interactions between the negatively-charged ribose-phosphate tRNA backbone and the positive charges in helix α4 (Bonnefond et al., 2011; Sauguet et al., 2011). Hence, by using aminoacyl-tRNAs as substrates, CDPSs represent a direct link between primary and secondary metabolism. The catalytic mechanism of CDPSs can be described using a ping-pong model. All CDPSs possess two surface-accessible pockets that contain active site residues important for substrate selection and catalysis. The different aminoacyl binding sites for the two aa-tRNA substrates are termed pocket 1 (P1) and pocket 2 (P2). Upon specific recognition of the first substrate, the first aminoacyl group is transferred to the conserved serine residue of P1. Here, interaction between the tRNA moiety and basic residues in the α4 helix generates an aminoacyl-enzyme intermediate (Moutiez et al., 2014). At the same time, the aminoacyl moiety of the second aa-tRNA interacts with P2 through the α6–α7 loop. Finally, the aminoacyl-enzyme intermediate reacts with the second aa-tRNA to generate a dipeptidyl-enzyme intermediate, which undergoes intramolecular cyclization through the involvement of a conserved tyrosine, leading to the CDP scaffold as the final product. These CDPs can be modified by closely associated tailoring enzymes. There are approximately 163 putative CDPS genes identified so far, and of these, 150 are reported in bacteria, distributed among six phyla (Actinobacteria, Bacteroidetes, Chlamydiae, Cyanobacteria, Firmicutes, and Proteobacteria). Most known CDPSs are found in Actinobacteria, with 77 CDPSs reported to date. Twelve CDPSs are

distributed among four eukaryotic phyla (Ascomycota, Annelida, Ciliophora, and Cnidaria), and one archaeon (*Haloterrigena hispanica*) CDPS has also been reported (Belin et al., 2012; Giessen and Marahiel, 2014; Tommonaro et al., 2012). Some bacterial CDPSs have been fully characterized, such as albonoursin in *Streptomyces noursei*, pulcherrimin in *Bacillus subtilis*, and mycocyclosin in *Mycobacterium tuberculosis* (Belin et al., 2012; Giessen et al., 2013).

The biosynthetic enzymes are usually physically and, as alluded to previously, transcriptionally associated with tailoring enzymes that specifically modify CDP-containing natural products. Putative tailoring enzymes that modify the initially assembled CDP scaffold can be found in almost all NRPS and CDPS gene clusters, and are responsible for introducing functional groups crucial for the biological activities of CDPs. In CDPS-dependent pathways, a large variety of different modification enzymes are found in close association with the respective CDPS genes (Belin et al., 2012; Giessen and Marahiel, 2014), including different types of oxidoreductases, hydrolases, transferases, and ligases. The most prevalent putative tailoring enzymes in CDPS clusters are cyclic dipeptide oxidases (CDOs). CDOs are composed of two distinct small subunits that assemble into an apparent megadalton protein complex. Depending on the substrate, the CDO can sequentially perform one or two dehydrogenation reactions. The precise reaction mechanism for this has not been elucidated, although three different scenarios have been proposed: direct dehydrogenation, α-hydroxylation followed by loss of water, and imine formation with subsequent rearrangement of the enamine (Gondry et al., 2001). Known CDOs include at least seven distinct P450 enzymes, five different types of α-ketoglutarate/FeII-dependent oxygenases, and three distinct flavin-containing mono-oxygenases. In addition to oxidoreductases, a large number of different C-, N-, and *O*-methyltransferases, α/β-hydrolases, peptide ligases, and acyl-CoA transferases have been found in CDPS gene clusters in which different transcription factors belonging to the LuxR and MarR families, among others, are observed. They are usually involved in regulating various processes in response to environmental stimuli like toxic chemicals and antibiotics, which may hint at the biological functions of CDPS-dependent modified CDPs (Ellison and Miller, 2006). Regarding NRPS-dependent pathways, a similar variety of modification enzymes has been reported, and again, enzymes that modulate the oxidation of the CDP scaffold and side chains are the most numerous (Belin et al., 2012). One distinguishing feature of fungal NRPS gene clusters is the prevalence of different prenyltransferases, which perform prenylations and reverse prenylations at various positions of tryptophan-containing CDP scaffolds (Yu et al., 2012). Judging by the diverse set of putative modification enzymes found within NRPS and CDPS gene clusters, it is assumed that highly modified CDPs represent a diverse family of microbial natural products with varied functions.

Moreover, it is worth noting that the CDP core, besides rendering these molecules resistant to proteolysis, also enables the crossing of the intestinal barrier and blood-brain barrier (BBB; Beck et al., 2012; Teixidó et al., 2009). Thus the combination of flexibility and stability provides the CDP molecules with biological properties and a wide array of therapeutic possibilities (Bellezza et al., 2014a,b). The ability to inhibit plasminogen activator inhibitor-1

(PAI-1), enabling intervention in cardiovascular disease and blood clotting functions (Einholm et al., 2003), was the first discovered biological action of CDPs, later followed by the discovery of antibacterial (Rhee, 2004), antitumor (Nicholson et al., 2006), antifungal, and antiviral activities (Kwak et al., 2013; Kwak et al., 2014; Mishra et al., 2017). Korean fermented vegetable kimchi is a rich source of Pro-based CDPs that have activities against multidrug resistant bacteria (Liu et al., 2017), and cyclo(L-Val-L-Pro) and cyclo(L-Phe-L-Pro), produced by vegetables fermented with *Lactobacillus plantarum* LBP-K10, can inhibit the growth of *Candida albicans* (Kwak et al., 2014). Cyclo(D-Tyr-D-Phe), extracted from fermented modified nutrient broth of *Bacillus* sp. N strain associated with the rhabditid entomopathogenic nematode, shows significant antitumor activity against A549 cells without cytotoxicity for normal fibroblast cells (Kumar et al., 2013). The pleiotropic actions of CDPs are reflected in their ability to bind an array of targets: by binding with high affinity to oxytocin receptors, thus acting as antagonists, CDPs can inhibit ejaculation (Borthwick et al., 2012; Clément et al., 2013). CDPs released by the coldwater marine sponge *Geodia barretti* synergistically exert chemical defense (Sjögren et al., 2011). Moreover, CHP, a catabolic product of TRH (thyrotropin releasing hormone), can control blood glucose levels (Choi et al., 2012; Jung et al., 2011, 2016; Koo et al., 2011; Lee et al., 2015, 2013; Park et al., 2012) and, associated to zinc, has already been patented in the United States as an antidiabetic drug with no side effects in humans (Uyemura et al., 2010).

2.2 CDPs in QS Systems

CDPs have been isolated from marine sponges (Schmitz et al., 1983), Gram negative (Jayatilake et al., 1996) and Gram positive marine bacteria (Stierle et al., 1988). Therefore, marine bacteria are a promising source for this class of bioactive compounds. It is known that marine sponges are an abundant source of novel microorganisms that produce compounds with potential pharmacologic activity (Hentschel et al., 2001). Marine sponges with their surfaces and internal spaces provide a highly specialized environmental niche containing high numbers of bacteria. They exceed the bacteria contained in seawater by two or three orders of magnitude (Engel et al., 2002; Friedrich et al., 2001). Sponge-bacteria associations are widely distributed and evolutionarily ancient, with a direct relationship between the size and density of sponges and the content of bacterial associates. Several data suggest an advantageous coexistence of microorganisms and sponges (Proksch et al., 2002). Autotrophy of cyanobacteria can provide host sponges with additional carbon sources and fixed nitrogen, specific associations with heterotrophic bacteria facilitate the metabolism of a wide range of organic compounds, and associated bacterial and cyanobacterial communities produce secondary metabolites that enhance the chemical defense of the host (Abbamondi et al., 2014; De Rosa et al., 2003). There is experimental evidence that sponge-associated microflora are species-specific (Friedrich et al., 2001; Schmidt et al., 2000; Webster and Hill, 2001; Webster et al., 2001) and represent a stable population (Friedrich et al., 2001;

Webster and Hill, 2001; Webster et al., 2001) capable of communicating with the sponge itself. Marine sponge-associated bacteria secrete QS signals such as *N*-acyl homoserine lactones (AHLs; Taylor et al., 2004) and CDPs (Tommonaro et al., 2012). Holden et al. (1999) reported that several Gram negative bacteria produced and secreted CDPs which, in turn, can activate and/or antagonize other LuxR-based QS systems. *Pseudomonas putida* WCS358 can produce and secrete four CDPs, some capable of interacting with the QS LuxI and LuxR homologues (Degrassi et al., 2002). A set of CDPs was isolated from a range of Gram negative bacteria and reported to modulate LuxR, TraR, or LasR activity in sensitive AHL biosensor strains previously considered specific for AHLs (Degrassi et al., 2002; Holden et al., 1999; Park et al., 2006). Therefore, the capacity of QS signals generated in one organism has been demonstrated to regulate the behavior of a second organism. Thus CDPs, isolated either individually or as mixtures from culture supernatants of *Pseudomonas aeruginosa*, *Pseudomonas fluorescens*, *P. putida*, *Pseudomonas alcaligenes*, *Proteus mirabilis*, *Enterobacter agglomerans*, *Vibrio vulnificus*, and *Citrobacter freundii*, represent interspecies and cross-kingdom signals (Campbell et al., 2009). Cyclo(D-Ala-L-Val) and cyclo(L-Pro-L-Tyr) inhibit the activity of regulatory LuxR-type proteins that are involved in AHL-dependent QS regulation (Campbell et al., 2009; Galloway et al., 2011). In addition, the lasI-dependent QS system represses the CDP biosynthesis, and this is a determinant factor in the underlying interaction with *Arabidopsis thaliana* plants, since cyclo(L-Pro-L-Tyr), cyclo(L-Pro-L-Val), and cyclo(L-Pro-L-Phe) appear to mimic the biological role of auxin, a natural phytohormone (Ortiz-Castro et al., 2011).

In the case of specific sponge-bacteria associations, associated bacteria may prosper or at least survive with sponge material. A ribosomal RNA study of axenic cell cultures of *Suberites domuncula* showed a 16S rRNA band specific for bacteria (Thakur et al., 2003). The presence of D-amino acids and unusual amino acids in sponge peptides supports the microbial origin of sponge peptides (Fusetani and Matsunaga, 1993). CDPs attributed to the sponge *Tedania ignis* (Schmitz et al., 1983) were produced by the associated bacterium *Micrococcus* sp. (Stierle et al., 1988), and theopalauamide, a cyclic glycopeptide isolated from the sponge *Theonella swinhoei*, is included in uncultivable symbiont "*Candidatus Entotheonella palauensis*" (Schmidt et al., 2000). In addition, several CDPs that regulate bacterial-sponge interactions have been isolated from a proteobacterium of the genus *Ruegeria* associated with the marine sponge *S. domuncula*, from strains of the genera *Staphylococcus* and *Bacillus* associated with *Ircinia variabilis*, and from the marine bacteria *Vibrio* sp. associated with the marine sponge *Dysidea avara* (De Rosa et al., 2003; Mitova et al., 2004).

It is known that bacteria establish pathogenic or symbiotic relationships with their eukaryotic hosts, as in the case of *P. aeruginosa*, a well-known human and plant pathogen that proliferates in the rhizosphere, a narrow zone of soil influenced by root exudates. To overcome host defenses, *P. aeruginosa* produces toxins, adhesins, pyocyanin, and other virulence factors (Battle et al., 2008; de Abreu et al., 2014) by a QS mechanism in which CDPs play a pivotal role (González et al., 2017). *P. aeruginosa* QS is rather complex: the las and rhl systems are

dependent on *N*-(3-oxododecanoyl)-L-homoserine lactone and *N*-butanoyl-L-homoserine lactone, respectively. These compounds are synthesized by the acyl-L-homoserine lactone synthases, encoded by the *lasI* and *rhlI* genes (de Kievit and Iglewski, 2000; Fuqua and Greenberg, 2002; Lee and Zhang, 2015). A third QS system involves the 2-heptyl-3-hydroxy-4-(1*H*)-quinolone and 2-heptyl-4-hydroxyquinolone, encoded by the *pqs* gene cluster (Gallagher et al., 2002; Lee and Zhang, 2015). All these systems connect signal transduction to transcription factors of the LysR-type, namely LasR, RhlR, and PqsR, which specifically respond to the cognate signal molecules and drive expression of hundreds of genes (Lee and Zhang, 2015). Signaling hierarchy, upstream of the pqs and rhl systems, is further defined by the signaling molecule, 2-(2-hydroxyphenyl)-thiazole-4-carbaldehyde (IQS, also called aeruginaldehyde), which is synthesized by the *ambBCDE* gene cluster and plays an important role in pathogenesis via the production of pyochelin siderophores (Dandekar and Greenberg, 2013; Lee et al., 2013; Lee and Zhang, 2015). The *ambBCDE* cluster encodes enzymes for L-2-amino-4-methoxy-trans-3-butenoic acid (AMB) biosynthesis, which occurs via a nonribosomal peptide synthase (NRPS) pathway and shows toxic effects to prokaryotes and eukaryotes (Rojas Murcia et al., 2015). By employing bioinformatics and functional approaches, González and co-workers (2017) recently identified NRPS from *P. aeruginosa* PAO1 wild-type (WT) strain and studied the role of CDPs in bacterial physiology and their interaction with plants. The authors showed that in mutants defective in putative MM-NRPS, the production of CDPs was altered and that these changes, although ineffective on virulence, interfered, at very high concentrations, with the QS systems by interacting with the binding site of the cognate AHL. By using a bacteria-plant interaction system (i.e., *P. aeruginosa-A. thaliana* co-cultivation), they observed that either the repression of root growth or the promotion of root branching exerted by selected WT and NRPS mutants was related to AHL-dependent QS status and was modified by CDP levels in vivo. CDPs are also responsible for food spoilage since QS systems govern bacterial behavior in food spoilage ecosystems (Gu et al., 2013; Skandamis and Nychas, 2012). Large yellow croaker (*Pseudosciaena crocea*), one of the most commercially important marine fish species in China, is highly susceptible to spoilage as a result of digestive enzymes and microbial activity within a short period of time postmortem even under refrigerated conditions. Microbial growth and its metabolism byproducts leads to the production of trimethylamines, organic acids, alcohols, sulfides, biogenic amines, aldehydes, and ketones with unpleasant and unacceptable off-flavors (Gram and Dalgaard, 2002). The microbial spoilage of chilled fish is chiefly connected with the presence of Gram negative proteolytic psychrotrophic bacteria, mainly *Shewanella* spp., *Pseudomonas* spp., and genera of the *Enterobacteriaceae* family (Gram and Dalgaard, 2002; Skandamis and Nychas, 2012), each species regulating the cell-cell communication by producing, secreting, and responding to small diffusible molecules to activate or repress a specific target gene expression. Various signaling compounds, including AHLs and AI-2, have been reported in spoiled milk, meat, vegetables, and aquatic product (Blana and Nychas, 2014; Liu et al., 2006; Rash et al., 2005). Several authors (Gu et al., 2013; Zhu et al., 2016) studied

the specific spoilage organism (SSO) of *P. crocea* by investigating the role of QS system of SSO isolated from spoiled fish. They found that Shewanella, mainly *Shewanella baltica* and *Shewanella putrefaciens*, was the predominant genera at the end of shelf-life of *P. crocea*. In cell-free *S. baltica* culture, AI-2 and two CDPs, cyclo-(L-Pro-L-Leu) and cyclo-(L-Pro-L-Phe), were detected. The production of biofilm, trimethylamines, and putrescine in these spoilers significantly increased in the presence of cyclo-(L-Pro-L-Leu), rather than cyclo-(L-Pro-L-Phe) and 4,5-dihydroxy-2,3-pentanedione (the AI-2 precursor). Exposure to exogenous cyclo-(L-Pro-L-Leu) upregulated the transcription levels of luxR, torA, and ODC. In the fish homogenate, under refrigerated storage, exogenous cyclo-(L-Pro-L-Leu) enhanced the growth rate of the dominant bacteria, H_2S-producing bacteria, while the exogenous AI-2 precursor retarded the growth of competing bacteria, such as *Enterobacteriaceae*. Cyclo-(L-Pro-L-Leu) stimulated the accumulation of metabolites on the spoilage process of homogenate, thus confirming that the spoilage potential of *S. baltica* in *P. crocea* is regulated by QS mediated by CDPs. Finally, because of the growing importance of bacterial microbiome/bacteriome, fungal microbiome/mycobiome, the role of CDPs as mediators between oral bacteria and fungal genus has been also investigated (Brown et al., 2015). Oral candidiasis is a major complication of HIV infection (Shiboski et al., 2001; Shiboski, 2002; Thompson et al., 2010). A study by Brown et al. (2015) focused on the interaction of *Candida* with other taxa in the oral metabiome. Oral metabolites are products of the host, the oral bacterial microbiome (bacteriome), and the oral fungal microbiome (mycobiome). Functional shifts in the bacteriome and mycobiome contribute to the difference in a healthy oral environment versus oral candidiasis, and a significant shift in correlations between disease and control samples indicates an underlying metabolic change in the ecosystem. By profiling the entire oral metabiome and by using correlation difference probability network analysis, the authors proved the significant role of cyclic mono and dipeptides as QS mediators between oral bacteria and fungal genus, and hypothesized a possible contribution of CDPs to the etiology of oral candidiasis. Marchesan et al. (2015), by analyzing microbial community composition in periodontitis affected subjects, discovered the presence of several periodontal pathogens of the phylum *Synergistetes*. The authors demonstrated that *Synergistetes* phylum was strongly associated with two novel metabolites—cyclo(Leu-Pro) and cyclo(Phe-Pro)—which, by acting as QS molecules, can cause periodontal dysbiosis and periodontal disease.

Endogenous or probiotic strains have been shown to attenuate the production of virulence factor by bacterial pathogens. Indeed, Li et al. (2011) demonstrated that vaginal resident *Lactobacillus reuteri* RC-14 produces the CDPs cyclo(L-Phe-L-Pro) and cyclo(L-Tyr-L-Pro) that interfere with the staphylococcal QS system agr, a key regulator of virulence genes. This leads to the repression of the expression of toxic shock syndrome toxin-1 by the prototypical menstrual *Staphylococcus aureus* strain responsible for the menstruation-associated toxic shock syndrome (Li et al., 2011).

3 CHP in Neurological Disorders

3.1 Background

Thyrotropin-releasing hormone is a tripeptide formed by pGlu-His-Pro-NH_2, which is generated in the hypothalamus following the action of the pyroglutamyl-peptidase enzyme before being transformed into a linear dipeptide (His-Pro-NH_2), then cyclized by a nonenzymatic process at 37°C to produce CHP, also known as histidylproline diketopiperazine (Minelli et al., 2008; Prasad and Peterkofsky, 1976). In the 1970s, distribution studies showed that CHP is ubiquitous in the central nervous system—a finding that prompted significant research effort to define the biological roles of the CDP. The administration of exogenous CHP to animals is followed by a variety of biological activities, such as attenuation of ketamine anesthesia, extension of pentobarbital-induced sleep, and alleviation of some pharmacological effects of alcohol (Prasad, 2001). Moreover, it plays a significant role in modulating food intake and body core temperature, pain awareness, and by acting as an endocrine effector, inhibits prolactin secretion (Morley et al., 1981; Prasad, 1995, 2001). All these effects seem to share common dopaminergic mechanisms. Faden et al. (1981) reported that TRH and TRH-like compounds improve neurological recovery after spinal trauma and enhance cognitive function, although presenting potent endocrine, analeptic, and autonomic actions that hinder the therapeutic use of TRH. However, strikingly, the same authors also showed that CHP, the metabolic product of TRH, retains all pharmacological activities without known side effects (Faden et al., 2004, 2005). Further support for the involvement of CHP in brain function and potential implications for neurological diseases arose in 2007 when Taubert et al. (2007) showed that the CDP is a specific substrate for Organic Cation Transporter 2, a sodium-dependent transporter highly expressed in the dopaminergic brain structures classically targeted in Parkinson disease, particularly the *substantia nigra pars compacta* (Taubert et al., 2007). Not only was CHP found to co-localize in these regions; it was further shown to protect neurons from cytotoxicity induced by salsolinol, a metabolite of L-DOPA linked to Parkinson.

3.2 Current Understanding

For more than a decade, Minelli and coworkers have been actively involved in defining the effects of CHP in the brain. Indeed, the first clues of the potential application of this molecule in treating neurological disorders came in late 2006, when they discovered that CHP protects dopaminergic PC12 cells from apoptosis only in the presence of experimental conditions that cause cellular stress. Moreover, it has been shown that the treatment with CDPs activates two heat-shock proteins (Hsp), hsp27 and alpha-B-crystallin (Minelli et al., 2006), proteins implicated in the correct protein folding. Moreover, Hsps by mitigating apoptosis induced by protein misfolding are deeply involved in neurodegenerative diseases. This effect had been

practically unnoticed at the time, while today it looks likely to acquire considerable significance by linking the cell-protective antiapoptotic effect of the compound to enhanced capacity to manage metabolic stresses such as the protein misfolding response. CHP attenuates the production of reactive oxygen species (ROS), and prevents glutathione (GSH) depletion caused by stressors such as glutamate, rotenone, paraquat, and beta-amyloid treatment, by triggering the nuclear accumulation of NF-E2-related factor-2 (Nrf2), a transcription factor that upregulates antioxidant-/electrophile-responsive element (ARE-EpRE)–related genes (see later for details). Based on these findings, it was reasoned that CHP, acting as a selective activator of the brain modulable Nrf2 pathway, may be a promising candidate as a neuroprotective agent acting through the induction of phase II genes (Minelli et al. 2009a,b). Oxidative stress is a condition in which the production of ROS exceeds the cellular buffering capacity. ROS are extremely reactive species that can cause irreparable damage to macromolecules, such as proteins, nucleic acids, and lipids, thus leading to cell death/genetic mutations. Neurons are terminally differentiated cells and thus extremely susceptible to oxidative stress. Indeed, they largely depend on surrounding glial cells for GSH availability (Hsu et al., 2005; Reynolds et al., 2007). GSH is an unconventional tripeptide that undergoing redox reactions can buffer increased ROS levels and repair oxidized cellular macromolecules. Several enzymes are involved in GSH action, and the majority are under the transcriptional control of Nrf2 (see later; Brigelius-Flohé and Flohé, 2011; Minelli et al., 2009a,b). Moreover, glial cells, by acting as the immune system of the central nervous system, respond to neuroinflammatory stimuli by increasing the production of reactive nitrogen species (RNS) such as nitric oxide (NO), a very diffusible molecule that can react with ROS, in particular with superoxide anion, to produce the highly reactive and toxic peroxynitrite. This condition has been recognized as nitrosative stress. The brain is therefore very sensitive to changes in redox status, and maintaining redox homeostasis is critical for preventing oxidative damage. When glial cells are overpowered by very high levels of ROS, brain cells experience oxidative stress and nitrosative stress, which act synergistically to disrupt normal neuronal processes. In fact, markers of oxidative stress and nitrosative stress are a defining feature of all neurodegenerative diseases and strongly corroborate a causal link between ROS/RNS and neurodegeneration (Gupta et al., 2014; Leszek et al., 2016; Tsang and Chung, 2009; Valko et al., 2007). Under conditions of oxidative stress, mitochondria and the process of energy generation by oxidative phosphorylation become dysfunctional, thus generating greater levels of ROS and decreasing ATP synthesis. It worth pointing out that mitochondrial dysfunction is strongly associated with neurodegenerative diseases. Indeed, in the presence of failing mitochondria, NADPH oxidase produces superoxide anions, which combined with NO, produced mainly by inducible nitric oxide synthase, generate the highly RNS peroxynitrite (Contestabile et al., 2003; Dasuri et al., 2013; Grottelli et al., 2016; Valko et al., 2007). Since mismanaged oxidative stress signals lead to apoptosis and apoptotic cells are themselves known to release ROS, one can imagine a self-perpetuating cycle of ROS-induced apoptosis driving the apoptotic release of further ROS, leading to additional apoptosis.

In mammals, oxidative stress damage is controlled mainly by the NF-E2-related factor 2 (Nrf2) Kelch-like ECH-associated protein 1 (Keap1) system, inherited from ancestors as an antistress response, aimed at preserving cellular homeostasis. Under basal conditions, Nrf2 is sequestered by cytoplasmic Keap1 and targeted for proteasomal degradation (Bellezza et al., 2010; Brigelius-Flohé and Flohé, 2011; Itoh et al., 1999). Under conditions of oxidative stress, the Nrf2-Keap1 interaction is dissolved in a dose-dependent manner, allowing Nrf2 to translocate to the nucleus where it heterodimerizes with one of the small Maf proteins. The heterodimers recognize the antioxidant response elements (AREs) that are enhancer sequences present in the regulatory regions of Nrf2 target genes, essential for the recruitment of key factors for transcription (Suzuki et al., 2013; Suzuki and Yamamoto, 2015). Nrf2 affects the expression of nearly 500 genes that encode proteins acting as redox balancing factors, detoxifying enzymes, stress response proteins, and metabolic enzymes (Fuse and Kobayashi, 2017; Hahn et al., 2015; Yang et al., 2016), thus Nrf2 can be regarded as master regulators of the oxidative stress response. It follows that CHP, with its ability to activate the Nrf2 system, can conceivably be regarded as an antioxidant compound. It was reasoned that this capacity to induce a protective antioxidation response might make the CDP a valuable treatment for neurological disease based on oxidative damage. However, since neurological disorders are multifactorial pathologies in which crucial roles are also played by endoplasmic reticulum (ER) stress, calcium loading, excitotoxicity, and inflammation, it can be hypothesized that the beneficial effects of the dipeptide could not be solely ascribed to the activation of Nrf2.

Indeed, stressful conditions lead to the activation of several pathways, including the unfolded protein response (UPR) that is induced by misfolded proteins accumulating in the lumen of the ER, a condition recognized as ER stress. ER stress leads to the activation of three stress sensor proteins located in the ER membrane PERK (protein kinase R (PKR)—like endoplasmic reticulum kinase), ATF6 (activating transcription factor 6), and IRE1 (inositol-requiring enzyme 1), via the dissociation of the molecular chaperone GRP78/Bip (binding immunoglobulin protein/78 kDa glucose-regulated protein). This results in the general inhibition of protein translation, through PERK-mediated eif2α phosphorylation, in order to alleviate ER protein load. Furthermore, through ATF6 and IRE1α branches molecular chaperones expression is upregulated to increase the folding capacity of the cell. When the stressful stimuli overcome cellular mending capacity, homeostatic conditions cannot be restored and the cell undergoes apoptosis. Indeed, a persistent stress condition causes the induction of the transcription factor CHOP (C/EBP homologous protein), which induces the cellular machinery to initiate the apoptotic program.

A role for CHP in the regulation of UPR Has been demonstrated by finding that the CDP counteracts ER stress induced by tunicamycin in microglial cells (Bellezza et al., 2014a,b). Indeed, CHP induces a protective UPR by activating eif2α and GRP78/Bip, and protects cells from apoptosis by reducing the expression of the proapoptotic protein CHOP. These molecular events significantly reduce the tunicamycin-induced decrease in cell viability (Bellezza et al.,

2014a,b). It is noteworthy that the PERK arm of UPR activates Nrf2 that, in turn, by reducing oxidative stress, can then lessen the amount of oxidized and thus misfolded proteins.

Various studies have proposed that Nrf2 plays a critical role in counteracting the NF-κB—driven inflammatory response in a variety of experimental models (Bellezza et al., 2010, 2014a, b; Brigelius-Flohé and Flohé, 2011; Sandberg et al., 2014). The term NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) refers to a family of transcription factors that controls inflammatory responses. The most studied NF-κB family member is the p50-p65 heterodimer which, upon inflammatory stimuli, induces the expression of proinflammatory mediators. NF-κB is maintained in an inactive state in the cytoplasm through the binding to its inhibitor, inhibitor of κB (IκBα). Canonical NF-κB activation pathway relies on the activation of IKK (IκB kinase) protein kinases that phosphorylate IκBα which, in turn, is degraded by the proteasome. This event leads to NF-κB activation and nuclear translocation with the consequent upregulation of NF-κB target genes (Bellezza et al., 2010).

At the transcriptional level, NF-κB competes with transcription coactivator CREB binding protein, thus repressing Nrf2 signaling. In addition, by recruiting histone deacetylase 3 (HDAC3) and causing a local hypoacetylation, NF-κB reduces Nrf2 signaling (Wang et al., 2012). In the presence of concurrent nuclear increases in these two transcription factors, NF-κB antagonizes Nrf2-induced gene transcription, whereas all the compounds that reduce the inflammatory response by suppressing NF-κB signaling activate the Nrf2 pathway (Grottelli et al., 2016; Kim et al., 2013; Li et al., 2008; Minelli et al., 2012). This link, first suggested by studies showing that Nrf2-deficient mice exhibit a neurodegenerative phenotype (Burton et al., 2006), was substantiated by the fact that the lack of Nrf2 is associated with an increase in cytokine production (Pan et al., 2012). In the Nrf2 proximal promoter, there are several κB sites (i.e., genomic sequences recognized and bound by NF-κB); therefore in the presence of a proinflammatory stimulus such as tumor necrosis factor α (TNFα), some cells respond by upregulating Nrf2, leading to feedback suppression of cytokine gene expression (Rushworth et al., 2012). In addition, NF-κB activation can modulate Nrf2 activity as a protective anti-inflammatory mechanism via the small GTPase RAC1 (Ras-related C3 botulinum toxin substrate 1). Once activated by LPS (lipopolysaccharide), RAC1, through Nrf2 activation, upregulates HO-1 (heme-oxygenase 1) expression, which shifts the cells to a more reducing environment, essential for terminating the NF-κB activation (Cuadrado et al., 2014). The molecular mechanism of CHP action on the NF-κB system was investigated by using a mouse ear inflammation model. It was observed that CHP reduces 12-otetradecanoylphorbol-13-acetate-induced edema. Moreover, CHP interferes with the crosstalk between the antioxidant Nrf2/HO-1 and the proinflammatory NF-κB pathways in murine immortalized microglial BV2 cells challenged with the proinflammatory molecule LPS. Indeed, cyclooxygenase-2 and matrix metalloproteinase 3, two gene products governed by NF-κB, were downregulated by CHP and upregulated in heme oxygenase-1 (HO-1) knock-down cells. On the basis of these data, showing that CHP suppresses the

proinflammatory NF-κB signaling via Nrf2-mediated HO-1 activation, the use of CHP as an in vivo antiinflammatory compound has been proposed (Minelli et al., 2012). It is becoming increasingly clear that neuroinflammation is one of the features shared by all neurodegenerative diseases (Bellezza et al., 2014a,b; Dinkova-Kostova et al., 2018; González-Reyes et al., 2017). Usually triggered by peripheral inflammation, the term describes a wide range of immune responses by the central nervous system cells, such as microglia, astrocytes, and blood brain barrier, each linked by a dynamic crosstalk. In the presence of prolonged and sustained inflammation, the neuroinflammatory response results in synaptic impairment, neuronal death, and eventually neurodegeneration (Boulamery and Desplat-Jégo, 2017; Lyman et al., 2014; Rustenhoven et al., 2017). As described previously, the effects of CHP could counteract this pathogenic state in two ways: by activating Nrf2 and inducing HO-1 activity, the compound might simultaneously drive a protective antioxidant response, mitigating oxidative stress damage, while inhibiting NF-κB signaling, reducing damage associated with inflammation (Minelli et al., 2012). Based on these considerations, the inhibition of glial inflammation by the CDP was hypothesized. Systemic administration of CHP exerts antiinflammatory effects in the central nervous system by downregulating systemic (hepatic) and local (cerebral) TNFα expression, thereby counteracting LPS-induced gliosis (Bellezza et al., 2014a,b). These effects are known to decrease the detrimental effect of inflammatory neurotoxins on neurons (Catorce and Gevorkian, 2016). These data suggested a beneficial effect of CHP in a neuroinflammatory setting and its potential therapeutic utility in neuroinflammatory diseases, and we suggested that the CDP might be used also to treat other neuropathological conditions. To test this possibility more directly, Minelli and coworkers tested the effects of CHP in the microglial cells of hSOD1G93A mice. These transgenic mice, expressing the human gene encoding for (superoxide dismutase 1) SOD1 mutated in Gly93-Ala (SOD1G93A), recapitulate several aspects of amyotrophic lateral sclerosis (ALS) and provide a powerful model system to identify pathophysiological mechanisms of the disease and to screen potential therapeutic compounds (Grottelli et al., 2015, 2016). In this setting, CHP acts as an antioxidant agent even in a SOD1G93A environment, and more importantly, its effects even offered the prospect of going beyond protection toward neuronal regrowth by strongly upregulating mRNA levels of the neuronal growth factor brain-derived neurotrophic factor, a molecule linked to the preservation of existing neuronal function but also the growth and differentiation of new neurons. Thus CHP may both inhibit the neuronal damage associated with oxidative stress and microglial inflammatory responses caused by SOD1 mutations, and act directly on neurons themselves to preserve and perhaps restore their function, suggesting its possible utility as a therapeutic agent to prevent or delay disease progression in ALS (Fig. 2).

3.3 Future Perspectives

Neurodegenerative diseases are multifactorial pathologies, although each disease is characterized by distinct etiopathogenetic causes. However, common pathogenic mechanisms, such as neuroinflammation, oxidative stress, and ER stress, underpin neurodegeneration. It has

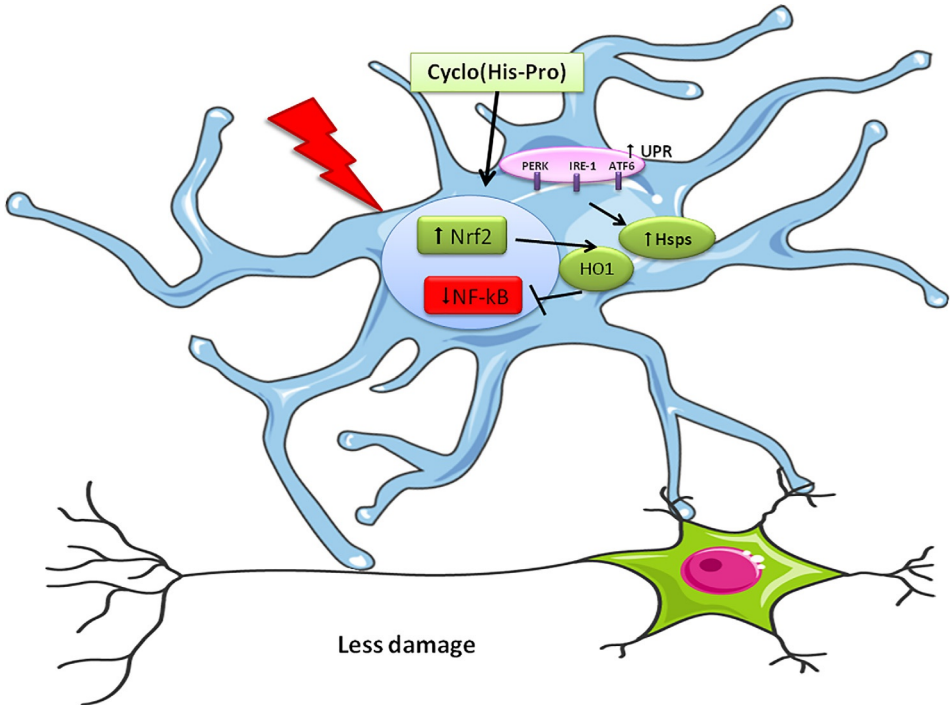

Fig. 2

Scheme of cyclo(His-Pro) action. Cyclo(His-Pro), by increasing protective unfolded protein response (UPR), by activating the antioxidant response through Nrf2 induction, and by downregulating proinflammatory response through NF-κB inhibition in microglial cells, protects neuronal cells from neurotoxic damage.

been shown that CHP can counteract each of these pathogenic pathways in several neurotoxin-exposed cellular models. So far, only the mutant SOD1 cells, the golden model for ALS, have been employed. It remains to be tested whether CHP is effective on other neurodegenerative disease-specific cellular and animal models.

Quite recently, it has been suggested that any unbalance of the gut microbiome leads to pathological signaling to the brain that might result in proinflammatory reactions, oxidative stress, and a general increase in cellular degeneration, thus contributing to multiple neurodegenerative diseases (Noble et al., 2017). The human gastrointestinal tract harbors a number of bacterial cells that outnumber by a factor of 10 the host's cells and encodes a number of genes that outnumber by a factor of 100 the host's genes. These human digestive-tract-associated microbes are now known as the *gut microbiome/microbiota*. Assessments of the number of bacterial species present in the human gut vary widely among studies, but it is generally accepted that individuals harbor more than 1000 microbial, species-level phylotypes (Lozupone et al., 2012) that can communicate via a QS mechanism (Bivar Xavier, 2018).

The role of the human gut microbiome in health and disease has been the topic of broad research, and a role for the bacterial commensals in various neurological conditions is well accepted (Byrd et al., 2018; Caballero-Villarraso et al., 2017; Cox and Weiner, 2018; Friedland and Chapman, 2017; Ho et al., 2018; Kitai and Tang, 2018; Marietta et al., 2018; Perez-Pardo et al., 2017; Roszyk and Puszczewicz, 2017; Sherwin et al., 2018; Thion et al., 2018; Yang and Duan, 2018). Indeed, the gastrointestinal tract is deeply connected with the central nervous system through the gut-brain axis, an interconnected and bidirectional network of neuroendocrine signals and immunological factors. It has been demonstrated that the gut microbiota is capable of communicating information derived from the ingested foods to the central nervous system to obtain a systemic response (Noble et al., 2017). In 1995, the presence of CHP in the gastrointestinal tract was connected to a role as a gut peptide of the entero-insular axis (Prasad, 1995). Currently, because of the highlighted role of CHP as a QS signal, capable of controlling behavior and functions of bacterial population-level responses, we propose a novel role of CHP as a modulator of the gut microbiota. Therefore, CHP, by acting directly on central nervous system cells and potentially on gut microbiota, can be considered a potential new drug for neurodegenerative diseases.

No information is currently available on the latter proposed role, since they might be validated only by preclinical trials. In this context, we hope to stimulate interest in the scientific community to test this hypothesis to produce novel therapeutic modalities for the plethora of diseases linked to gut-microbiome dysfunction.

4 Conclusion

It has been demonstrated that CHP is an endogenous CDP that can reduce oxidative and ER stress as well as inflammation, the main culprits of several neurological disorders. Thus we propose that this CDP, even orally administered, can cross the blood brain barrier and exert its beneficial effects on glial cells, whose uncontrolled response is currently recognized as one of the several causes of neuronal death. Moreover, because CHP can act as QS signal, it is plausible to suggest that this dipeptide can modulate the gut microbiome for clinical benefit in the diverse pathologies in which microbiome dysregulation is implicated.

Thus by acting directly to cease several causes of neurodegeneration and by acting indirectly on the gut microbiome linked to neurological diseases, we can potentially relieve many of the diverse contributors to neurodegenerative disease pathogenesis.

Glossary

Amyotrophic lateral sclerosis (ALS) A neurodegenerative disease characterized by muscle spasticity, rapidly progressive weakness due to muscle atrophy, and difficulty in speaking (dysarthria), swallowing (dysphagia), and breathing (dyspnea) due to degeneration of the upper and lower motor neurons. Individuals affected by the disorder may ultimately lose

the ability to control all voluntary movement, although bladder and bowel function and the muscles responsible for eye movement are usually spared until the final stages of the disease. Cognitive function is generally spared for most patients.

Biofilms A structured community of bacterial cells enclosed in a self-produced protective polymeric matrix and adherent to an inert or living surface.

Blood-brain barrier (BBB) A highly selective permeability barrier that separates the circulating blood from the brain extracellular fluid (BECF) in the CNS. Formed by endothelial cells that are connected by tight junctions, it allows the passage of molecules crucial to neural function and prevents the entry of potential neurotoxins.

Cyclic dipeptides (CDPs), or 2,5-diketopiperazines Relatively simple compounds resulting from nonenzymatic cyclization of dipeptides and their amides. They are the most common peptide derivatives found in nature and are synthesized by proteobacterial species as well as by humans. CDPs are characterized by stability to proteolysis and promotion of interactions with biological targets.

Cyclic scaffold A six-membered ring that, due to its stable structural characteristics, represents a significant pharmacophore in medicinal chemistry.

Human microbiome The human body comprises around 10 trillion cells but harbors 100 trillion bacteria, for example, on the skin and in the gut. This is the human "microbiome" and has a huge impact on human health. Nevertheless, humans, in turn, can affect their microbiome by influencing the species of bacteria that take up residence in and on their bodies.

Inflammation A response of the innate immune system to harmful stimuli such as pathogens, damaged cells, or irritants. It is a protective attempt by the organism to remove the injurious stimuli and to initiate the healing process. Classical signs are pain, heat, redness, swelling, and loss of function.

Lipopolysaccharide (LPS) A glycolipid of Gram negative bacteria of the outer membrane. It is recognized by toll-like receptor 4 (TLR4) in immune cells, where it induces the activation of a proinflammatory response.

Microglia A type of nonneural cell that constitutes the resident macrophages of the brain and spinal cord and acts as the first and main form of active immune defense in the CNS.

NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) A family of transcription factors that controls inflammatory responses. The most studied NF-κB family member is the p50-p65 heterodimer, which upon inflammatory stimuli induces the expression of proinflammatory mediators.

Quorum sensing (QS) A mechanism of cell-cell communication via secreted signaling molecules. Secreted autoinducers regulate the expression of a particular set of genes once the cell population density is sufficient to produce a threshold accumulation of the secreted autoinducer.

Reactive oxygen species (ROS) A number of reactive molecules and free radicals derived from molecular oxygen, such as singlet oxygen, superoxides, peroxides, the hydroxyl radical, and hypochlorous acid.

Thyrotropin-releasing hormone (TRH) A tripeptide hormone produced by the hypothalamus that stimulates the release of the thyroid-stimulating hormone and prolactin from the anterior pituitary.

Unfolded-protein response (UPR) An evolutionarily conserved response related to the ER stress response. The initial intent of the UPR is to adapt to the changing environment and reestablish normal ER function. When adaptation fails, ER-initiated pathways signal alarm by inducing the expression of genes encoding mediators of host defense. Excessive and prolonged ER stress triggers cell suicide, usually in the form of apoptosis, representing a last resort of multicellular organisms to dispense with dysfunctional cells.

Virulence factors Molecules expressed and secreted by pathogens (bacteria, viruses, fungi, and protozoa) that enable them to replicate and disseminate within a host in part by subverting or eluding host defenses.

Abbreviations

aaRS	amino acid tRNA synthetase
AHSL	acyl homoserine lactone
AIP	autoinducer peptides
ALS	amyotrophic lateral sclerosis
ARE	antioxidant response elements
ATF6	activating transcription factor 6
CDO	cyclic dipeptide oxidases
CDP	cyclic dipeptides
CDPS	CDP synthase
CHOP	C/EBP homologous protein
CHP	cyclo(His-Pro)
ER	endoplasmic reticulum
GRP78/Bip	binding immunoglobulin protein/78 kDa glucose-regulated protein
GSH	glutathione
HO-1	heme oxygenase-1
Hsp	heat-shock protein
IKK	IκB kinase
IRE1	inositol-requiring enzyme 1
IκBα	inhibitor of κB
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
Nrf2	NF-E2-related factor-2
NRPS	nonribosomal peptide synthetases
PCP	peptidyl carrier protein
PEG	polyethylene glycol
PERK	protein kinase R (PKR)-like endoplasmic reticulum kinase

QS	quorum sensing
RAC1	Ras-related C3 botulinum toxin substrate 1
RNS	reactive nitrogen species
ROS	reactive oxygen species
SOD1	superoxide dismutase 1
TNFα	tumor necrosis factor α
TRH	thyrotropin releasing hormone
UPR	unfolded protein response
WT	wild-type

References

Abbamondi, G.R., De Rosa, S., Iodice, C., Tommonaro, G., 2014. Cyclic dipeptides produced by marine sponge-associated bacteria as quorum sensing signals. Nat. Prod. Commun. 9, 229–232.

Balibar, C.J., Walsh, C.T., 2006. GliP, a multimodular nonribosomal peptide synthetase in Aspergillus fumigatus, makes the diketopiperazine scaffold of gliotoxin. Biochemistry 45, 15029–15038.

Bassler, B., Vogel, J., 2013. Bacterial regulatory mechanisms: the gene and beyond. Curr. Opin. Microbiol. 16, 109–111.

Battle, S.E., Meyer, F., Rello, J., Kung, V.L., Hauser, A.R., 2008. Hybrid pathogenicity island PAGI-5 contributes to the highly virulent phenotype of a *Pseudomonas aeruginosa* isolate in mammals. J. Bacteriol. 190, 7130–7140.

Beck, J.G., Chatterjee, J., Laufer, B., Kiran, M.U., Frank, A.O., Neubauer, S., Ovadia, O., Greenberg, S., Gilon, C., Hoffman, A., Kessler, H., 2012. Intestinal permeability of cyclic peptides: common key backbone motifs identified. J. Am. Chem. Soc. 134, 12125–12133.

Belin, P., Moutiez, M., Lautru, S., Seguin, J., Pernodet, J.-L., Gondry, M., 2012. The nonribosomal synthesis of diketopiperazines in tRNA-dependent cyclodipeptide synthase pathways. Nat. Prod. Rep. 29, 961.

Bellezza, I., Mierla, A.L., Minelli, A., 2010. Nrf2 and NF-κB and their concerted modulation in cancer pathogenesis and progression. Cancers (Basel) 2, 483–497.

Bellezza, I., Grottelli, S., Mierla, A.L., Cacciatore, I., Fornasari, E., Roscini, L., Cardinali, G., Minelli, A., 2014a. Neuroinflammation and endoplasmic reticulum stress are coregulated by cyclo(His-Pro) to prevent LPS neurotoxicity. Int. J. Biochem. Cell Biol. 51, 159–169.

Bellezza, I., Peirce, M.J., Minelli, A., 2014b. Cyclic dipeptides: from bugs to brain. Trends Mol. Med. 20, 551–558.

Bivar Xavier, K., 2018. Bacterial interspecies quorum sensing in the mammalian gut microbiota. C. R. Biol. 341 (5), 300. pii: S1631-0691(18), 30051-9.

Blana, V.A., Nychas, G.J., 2014. Presence of quorum sensing signal molecules in minced beef stored under various temperature and packaging conditions. Int. J. Food Microbiol. 173, 1–8.

Bockus, A.T., McEwen, C.M., Lokey, R.S., 2013. Form and function in cyclic peptide natural products: a pharmacokinetic perspective. Curr. Top. Med. Chem. 13, 821–836.

Bonnefond, L., Arai, T., Sakaguchi, Y., Suzuki, T., Ishitani, R., Nureki, O., 2011. Structural basis for nonribosomal peptide synthesis by an aminoacyl-tRNAsynthetase paralog. Proc. Natl. Acad. Sci. U. S. A. 108, 3912–3917.

Borthwick, A.D., 2012. 2,5-Diketopiperazines: synthesis, reactions, medicinal chemistry, and bioactive natural products. Chem. Rev. 112, 3641–3716.

Borthwick, A.D., Da Costa, N.C., 2017. 2,5-Diketopiperazines in food and beverages: taste and bioactivity. Crit. Rev. Food Sci. Nutr. 57, 718–742.

Borthwick, A.D., Liddle, J., Davies, D.E., Exall, A.M., Hamlett, C., Hickey, D.M., Mason, A.M., Smith, I.E., Nerozzi, F., Peace, S., Pollard, D., Sollis, S.L., Allen, M.J., Woollard, P.M., Pullen, M.A., Westfall, T.D., Stanislaus, D.J., 2012. Pyridyl-2,5-diketopiperazines as potent, selective, and orally bioavailable oxytocin antagonists: synthesis, pharmacokinetics, and in vivo potency. J. Med. Chem. 55, 783–796.

Boulamery, A., Desplat-Jégo, S., 2017. Regulation of neuroinflammation: what role for the tumor necrosis factor-like weak inducer of apoptosis/Fn14 pathway? Front. Immunol. 8, 1534.
Brigelius-Flohé, R., Flohé, L., 2011. Basic principles and emerging concepts in the redox control of transcription factors. Antioxid. Redox Signal. 15, 2335–2381.
Brown, R.E., Ghannoum, M.A., Mukherjee, P.K., Gillevet, P.M., Sikaroodi, M., 2015. Quorum-sensing dysbiotic shifts in the HIV-infected oral metabiome. PLoS One 10, e0123880.
Burton, N.C., Kensler, T.W., Guilarte, T.R., 2006. In vivo modulation of the Parkinsonian phenotype by Nrf2. Neurotoxicology 27, 1094–1100.
Byrd, A.L., Belkaid, Y., Segre, J.A., 2018. The human skin microbiome. Nat. Rev. Microbiol. 16, 143–155.
Caballero-Villarraso, J., Galvan, A., Escribano, B.M., Túnez, I., 2017. Interrelationships between gut microbiota and the host: paradigms, role in neurodegenerative diseases and future prospects. CNS Neurol. Disord. Drug Targets 16, 945–964.
Campbell, J., Lin, Q., Geske, G.D., Blackwell, H.E., 2009. New and unexpected insights into the modulation of Lux R-type quorum sensing by cyclic dipeptides. ACS Chem. Biol. 4, 1051–1059.
Catorce, M.N., Gevorkian, G., 2016. LPS-induced murine neuroinflammation model: main features and suitability for pre-clinical assessment of nutraceuticals. Curr. Neuropharmacol. 14, 155–164.
Chen, M.Z., Dewis, M.L., Kraut, K., Merritt, D., Reiber, L., Trinnaman, L., Da Costa, N.C., 2009. 2,5 Diketopiperazines(cyclic dipeptides) in beef: identification, synthesis, and sensory evaluation. J. Food Sci. 74, C100–C105.
Choi, S.A., Suh, H.J., Yun, J.W., Choi, J.W., 2012. Differential gene expression in pancreatic tissues of streptozocin-induced diabetic rats and genetically-diabetic mice in response to hypoglycemic dipeptide cyclo(His-Pro) treatment. Mol. Biol. Rep. 39, 8821–8835.
Clardy, J., Walsh, C., 2004. Lessons from natural molecules. Nature 432, 829–837.
Clardy, J., Fischbach, M.A., Walsh, C.T., 2006. New antibiotics from bacterial natural products. Nat. Biotechnol. 24, 1541–1550.
Clément, P., Bernabé, J., Compagnie, S., Alexandre, L., McCallum, S., Giuliano, F., 2013. Inhibition of ejaculation by the non-peptide oxytocin receptor antagonist GSK557296: a multi-level site of action. Br. J. Pharmacol. 169, 1477–1485.
Contestabile, A., Monti, B., Contestabile, A., Ciani, E., 2003. Brain nitric oxide and its dual role in neurodegeneration/neuroprotection: understanding molecular mechanisms to devise drug approaches. Curr. Med. Chem. 10, 2147–2174.
Cook, L.C., Federle, M.J., 2014. Peptide pheromone signaling in Streptococcus and Enterococcus. FEMS Microbiol. Rev. 38, 473–492.
Cornacchia, C., Cacciatore, I., Baldassarre, L., Mollica, A., Feliciani, F., Pinnen, F., 2012. 2,5-Diketopiperazines as neuroprotective agents. Mini Rev. Med. Chem. 12, 2–12.
Cornforth, D.M., Popat, R., McNally, L., Gurney, J., Scott-Phillips, T.C., Ivens, A., Diggle, S.P., Brown, S.P., 2014. Combinatorial quorum sensing allows bacteria to resolve their social and physical environment. Proc. Natl. Acad. Sci. U. S. A. 111, 4280–4284.
Correia, T., Grammel, N., Ortel, I., Keller, U., Tudzynski, P., 2003. Molecular cloning and analysis of the ergopeptine assembly system in the ergot fungus *Claviceps purpurea*. Chem. Biol. 10, 1281–1292.
Cox, L.M., Weiner, H.L., 2018. Microbiota signaling pathways that influence neurologic disease. Neurotherapeutics 15, 135–145.
Cuadrado, A., Martin-Moldes, Z., Ye, J., Lastres-Becker, I., 2014. Transcription factors NRF2 and NF-kappaB are coordinated effectors of the Rho family, GTP-binding protein RAC1 during inflammation. J. Biol. Chem. 289, 15244–15258.
Dandekar, A.A., Greenberg, E.P., 2013. Microbiology: plan B for quorum sensing. Nat. Chem. Biol. 9, 292–293.
Dasuri, K., Zhang, L., Keller, J.N., 2013. Oxidative stress, neurodegeneration, and the balance of protein degradation and protein synthesis. Free Radic. Biol. Med. 62, 170–185.
de Abreu, P.M., Farias, P.G., Paiva, G.S., Almeida, A.M., Morais, P.V., 2014. Persistence of microbial communities including *Pseudomonas aeruginosa* in a hospital environment: a potential health hazard. BMC Microbiol. 14, 118.

de Kievit, T.R., Iglewski, B.H., 2000. Bacterial quorum sensing in pathogenic relationships. Infect. Immun. 68, 4839–4849.

De Rosa, S., Mitova, M., Tommonaro, G., 2003. Marine bacteria associated with sponge as source of cyclic peptides. Biomol. Eng. 20, 311–316.

Degrassi, G., Aguilar, C., Bosco, M., Zahariev, S., Pongor, S., Venturi, V., 2002. Plant growth-promoting *Pseudomonas putida* WCS358 produces and secretes four cyclic dipeptides: cross-talk with quorum sensing bacterial sensors. Curr. Microbiol. 45, 250–254.

Diggle, S.P., Gardner, A., West, S., Griffin, A.S., 2007. Evolutionary theory about bacterial quorum sensing: when is a signal not a signal? Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci. 362, 1241–1249.

Dinkova-Kostova, A.T., Kostov, R.V., Kazantsev, A.G., 2018. The role of Nrf2 signaling in counteracting neurodegenerative diseases. FEBS J. https://doi.org/10.1111/febs.14379.

Eguchi, C., Kakuta, A., 1974. Cyclic dipeptides, I. Thermodynamics of the cis-trans isomerization of the side chains in cyclic dipeptides. J. Am. Chem. Soc. 96, 3985–3989.

Einholm, A.P., Pedersen, K.E., Wind, T., Kulig, P., Overgaard, M.T., Jensen, J.K., Bødker, J.S., Christensen, A., Charlton, P., Andreasen, P.A., 2003. Biochemical mechanism of action of a diketopiperazine inactivator of plasminogen activator inhibitor-1. Biochem. J. 373, 723–732.

Ellison, D.W., Miller, V.L., 2006. Regulation of virulence by members of the MarR/SlyA family. Curr. Opin. Microbiol. 9, 153–159.

Engel, S., Jensen, P.R., Fenical, W., 2002. Chemical ecology of marine microbial defense. J. Chem. Ecol. 28, 1971–1985.

Faden, A.I., Jacobs, T.P., Holaday, J.W., 1981. Thyrotropin-releasing hormone improves neurologic recovery after spinal trauma in cats. N. Engl. J. Med. 305, 1063–1067.

Faden, A.I., Knoblach, S.M., Movsesyan, V.A., Cernak, I., 2004. Novel small peptides with neuroprotective and nootropic properties. J. Alzheimers Dis. 6, S93–S97.

Faden, A.I., Movsesyan, V.A., Knoblach, S.M., Ahmed, F., Cernak, I., 2005. Neuroprotective effects of novel small peptides in vitro and after brain injury. Neuropharmacology 49, 410–424.

Felnagle, E.A., Jackson, E.E., Chan, Y.A., Podevels, A.M., Berti, A.D., McMahon, M.D., Thomas, M.G., 2008. Nonribosomal peptide synthetases involved in the production of medically relevant natural products. Mol. Pharm. 5, 191–211.

Friedland, R.P., Chapman, M.R., 2017. The role of microbial amyloid in neurodegeneration. PLoS Pathog. 13, e1006654.

Friedrich, A.B., Fischer, I., Proksch, P., Hacker, J., Hentschel, U., 2001. Temporal variation of the microbial community associated with the mediterranean sponge *Aplysina aerophoba*. FEMS Microbiol. Ecol. 38, 105–113.

Fuqua, C., Greenberg, E.P., 2002. Listening in on bacteria: acylhomoserine lactone signalling. Nat. Rev. Mol. Cell Biol. 3, 685–695.

Fuse, Y., Kobayashi, M., 2017. Conservation of the Keap1-Nrf2 system: an evolutionary journey through stressful space and time. Molecules. 22, pii: E436.

Fusetani, N., Matsunaga, S., 1993. Bioactive sponge peptides. Chem. Rev. 93, 1793–1806.

Gallagher, L.A., McKnight, S.L., Kuznetsova, M.S., Pesci, E.C., Manoil, C., 2002. Functions required for extracellular quinolone signaling by *Pseudomonas aeruginosa*. J. Bacteriol. 184, 6472–6480.

Galloway, W.R.J.D., Hodgkinson, J.T., Bowden, S.D., Welch, M., Spring, D.R., 2011. Quorum sensing in gram-negative bacteria: small molecule modulation of AHL and AI-2 quorum sensing pathways. Chem. Rev. 111, 28–67.

García-Estrada, C., Ullán, R.V., Albillos, S.M., Fernández-Bodega, M.Á., Durek, P., vonDöhren, H., Martín, J.F., 2011. A single cluster of coregulated genes encodes the biosynthesis of the mycotoxins roquefortine C and meleagrin in *Penicillium chrysogenum*. Chem. Biol. 18, 1499–1512.

Gardiner, D.M., Cozijnsen, A.J., Wilson, L.M., Pedras, M.S.C., Howlett, B.J., 2004. The sirodesmin biosynthetic gene cluster of the plant pathogenic fungus *Leptosphaeria maculans*. Mol. Microbiol. 53, 1307–1318.

Gautschi, M., Schmid, J.P., Peppard, T.L., Ryan, T.P., Tuorto, R.M., Yang, X., 1997. Chemical characterization of diketopiperazines in beer. J. Agric. Food Chem. 45, 3183–3189.

Giessen, T.W., Marahiel, M.A., 2012. Ribosome-independent biosynthesis of biologically active peptides: application of synthetic biology to generate structural diversity. FEBS Lett. 586, 2065–2075.
Giessen, T., Marahiel, M., 2014. The tRNA-dependent biosynthesis of modified cyclic dipeptides. Int. J. Mol. Sci. 15, 14610–14631.
Giessen, T.W., Von Tesmar, A.M., Marahiel, M.A., 2013. Insights into the generation of structural diversity in a tRNA-dependent pathway for highly modified bioactive cyclic dipeptides. Chem. Biol. 20, 828–838.
Ginz, M., Engelhardt, U.H., 2000. Identification of proline-based diketopiperazines in roasted coffee. J. Agric. Food Chem. 48, 3528–3532.
Gondry, M., Lautru, S., Fusai, G., Meunier, G., Ménez, A., Genet, R., 2001. Cyclic dipeptide oxidase from *Streptomyces noursei*. Eur. J. Biochem. 268, 1712–1721.
Gondry, M., Sauguet, L., Belin, P., Thai, R., Amouroux, R., Tellier, C., Tuphile, K., Jacquet, M., Braud, S., Courcon, M., Masson, C., Dubois, S., Lautru, S., Lecoq, A., Hashimoto, S., Genet, R., Pernodet, J.L., 2009. Cyclodipeptide synthases are a family of tRNA-dependent peptide bond-forming enzymes. Nat. Chem. Biol. 5, 414–420.
Gonzalez, J.F., Ortin, I., de la Cuesta, E., Menendez, J.C., 2012. Privileged scaffolds in synthesis: 2,5-piperazinediones as templates for the preparation of structurally diverse heterocycles. Chem. Soc. Rev. 41, 6902–6915.
González, O., Ortíz-Castro, R., Díaz-Pérez, C., Díaz-Pérez, A.L., Magaña-Dueñas, V., López-Bucio, J., Campos-García, J., 2017. Non-ribosomal peptide synthases from *Pseudomonas aeruginosa* play a role in cyclodipeptide biosynthesis, quorum-sensing regulation, and root development in a plant host. Microb. Ecol. 73, 616–629.
González-Reyes, R.E., Nava-Mesa, M.O., Vargas-Sánchez, K., Ariza-Salamanca, D., Mora-Muñoz, L., 2017. Involvement of astrocytes in Alzheimer's disease from a neuroinflammatory and oxidative stress perspective. Front. Mol. Neurosci. 10, 427.
Gram, L., Dalgaard, P., 2002. Fish spoilage bacteria-problems and solutions. Curr. Opin. Biotechnol. 13, 262–266.
Grottelli, S., Bellezza, I., Morozzi, G., Peirce, M.J., Marchetti, C., Cacciatore, I., Costanzi, E., Minelli, A., 2015. Cyclo(His-Pro) protects SOD1G93A microglial cells from Paraquat-induced toxicity. J. Clin. Cell. Immunol. 6, 287.
Grottelli, S., Ferrari, I., Pietrini, G., Peirce, M.J., Minelli, A., Bellezza, I., 2016. The role of cyclo(His-Pro) in neurodegeneration. Int. J. Mol. Sci. 17, pii: E1332.
Gruenewald, S., Mootz, H.D., Stehmeier, P., Stachelhaus, T., 2004. In vivo production of artificial nonribosomal peptide products in the heterologous host *Escherichia coli*. Appl. Environ. Microbiol. 70, 3282–3291.
Gu, Q., Fu, L., Wang, Y., Lin, J., 2013. Identification and characterization of extracellular cyclic dipeptides as quorum-sensing signal molecules from *Shewanella baltica*, the specific spoilage organism of *Pseudosciaena crocea* during 4°C storage. J. Agric. Food Chem. 61, 11645–11652.
Gupta, S.P., Yadav, S., Singhal, N.K., Tiwari, M.N., Mishra, S.K., Singh, M.P., 2014. Does restraining nitric oxide biosynthesis rescue from toxins-induced parkinsonism and sporadic Parkinson's disease? Mol. Neurobiol. 49, 262–275.
Hahn, M.E., Timme-Laragy, A.R., Karchner, S.I., Stegeman, J.J., 2015. Nrf2 and Nrf2-related proteins in development and developmental toxicity: insights from studies in zebrafish (*Danio rerio*). Free Radic. Biol. Med. 88, 275–289.
Hallmann, A., 2011. Evolution of reproductive development in the volvocine algae. Sex. Plant Reprod. 24, 97–112.
Hawver, L.A., Jung, S.A., Ng, W.L., 2016. Specificity and complexity in bacterial quorum-sensing systems. FEMS Microbiol. Rev. 40, 738–752.
Healy, F.G., Krasnoff, S.B., Wach, M., Gibson, D.M., Loria, R., 2002. Involvement of a cytochrome P450 monooxygenase in thaxtomin A biosynthesis by *Streptomyces acidiscabies*. J. Bacteriol. 184, 2019–2029.
Hense, B.A., Schuster, M., 2015. Core principles of bacterial autoinducer systems. Microbiol. Mol. Biol. Rev. 79 (1), 153–169.
Hentschel, U., Schmid, M., Wagner, M., Fieseler, L., Gernert, C., Hacker, J., 2001. Isolation and phylogenetic analysis of bacteria with antimicrobial activities from the Mediterranean sponges *Aplysina aerophoba* and *Aplysina cavernicola*. FEMS Microbiol. Ecol. 35, 305–312.

Ho, L., Ono, K., Tsuji, M., Mazzola, P., Singh, R., Pasinetti, G.M., 2018. Protective roles of intestinal microbiota derived short chain fatty acids in Alzheimer's disease-type beta-amyloid neuropathological mechanisms. Expert. Rev. Neurother. 18, 83–90.

Hogan, D.A., 2006. Talking to themselves: autoregulation and quorum sensing in fungi. Eukaryot. Cell 5, 613–619.

Holden, M.T., Ram Chhabra, S., de Nys, R., Stead, P., Bainton, N.J., Hill, P.J., Manefield, M., Kumar, N., Labatte, M., England, D., Rice, S., Givskov, M., Salmond, G.P., Stewart, G.S., Bycroft, B.W., Kjelleberg, S., Williams, P., 1999. Quorum-sensing cross talk: isolation and chemical characterization of cyclic dipeptides from *Pseudomonas aeruginosa* and other gram-negative bacteria. Mol. Microbiol. 33, 1254–1266.

Hsu, M., Srinivas, B., Kumar, J., Subramanian, R., Andersen, J., 2005. Glutathione depletion resulting in selective mitochondrial complex I inhibition in dopaminergic cells is via an NO-mediated pathway not involving peroxynitrite: implications for Parkinson's disease. J. Neurochem. 92, 1091–1103.

Huang, R., Zhou, X., Xu, T., Yang, X., Liu, Y., 2010. Diketopiperazines from marine organisms. Chem. Biodivers. 7, 2809–2829.

Itoh, K., Ishii, T., Wakabayashi, N., Yamamoto, M., 1999. Regulatory mechanisms of cellular response to oxidative stress. Free Radic. Res. 31, 319–324.

Jayatilake, G.S., Thornton, M.P., Leonard, A.C., Grimwade, J.E., Baker, B.J., 1996. Metabolites from an Antarctic sponge-associated bacterium, *Pseudomonas aeruginosa*. J. Nat. Prod. 59, 293–296.

Jung, E.Y., Lee, H.S., Choi, J.W., Ra, K.S., Kim, M.R., Suh, H.J., 2011. Glucose tolerance and antioxidant activity of spent brewer's yeast hydrolysate with a high content of cyclo-His-Pro (CHP). J. Food Sci. 76, C272–C278.

Jung, E.Y., Hong, Y.H., Park, C., Suh, H.J., 2016. Effects of cyclo-His-Pro-enriched yeast hydrolysate on blood glucose levels and lipid metabolism in obese diabetic ob/ob mice. Nutr. Res. Pract. 10, 154–160.

Kim, S.W., Lee, H.K., Shin, J.H., Lee, J.K., 2013. Up-down regulation of HO-1 and iNOS gene expressions by ethyl pyruvate via recruiting p300 to Nrf2 and depriving it from p65. Free Radic. Biol. Med. 65, 468–476.

Kitai, T., Tang, W.H.W., 2018. Gut microbiota in cardiovascular disease and heart failure. Clin. Sci. (Lond.) 132, 85–91.

Koglin, A., Walsh, C.T., 2009. Structural insights into nonribosomal peptide enzymatic assembly lines. Nat. Prod. Rep. 26, 987–1000.

Koo, K.B., Suh, H.J., Ra, K.S., Choi, J.W., 2011. Protective effect of cyclo(His-Pro) on streptozotocin-induced cytotoxicity and apoptosis in vitro. J. Microbiol. Biotechnol. 21, 218–227.

Kumar, N., Gorantla, J.N., Mohandas, C., Nambisan, B., Lankalapalli, R.S., 2013. Isolation and antifungal properties of cyclo(d-Tyr-l-Leu) diketopiperazine isolated from *Bacillus* sp. associated with rhabditid entomopathogenic nematode. Nat. Prod. Res. 27, 2168–2172.

Kwak, M.K., Liu, R., Kwon, J.O., Kim, M.K., Kim, A.H., Kang, S.O., 2013. Cyclic dipeptides from lactic acid bacteria inhibit proliferation of the influenza A virus. J. Microbiol. 51, 836–843.

Kwak, M.K., Liu, R., Kim, M.K., Moon, D., Kim, A.H., Song, S.H., Kang, S.O., 2014. Cyclic dipeptides from lactic acid bacteria inhibit the proliferation of pathogenic fungi. J. Microbiol. 52, 64–70.

Lahoud, G., Hou, Y.-M., 2010. Biosynthesis: a new (old) way of hijacking tRNA. Nat. Chem. Biol. 6, 795–796.

Lazos, O., Tosin, M., Slusarczyk, A.L., Boakes, S., Cortés, J., Sidebottom, P.J., Leadlay, P.F., 2010. Biosynthesis of the putative siderophore erythrochelin requires unprecedented crosstalk between separate nonribosomal peptide gene clusters. Chem. Biol. 17, 160–173.

Lee, J., Zhang, L., 2015. The hierarchy quorum sensing network in *Pseudomonas aeruginosa*. Protein Cell 6, 26–41.

Lee, J., Wu, J., Deng, Y., Wang, J., Wang, C., Wang, J., Chang, C., Dong, Y., Williams, P., Zhang, L.-H., 2013. A cell-cell communication signal integrates quorum sensing and stress response. Nat. Chem. Biol. 9, 339–343.

Lee, H.J., Son, H.S., Park, C., Suh, H.J., 2015. Preparation of yeast hydrolysate enriched in cyclo-His-Pro (CHP) by enzymatic hydrolysis and evaluation of its functionality. Prev. Nutr. Food Sci. 20, 284–291.

Lehrer, R.I., Cole, A.M., Selsted, M.E., 2012. θ-Defensins: cyclic peptides with endless potential. J. Biol. Chem. 287, 27014–27019.

Leszek, J., Barreto, G.E., Gąsiorowski, K., Koutsouraki, E., Ávila-Rodrigues, M., Aliev, G., 2016. Inflammatory mechanisms and oxidative stress as key factors responsible for progression of neurodegeneration: role of brain innate immune system. CNS Neurol. Disord. Drug Targets 15, 1–8.

Li, W., Khor, T.O., Xu, C., Shen, G., Jeong, W.S., Yu, S., Kong, A.N., 2008. Activation of Nrf2-antioxidant signaling attenuates NFkappaB-inflammatory response and elicits apoptosis. Biochem. Pharmacol. 76, 1485–1489.

Li, J., Wang, W., Xu, S.X., Magarvey, N.A., McCormick, J.K., 2011. *Lactobacillus reuteri*-produced cyclic dipeptides quench agr-mediated expression of toxic shock syndrome toxin-1 in staphylococci. Proc. Natl. Acad. Sci. U. S. A. 108 (8), 3360–3365.

Liskamp, R.M.J., Rijkers, D.T.S., Kruijtzer, J.A.W., Kemmink, J., 2011. Peptides and proteins as a continuing exciting source of inspiration for peptidomimetics. ChemBioChem 12, 1626–1653.

Liu, M., Gray, J.M., Griffiths, M.W., 2006. Occurrence of proteolytic activity an N-acylhomoserine lactone signals in the spoilage of aerobically chill-stored proteinaceous raw foods. J. Food Prot. 69, 2729–2737.

Liu, R., Kim, A.H., Kwak, M.K., Kang, S.O., 2017. Proline-based cyclic dipeptides from Korean fermented vegetable kimchi and from *Leuconostoc mesenteroides* LBP-K06 have activities against multidrug-resistant bacteria. Front. Microbiol. 8, 761.

Lozupone, C.A., Stombaugh, J.I., Gordon, J.I., Jansson, J.K., Knight, R., 2012. Diversity, stability and resilience of the human gut microbiota. Nature 489, 220–230.

Lyman, M., Lloyd, D.G., Ji, X., Vizcaychipi, M.P., Ma, D., 2014. Neuroinflammation: the role and consequences. Neurosci. Res. 79, 1–12.

Maiya, S., Grundmann, A., Li, S.-M., Turner, G., 2006. The fumitremorgin gene cluster of *Aspergillus fumigatus*: identification of a gene encoding brevianamide F synthetase. ChemBioChem 7, 1062–1069.

Marchesan, J.T., Morelli, T., Moss, K., Barros, S.P., Ward, M., Jenkins, W., Aspiras, M.B., Offenbacher, S., 2015. Association of synergistetes and cyclodipeptides with periodontitis. J. Dent. Res. 94 (10), 1425–1431.

Marietta, E., Horwath, I., Taneja, V., 2018. Microbiome, immunomodulation, and the neuronal system. Neurotherapeutics 15, 23–30.

Menegatti, S., Hussain, M., Naik, A.D., Carbonell, R.G., Rao, B.M., 2013. mRNA display selection and solid-phase synthesis of Fc-binding cyclic peptide affinity ligands. Biotechnol. Bioeng. 110, 857–870.

Minelli, A., Bellezza, I., Grottelli, S., Pinnen, F., Brunetti, L., Vacca, M., 2006. Phosphoproteomic analysis of the effect of cyclo-[His-Pro] dipeptide on PC12 cells. Peptides 27, 105–113.

Minelli, A., Bellezza, I., Grottelli, S., Galli, F., 2008. Focus on cyclo(His-Pro): history and perspectives as antioxidant peptide. Amino Acids 35, 283–289.

Minelli, A., Conte, C., Grottelli, S., Bellezza, I., Cacciatore, I., Bolaños, J.P., 2009a. Cyclo(His-Pro) promotes cytoprotection by activating Nrf2-mediated up-regulation of antioxidant defence. J. Cell. Mol. Med. 13, 1149–1161.

Minelli, A., Conte, C., Grottelli, S., Bellezza, I., Emiliani, C., Bolaños, J.P., 2009b. Cyclo(His-Pro) up-regulates heme oxygenase 1 via activation of Nrf2-ARE signalling. J. Neurochem. 111, 956–966.

Minelli, A., Grottelli, S., Mierla, A., Pinnen, F., Cacciatore, I., Bellezza, I., 2012. Cyclo(His-Pro) exerts anti-inflammatory effects by modulating NF-κB and Nrf2 signalling. Int. J. Biochem. Cell Biol. 44, 525–535.

Mishra, A.K., Choi, J., Choi, S.J., Baek, K.H., 2017. Cyclodipeptides: an overview of their biosynthesis and biological activity. Molecules 22 (10), 1796.

Mitova, M., Tommonaro, G., Hentschel, U., Müller, W.E.G., De Rosa, S., 2004. Exocellular cyclic dipeptides from a *Ruegeria* strain associated with cell cultures of *Suberites domuncula*. Mar. Biotechnol. 6, 95–103.

Monnet, V., Juillard, V., Gardan, R., 2016. Peptide conversations in gram-positive bacteria. Crit. Rev. Microbiol. 42, 339–351.

Morley, J.E., Levine, A.S., Prasad, C., 1981. Histidyl-proline diketopiperazine decreases food intake in rats. Brain Res. 210, 475–478.

Moussa, S.H., Kuznetsov, V., Tran, T.A., Sacchettini, J.C., Young, R., 2012. Protein determinants of phage T4 lysis inhibition. Protein Sci. 21, 571–582.

Moutiez, M., Schmitt, E., Seguin, J., Thai, R., Favry, E., Belin, P., Mechulam, Y., Gondry, M., 2014. Unravelling the mechanism of non-ribosomal peptide synthesis by cyclodipeptide synthases. Nat. Commun. 5, 5141.

Ng, W.L., Bassler, B.L., 2009. Bacterial quorum-sensing network architectures. Annu. Rev. Genet. 43, 197–222.

Nicholson, B., Lloyd, G.K., Miller, B.R., Palladino, M.A., Kiso, Y., Hayashi, Y., et al., 2006. NPI-2358 is a tubulin-depolymerizing agent: in vitro evidence for activity as a tumor vascular-disrupting agent. Anti-Cancer Drugs 17, 25–31.

Noble, E.E., Hsu, T.M., Kanoski, S.E., 2017. Gut to brain dysbiosis: mechanisms linking western diet consumption, the microbiome, and cognitive impairment. Front. Behav. Neurosci. 11, 9.

Ortiz-Castro, R., Díaz-Pérez, C., Martínez-Trujillo, M., del Río, R.E., Campos-García, J., López-Bucio, J., 2011. Transkingdom signaling based on bacterial cyclodipeptides with auxin activity in plants. Proc. Natl. Acad. Sci. U. S. A. 108, 7253–7258.

Pan, H., Wang, H., Wang, X., Zhu, L., Mao, L., 2012. The absence of Nrf2 enhances NF-kappaB-dependent inflammation following scratch injury in mouse primary cultured astrocytes. Mediat. Inflamm. 2012217580.

Park, D.K., Lee, K.E., Baek, C.H., Kim, I.H., Kwon, J.H., Lee, W.K., Lee, K.H., Kim, B.S., Choi, S.H., Kim, K.S., 2006. Cyclo(Phe-Pro) modulates the expression of ompU in *Vibrio* spp. J. Bacteriol. 188, 2214–2221.

Park, S.W., Choi, S.A., Yun, J.W., Choi, J.W., 2012. Alterations in pancreatic protein expression in STZ-induced diabetic rats and genetically diabetic mice in response to treatment with hypoglycemic dipeptide cyclo(His-Pro). Cell. Physiol. Biochem. 29, 603–616.

Perez-Pardo, P., Hartog, M., Garssen, J., Kraneveld, A.D., 2017. Microbes tickling your tummy: the importance of the gut-brain axis in Parkinson's disease. Curr. Behav. Neurosci. Rep. 4, 361–368.

Prasad, C., 1995. Bioactive cyclic dipeptides. Peptides 16, 1511–1564.

Prasad, C., 2001. Role of endogenous cyclo(His-Pro) in voluntary alcohol consumption by alcohol-preferring C57Bl mice. Peptides 22, 2113–2118.

Prasad, C., Peterkofsky, A., 1976. Demonstration of pyroglutamyl peptidase and amidase activities toward thyrotropin-releasing hormone in hamster hypothalamic extracts. J. Biol. Chem. 251, 3229–3234.

Proksch, P., Edrada, R.A., Ebel, R., 2002. Drugs from the seas—current status and microbiological implications. Appl. Microbiol. Biotechnol. 59 (2–3), 125–134.

Prosperini, A., Berrada, H., Ruiz, M.J., Caloni, F., Coccini, T., Spicer, L.J., Perego, M.C., Lafranconi, A., 2017. A review of the mycotoxin enniatin B. Front. Public Health 5, 304.

Rash, M., Andersen, J.B., Nielsen, K.F., Flodgaard, L.R., Christensen, H., Givskov, M., Gram, L., 2005. Involvement of bacterial quorum-sensing signals in spoilage of bean sprouts. Appl. Environ. Microbiol. 71, 3321–3330.

Reynolds, A., Laurie, C., Mosley, R.L., Gendelman, H.E., 2007. Oxidative stress and the pathogenesis of neurodegenerative disorders. Int. Rev. Neurobiol. 82, 297–325.

Rhee, K.H., 2004. Cyclic dipeptides exhibit synergistic, broad spectrum antimicrobial effects and have anti-mutagenic properties. Int. J. Antimicrob. Agents 24, 423–427.

Rocha-Estrada, J., Aceves-Diez, A.E., Guarneros, G., de la Torre, M., 2010. The RNPP family of quorum-sensing proteins in Gram-positive bacteria. Appl. Microbiol. Biotechnol. 87, 913–923.

Rojas Murcia, N., Lee, X., Waridel, P., Maspoli, A., Imker, H.J., Chai, T., Walsh, C.T., Reimmann, C., 2015. The *Pseudomonas aeruginosa* antimetabolite L-2-amino-4-methoxy-trans-3-butenoic acid (AMB) is made from glutamate and two alanine residues via a thiotemplate-linked tripeptide precursor. Front. Microbiol. 6, 170.

Rosier, A., Bishnoi, U., Lakshmanan, V., Sherrier, D.J., Bais, H.P., 2016. A perspective on inter-kingdom signaling in plant-beneficial microbe interactions. Plant Mol. Biol. 90, 537–548.

Roszyk, E., Puszczewicz, M., 2017. Role of human microbiome and selected bacterial infections in the pathogenesis of rheumatoid arthritis. Reumatologia 55, 242–250.

Rushworth, S.A., Zaitseva, L., Murray, M.Y., Shah, N.M., Bowles, K.M., Mac Ewan, D.J., 2012. The high Nrf2 expression in human acute myeloid leukemia is driven by NF-kappaB and underlies its chemo-resistance. Blood 120, 5188–5198.

Rustenhoven, J., Jansson, D., Smyth, L.C., Dragunow, M., 2017. Brain pericytes as mediators of neuroinflammation. Trends Pharmacol. Sci. 38, 291–304.

Ryan, R.P., An, S.Q., Allan, J.H., McCarthy, Y., Dow, J.M., 2015. The DSF family of cell-cell signals: an expanding class of bacterial virulence regulators. PLoS Pathog. 11, e1004986.

Sandberg, M., Patil, J., D'Angelo, B., Weber, S.G., Mallard, C., 2014. NRF2-regulation in brain health and disease: implication of cerebral inflammation. Neuropharmacology 79, 298–306.

Sauguet, L., Moutiez, M., Li, Y., Belin, P., Seguin, J., Le Du, M.H., Thai, R., Masson, C., Fonvielle, M., Pernodet, J.L., Charbonnier, J.B., Gondry, M., 2011. Cyclodipeptide synthases, a family of class-I aminoacyl-tRNA synthetase-like enzymes involved in non-ribosomal peptide synthesis. Nucleic Acids Res. 39, 4475–4489.

Schluter, J., Schoech, A.P., Foster, K.R., Mitri, S., 2016. The evolution of quorum sensing as a mechanism to infer kinship. PLoS Comput. Biol. 12, e1004848.
Schmidt, E.W., Obraztsova, A.Y., Davidson, S.K., Faulkner, D.J., Haygood, M.G., 2000. Identification of the antifungal peptide-containing symbiont of the marine sponge *Theonella swinhoei* as a novel δ-proteobacterium, "Candidatus Entotheonella palauensis" Mar. Biol. 136, 969–977.
Schmitz, F.J., Vanderah, D.J., Hollenbeak, K.H., Enwall, C.E.L., Gopichand, Y., SenGupta, P.K., Hossain, M.B., van der Helm, D., 1983. Metabolites from the marine sponge *Tedania ignis*. A new atisanediol and several known diketopiperazines. J. Org. Chem. 48, 3941–3945.
Schultz, A.W., Oh, D.-C., Carney, J.R., Williamson, R.T., Udwary, D.W., Jensen, P.R., Gould, S.J., Fenical, W., Moore, B.S., 2008. Biosynthesis and structures of cyclomarins and cyclomarazines, prenylated cyclic peptides of marine actinobacterial origin. J. Am. Chem. Soc. 130, 4507–4516.
Schwarzer, D., Finking, R., Marahiel, M.A., 2003. Nonribosomal peptides: from genes to products. Nat. Prod. Rep. 20, 275–287.
Sherwin, E., Dinan, T.G., Cryan, J.F., 2018. Recent developments in understanding the role of the gut microbiota in brain health and disease. Ann. N. Y. Acad. Sci. 1420 (1), 5–25.
Shiboski, C.H., 2002. HIV-related oral disease epidemiology among women: year 2000 update. Oral Dis. 8 (Suppl 2), 44–48.
Shiboski, C.H., Wilson, C.M., Greenspan, D., Hilton, J., Greenspan, J.S., Moscicki, A.B., Adolescent Medicine HIV/AIDS Research Network, 2001. HIV-related oral manifestations among adolescents in a multicenter cohort study. J. Adolesc. Health 29, 109–114.
Sjögren, M., Jonsson, P.R., Dahlström, M., Lundälv, T., Burman, R., Göransson, U., Bohlin, L., 2011. Two brominated cyclic dipeptides released by the coldwater marine sponge *Geodia barretti* act in synergy as chemical defense. J. Nat. Prod. 74, 449–454.
Skandamis, P.N., Nychas, G.J., 2012. Quorum sensing in the context of food microbiology. Appl. Environ. Microbiol. 78, 5473–5482.
Sprague Jr., G.F., Winans, S.C., 2006. Eukaryotes learn to count: quorum sensing by yeast. Genes Dev. 20, 1045–1049.
Stierle, A.C., Cardellina IInd, J.H., Singleton, F.L., 1988. A marine *Micrococcus* produces metabolites ascribed to the sponge *Tedania ignis*. Experientia 44, 1021.
Strieker, M., Tanović, A., Marahiel, M.A., 2010. Nonribosomal peptide synthetases: structures and dynamics. Curr. Opin. Struct. Biol. 20, 234–240.
Suzuki, T., Yamamoto, M., 2015. Molecular basis of the Keap1-Nrf2 system. Free Radic. Biol. Med. 88, 93–100.
Suzuki, T., Motohashi, H., Yamamoto, M., 2013. Toward clinical application of the Keap1-Nrf2 pathway. Trends Pharmacol. Sci. 34, 340–346.
Tapeinou, A., Matsoukas, M.T., Simal, C., Tselios, T., 2015. Cyclic peptides on a merry-go-round; towards drug design. Biopolymers 104, 453–461.
Taubert, D., Grimberg, G., Stenzel, W., Schömig, E., 2007. Identification of the endogenous key substrates of the human organic cation transporter OCT2 and their implication in function of dopaminergic neurons. PLoS One 2, e385.
Taylor, M.W., Schupp, P.J., Baillie, H.J., Charlton, T.S., de Nys, R., Kjelleberg, S., Steinberg, P.D., 2004. Evidence for acyl homoserine lactone signal production in bacteria associated with marine sponges. Appl. Environ. Microbiol. 70, 4387–4389.
Teixidó, M., Zurita, E., Prades, R., Tarrago, T., Giralt, E., 2009. A novel family of diketopiperazines as a tool for the study of transport across the blood-brain barrier (BBB) and their potential use as BBB-shuttles. Adv. Exp. Med. Biol. 611, 227–228.
Thakur, N.L., Hentschel, U., Krasko, A., Pabel, C.T., Anil, A.C., Muller, W.E.G., 2003. Antibacterial activity of the sponge *Suberites domuncula* and its primmorphs: potential basis for epibacterial chemical defense. Aquat. Microb. Ecol. 31, 77–83.
Thion, M.S., Low, D., Silvin, A., Chen, J., Grisel, P., Schulte-Schrepping, J., Blecher, R., Ulas, T., Squarzoni, P., Hoeffel, G., Coulpier, F., Siopi, E., David, F.S., Scholz, C., Shihui, F., Lum, J., Amoyo, A.A., Larbi, A., Poidinger, M., Buttgerei, A., Lledo, P.M., Greter, M., Chan, J.K.Y., Amit, I., Beyer, M., Schultze, J.L.,

Schlitzer, A., Pettersson, S., Ginhoux, F., Garel, S., 2018. Microbiome influences prenatal and adult microglia in a sex-specific manner. Cell 172, 500–516e16.
Thompson IIIrd, G.R., Patel, P.K., Kirkpatrick, W.R., Westbrook, S.D., Berg, D., Erlandsen, J., Redding, S.W., Patterson, T.F., 2010. Oropharyngeal candidiasis in the era of antiretroviral therapy. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod. 109, 488–495.
Tommonaro, G., Abbamondi, G.R., Iodice, C., Tait, K., De Rosa, S., 2012. Diketopiperazines produced by the halophilic archaeon, *Haloterrigena hispanica*, activate AHL bioreporters. Microb. Ecol. 63, 490–495.
Tsang, A.H., Chung, K.K., 2009. Oxidative and nitrosative stress in Parkinson's disease. Biochim. Biophys. Acta 1792, 643–650.
Uyemura, K., Dhanani, S., Yamaguchi, D.T., Song, M.K., 2010. Metabolism and toxicity of high doses of cyclo(His-Pro) plus zinc in healthy human subjects. J. Drug Metab. Toxicol. 1, 105.
Valko, M., Leibfritz, D., Moncol, J., Cronin, M.T., Mazur, M., Telser, J., 2007. Free radicals and antioxidants in normal physiological functions and human disease. Int. J. Biochem. Cell Biol. 39, 44–84.
Verdine, G.L., Hilinski, G.J., 2012. Stapled peptides for intracellular drug targets. Methods Enzymol. 503, 3–33.
Wang, B., Zhu, X.L., Kim, Y., Li, J., Huang, S.Y., Saleem, S., et al., 2012. Histone deacetylase inhibition activates transcription factor Nrf2 and protects against cerebral ischemic damage. Free Radic. Biol. Med. 52, 928–936.
Webster, N.S., Hill, R.T., 2001. The culturable microbial community of the great barrier reef sponge *Rhopaloeides odorabile* is dominated by an α-proteobacterium. Mar. Biol. 138, 843–851.
Webster, N.S., Wilson, K.J., Blackall, L.L., Hill, R.T., 2001. Phylogenetic diversity of bacteria associated with the marine sponge *Rhopaloeides odorabile*. Appl. Environ. Microbiol. 67, 434–444.
Weitz, J.S., Mileyko, Y., Joh, R.I., Voit, E.O., 2008. Collective decision making in bacterial viruses. Biophys. J. 95, 2673–2680.
Wynendaele, E., Gevaert, B., Stalmans, S., Verbeke, F., De Spiegeleer, B., 2015. Exploring the chemical space of quorum sensing peptides. Biopolymers 104, 544–551.
Yang, H., Duan, Z., 2018. The local defender and functional mediator: Gut microbiome. Digestion 97, 137–145.
Yang, L., Palliyaguru, D.L., Kensler, T.W., 2016. Frugal chemoprevention: targeting Nrf2 with foods rich in sulforaphane. Semin. Oncol. 43, 146–153.
Yin, W.-B., Grundmann, A., Cheng, J., Li, S.-M., 2009. Acetylaszonalenin biosynthesis in *Neosartorya fischeri*: identification of the biosynthetic gene cluster by genomic mining and functional proof of the genes by biochemical investigation. J. Biol. Chem. 284, 100–109.
Yu, X., Liu, Y., Xie, X., Zheng, X.-D., Li, S.-M., 2012. Biochemical characterization of indole prenyltransferases: filling the last gap of prenylation positions by a 5-dimethylallyltryptophan synthase from *Aspergillus clavatus*. J. Biol. Chem. 287, 1371–1380.
Zhu, J., Zhao, A., Feng, L., Gao, H., 2016. Quorum sensing signals affect spoilage of refrigerated large yellow croaker (*Pseudosciaena crocea*) by *Shewanella baltica*. Int. J. Food Microbiol. 217, 146–155.
Zouhir, S., Perchat, S., Nicaise, M., Perez, J., Guimaraes, B., Lereclus, D., Nessler, S., 2013. Peptide-binding dependent conformational changes regulate the transcriptional activity of the quorum-sensor NprR. Nucleic Acids Res. 41, 7920–7933.

Further Reading

Chen, J.-H., Lan, X.-P., Liu, Y., Jia, A.-Q., 2012. The effects of diketopiperazines from *Callyspongia* sp. on release of cytokines and chemokines in cultured J774A.1 macrophages. Bioorg. Med. Chem. Lett. 22, 3177–3180.
Choi, S.A., Yun, J.W., Park, H.S., Choi, J.W., 2013. Hypoglycemic dipeptide cyclo(His-Pro) significantly altered plasma proteome in streptozocin-induced diabetic rats and genetically-diabetic (ob/ob) mice. Mol. Biol. Rep. 40, 1753–1765.
Giessen, T.W., von Tesmar, A.M., Marahiel, M.A., 2010. A tRNA-dependent two-enzyme pathway for the generation of singly and doubly methylated ditryptophan 2,5-diketopiperazines. Biochemistry 52, 4274–4283.

Mander, P., Brown, G.C., 2005. Activation of microglial NADPH oxidase is synergistic with glial iNOS expression in inducing neuronal death: a dual-key mechanism of inflammatory neurodegeneration. J. Neuroinflammation 2, 20.

Miller, B.R., Gulick, A.M., 2016. Structural biology of nonribosomal peptide synthetases. Methods Mol. Biol. 1401, 3–29.

Reimer, J.M., Aloise, M.N., Harrison, P.M., Schmeing, T.M., 2016. Synthetic cycle of the initiation module of a formylating nonribosomal peptide synthetase. Nature 529, 239–242.

Schmitz, F.J., Schulz, M.M., Siripitayananon, J., Hossain, M.B., van der Helm, D., 1993. New diterpenes from the gorgonian Solenopodium excavatum. J. Nat. Prod. 56, 1339–1349.

Seguin, J., Moutiez, M., Li, Y., Belin, P., Lecoq, A., Fonvielle, M., Charbonnier, J.B., Pernodet, J.L., Gondry, M., 2011. Nonribosomal peptide synthesis in animals: the cyclodipeptide synthase of Nematostella. Chem. Biol. 18, 1362–1368.