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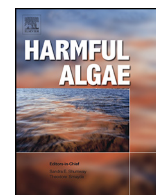

Review

The genetics, biosynthesis and regulation of toxic specialized metabolites of cyanobacteria

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ABSTRACT

The production of toxic metabolites by cyanobacterial blooms represents a significant threat to the health of humans and ecosystems worldwide. Here we summarize the current state of the knowledge regarding the genetics, biosynthesis and regulation of well-characterized cyanotoxins, including the microcystins, nodularin, cylindrospermopsin, saxitoxins and anatoxins, as well as the lesser-known marine toxins (e.g. lyngbyatoxin, aplysiatoxin, jamaicamides, barbamide, curacin, hectochlorin and apratoxins).

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1. Microcystin and nodularin

Bloom-forming freshwater cyanobacteria such as *Microcystis*, *Planktothrix* and *Anabaena* frequently produce hepatotoxic microcystins (MCYSTs), a family of heptapeptides that has been repeatedly implicated in fatal intoxications of humans (Jochimsen et al., 1998) and livestock (e.g. Van Halderen et al., 1995; Frazier et al., 1998). The closely related pentapeptide nodularin (NOD) occurs frequently in cyanobacteria of the species *Nodularia spumigena* that are infamous for mass developments in brackish water bodies such as the Baltic Sea (Moffitt and Neilan, 2004).

MCYSTs and NODs inhibit eukaryotic protein phosphatases of types 1 and 2a and are able to penetrate liver cells via active transport (Runnegar et al., 1995). Although both hepatotoxins are predominantly reported from aquatic habitats they have also been detected in cyanobacteria from terrestrial ecosystems, in particular those found in symbiotic associations with lichen and cycads (Oksanen et al., 2004; Gehringer et al., 2012).

Increasing eutrophication as well as global warming is expected to further promote mass developments of toxic cyanobacteria (Paerl et al., 2011). The presence of cyanobacterial harmful algal blooms is not only connected with adverse effects in the impacted ecosystems but also with significant economic loss (Steffensen, 2008). One of the most recent emergency cases was reported from the city of Toledo (Lake Erie, US) in 2014. Authorities had to shut down the water supply to the city due to elevated levels of MCYST (Cha and Stow, 2015). The single event with the most reported fatalities attributed to MCYST occurred at a hemodialysis unit in Caruaru, Brasil where at least 50 deceased patients showed symptoms of acute liver damage after exposure to contaminated water (Jochimsen et al., 1998).

The World Health Organization (WHO) provisional guideline for MCYST-LR in drinking water is 0.001 mg L^{-1}, based on a daily water intake of 2 L by a 60 kg adult. The analytical detection of MCYST is commonly based either on chemical, enzymatic, immunogenic or molecular analytics or a combination of the different techniques (McElhiney and Lawton, 2005). State of the art chemical detection conventionally utilizes LC–MS and relies on available quantitative standards for the most common congeners of MCYST (McElhiney and Lawton, 2005). Another technique frequently applied is MALDI–TOF–MS that is able to differentiate between toxic and nontoxic strains on a single colony or single filament level without prior solvent extraction. MALDI–TOF–MS is thus suitable for population studies in the field (Via-Ordorika et al., 2004; Welker and Erhard, 2007). The approach can, however, only provide a semi-quantitative overview and is thus not applicable for routine monitoring of toxic cyanobacteria.

Immunogenic detection of MCYST utilizes highly specific monoclonal antibodies developed against cyanotoxins. The antibodies are able to quantify the toxins in complex mixtures in a competitive ELISA setup (Weller et al., 2001). Alternatively, the toxins may be quantified based on their bioactivity with a protein phosphatase inhibition assay (McElhiney and Lawton, 2005). Both immunogenic and enzymatic techniques can not differentiate between different toxin isoforms but can provide a quantitative assessment about the total amount of hepatotoxins in a sample.

A recent study has revealed that up to 60% of MCYST is covalently bound to proteins and thus not detectable by LC–MS or any other technique based on solvent extraction (Meissner et al., 2013). Thus, in order to assess the total amount of MCYST a combination of chemical analytics with an immunogenic assay of the protein fraction is desirable.

Molecular techniques for the detection of MCYST and NOD biosynthesis genes commonly utilize PCR or real-time PCR approaches. Sequencing techniques allow for an assignment of the producing species and the identification of different genotypes and are suitable for population analyses. However, due to the frequent occurrence of mutants impaired in toxin production (but still containing genes) and due to the variations in production levels observed for different strains, molecular analyses cannot be used for a quantitative evaluation of toxins in toxigenic strains.

1.1. Biosynthesis

The common structure of the microcystins is cyclo (D-Ala-X-D-MeAsp-Z-Adda-D-Glu-Mdha) in which X and Z represent variable amino acids, D-MeAsp is D-erythro-ß-methyl-aspartic acid, Mdha is *N*-methyldehydroalanine, and Adda is (2*S*,3*S*,8*S*,9*S*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid (Botes et al., 1984). More than 80 isoforms of MCYST have been described in the literature. NODs are closely related pentapeptides with the structure cyclo(D-MeAsp-L-Arg-Adda-D-Glu-Mdhb), in which Mdhb is 2-(methylamino)-2-dehydrobutyric acid (Rinehart et al., 1988). MCYSTs and NODs are synthesized by giant multienzyme complexes composed of nonribosomal peptide synthetases (NRPS), polyketide synthases (PKS) and further tailoring enzymes (Tillett et al., 2000; Nishizawa et al., 2001; Moffitt and Neilan, 2004). NRPS complexes assemble peptides using a step-by-step mechanism where a single module is responsible for the activation, thioester formation, condensation and optionally modification of a single amino acid unit (Grunewald and Marahiel, 2006). In *Microcystis aeruginosa* PCC 7806, the MCYST synthetase (*mcy*) gene cluster spans 55 kb and encodes ten ORFs (Tillett et al., 2000). In *Nodularia spumigena* NSOR10, the NOD (*nda*) synthetase gene cluster spans 48 kb and encodes nine ORFs (Moffitt and Neilan, 2004) (Fig. 1a and b).

The MCYST and NOD synthetase complexes are composed of seven and five NRPS modules, respectively (Dittmann et al., 2012). Both multienzyme complexes feature PKS modules that are responsible for the formation of the unique Adda side chain (Dittmann et al., 2012).

Remarkably, toxic and nontoxic strains of the same species have been identified and these are typically mixed in blooms. Although the ratio between toxic and nontoxic strains may change during a season there is typically no segregation observed between toxic and nontoxic genotypes. The assessment of the toxic potential of blooms thus requires sensitive techniques that go beyond mere species identification. An exception of the mixed community phenomenon of is found for strains of *Nodularia spumigena* that invariably produce the pentapeptide NOD.

1.2. Regulation

Several studies have assessed the impact of environmental factors, including light, iron limitation, temperature and pH on cellular MCYST and NOD content (Sivonen and Jones, 1999). Variations observed for the different environmental stimuli are strain dependent and typically not exceeding a factor of four (Sivonen and Jones, 1999). Orr and Jones (1998) have postulated a direct correlation between MCYST production and growth rates (Orr and Jones, 1998). This hypothesis is in agreement with the fact that MCYST typically accumulates in parallel to growth. The toxin was thus regarded as a constitutive cell component. These findings are at least in part in contradiction to the later evaluation of the transcriptional response of MCYST biosynthesis (*mcy*) genes to environmental stimuli. A number of studies revealed that high light and iron limitation, led to a significant increase in *mcy* transcription (Kaebernick et al., 2000; Sevilla et al., 2008). High light was also shown to increase the transcriptional level of NOD biosynthesis genes (Kopf et al., 2015). Nitrogen limitation, in contrast, led to a significant decrease in *mcy* gene expression (Harke and Gobler, 2013). Correspondingly, MCYST cell quotas

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