Microbiological Research 207 (2018) 161–169

Contents lists available at ScienceDirect

Microbiological Research

journal homepage: www.elsevier.com/locate/micres

For the greater good: Programmed cell death in bacterial communities

Stijn H. Peeters[a,*], Marien I. de Jonge[b]

[a] Department of Microbiology, Institute for Water and Wetland Research, Radboud University, Nijmegen, The Netherlands
[b] Section of Pediatric Infectious Diseases, Laboratory of Medical Immunology, Radboud Institute for Molecular Life Sciences, Radboud University Medical Center, Nijmegen, The Netherlands

ARTICLE INFO

Keywords:
Programmed cell death
Multicellularity
Bacteria

ABSTRACT

For a long a time programmed cell death was thought to be a unique characteristic of higher eukaryotes, but evidence has accumulated showing that programmed cell death is a universal phenomenon in all life forms. Many different types of bacterial programmed cell death systems have been identified, rivalling the eukaryotic systems in diversity. Bacteria are singular, seemingly independently living organisms, however they are part of complex communities. Being part of a community seems indispensable for survival in different environments. This review is focussed on the mechanism of and reasons for bacterial programmed cell death in the context of bacterial communities.

1. An introduction to programmed cell death

In the past, three different types of cell death were identified: necrosis, autophagic cell death and apoptosis (Liu and Levine, 2015; Clarke, 1990). Necrosis was regarded as an unregulated and uncontrollable process. Autophagic cell death or autophagy was considered to cause accidental cell death by over-activity, but is now also thought to promote cellular survival in response to stressors at normal levels. Only apoptosis was considered to intentionally lead to cell death and was therefore also thought to be the sole form of programmed cell death (PCD), where PCD is defined as all genetically encoded (hence, programmed) processes that lead to PCD (Bayles, 2014). It has now become apparent that apoptosis does not tell the complete story of programmed cell death. Purely unregulated necrosis was questioned for more than 15 years, currently there is more and more evidence for controlled necrosis (Berghe et al., 2014) and also for controlled autophagy (Marsh et al., 2007). Multiple pathways leading to programmed cell death have now been identified, such as apoptosis (Green and Reed, 1998), necroptosis or regulated necrosis (Pasparakis and Vandenabeele, 2015), parthanatos, accumulation of specific proteins as a consequence of genomic stress (Fatokun et al., 2014), autosis or regulated autophagy (Liu and Levine, 2015) and ferroptosis, an iron-dependent form of cell death (Dixon et al., 2012).

PCD in multicellular life is essential for four processes: (1) sculpting, of which an example is the formation of the interdigital regions in mammals (Jacobson et al., 1997), (2) removal of unwanted structures, a process which is for example very important during metamorphosis of a tadpole to a frog (Jiang et al., 1997; Nishikawa and Hayashi, 1995). (3) Controlling cell numbers, by killing cells after they have served their purpose as happens with T-cells after the infection has subsided (4). Eliminating non-functional or harmful cells, by killing cells infected with a virus or cells damaged beyond repair (Ju et al., 1995; Cohen, 1991). PCD is therefore an important tool in the toolbox of multicellular life.

Programmed cell death intuitively seems to be the domain of multicellular organisms, as a single cell cannot benefit from their own demise. PCD was therefore long thought to be a unique characteristic of multicellular life, however there is increasing evidence showing that PCD is universal for all known forms of life (Berghe et al., 2014). The question therefore remains: why does programmed cell death exist in bacteria? The evidence and reasons for programmed cell death in bacteria are summarized in this review.

2. Uni- and multicellular life of bacteria

One of the main reasons for which programmed cell death in bacteria seems counterintuitive is the unicellular nature of bacteria. However, although many bacteria live as singular units, many species also spend part of their lives as part of a complex community, others have embraced multicellular lifestyles and have abandoned unicellular growth as reviewed by Claessen et al. (Claessen et al., 2014). To organize this type of multicellularity, organisms first have to cluster to become a coherent whole. In bacteria, this can be achieved in multiple ways, for example by aggregation in the form of biofilms (Hall-Stoodley et al., 2004), by incomplete cell fission after cell division resulting in chains of cells, a feature of filamentous cyanobacteria (Flores and

* Corresponding author.
E-mail address: speeters@science.ru.nl (S.H. Peeters).

https://doi.org/10.1016/j.micres.2017.11.016
Received 28 June 2017; Received in revised form 25 November 2017; Accepted 28 November 2017
Available online 01 December 2017
0944-5013/

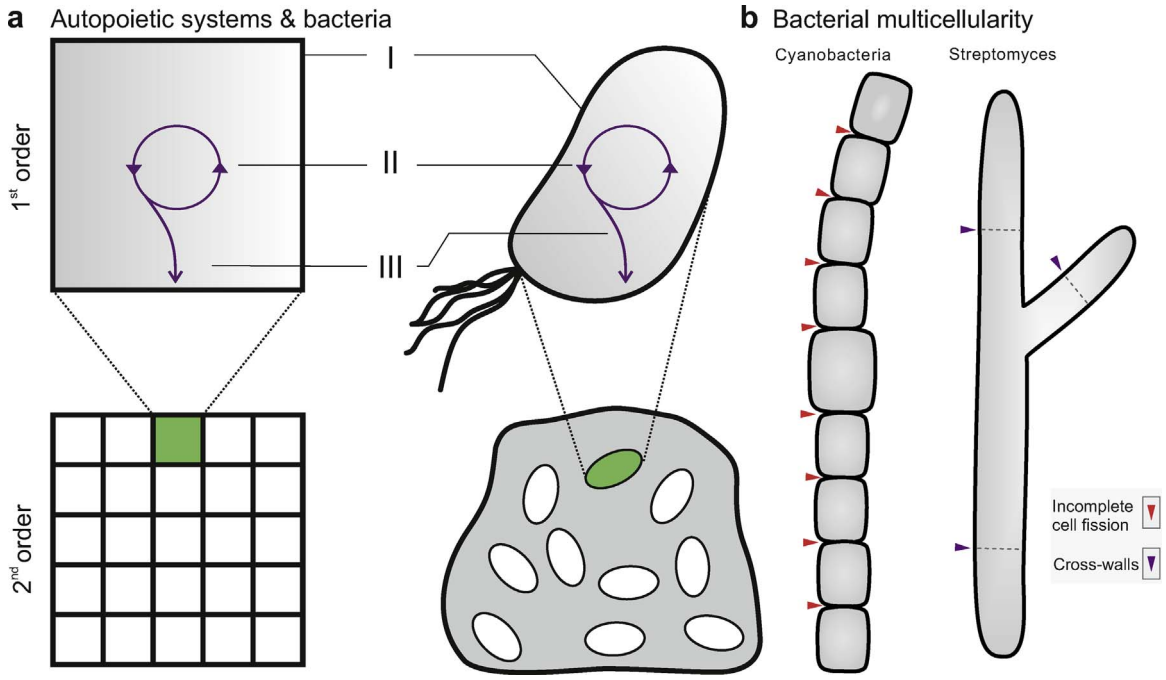

Fig. 1. Autopoietic systems and bacterial multicellularity. a) A comparison between a first- and second order autopoietic system, a single bacterium and a biofilm. Three rules of autopoiesis apply, based on Thompson et al.(Thompson, 2007). (I) A semi-permeable barrier that separates the inside from the outside. (II) A network of reactions, where the components of this network are produced by the reactions within this network. (III) The barrier and the network are interdependent, where the barrier is produced by the network, and the network is regulated by the conditions created by the barrier. b) Apart from the bacterial biofilm (Hall-Stoodley et al., 2004), incomplete fission as seen in cyanobacteria (Flores and Herrero, 2010) and the formation of syncytial filaments in Streptomyces (Jakimowicz and van Wezel, 2012) are also types of bacterial multicellularity.

Herrero, 2010), or by forming syncytial filaments in *Streptomyces* resulting from the formation of cross-walls that divide the hyphae (Jakimowicz and van Wezel, 2012) (Fig. 1b). Connections between the cells are therefore created by the extracellular matrix in the case of a biofilm, and by physical, cell-to-cell, connections in syncytial filaments and filamentous cyanobacteria (Claessen et al., 2014; Hall-Stoodley et al., 2004; Flores and Herrero, 2010; Jakimowicz and van Wezel, 2012).

Bacteria are clearly living organisms, but can multiple cells also form a single coherent unit which is 'alive'? To test this hypothesis the rules for autopoiesis may be applied. Maturana & Varela originally conceived the idea of autopoiesis in the context of biological systems. In a further development, Thompson further defines autopoiesis as follows (Thompson, 2007; Varela et al., 1974): (A) there is a semi-permeable barrier that separates the inside from the outside. (B) There also has to be a network of reactions, where the components of this network are produced by the reactions within this network. (C) The barrier and the network have to be interdependent, where the barrier is produced by the network, and the network is regulated by the conditions created by the barrier. Physical systems which are alive are thought adhere to these rule and are therefore automatically thought to be autopoietic (Fleischaker, 1988). The reciprocal idea that something is autopoietic and thus alive is not universally accepted (Luisi, 2003). Regardless, when the three rules of autopoiesis apply to a physical object, it can be seen as alive.

When the three rules are applied to bacterial communities they can be considered either a collective that is autopoietic or multicellular life forms of life, as can be demonstrated in the case of a biofilm. Biofilms have a semi-permeable barrier in the form of the extracellular matrix. (Rule A) and contain a network of reactions maintaining the extracellular matrix, where the reactions are performed by the bacteria contained within the biofilm (Rule B). These bacteria can also communicate with each other through quorum sensing or channel-mediated electric signalling, enabling coordination and cooperation in maintenance of this barrier (Li and Tian, 2012; Humphries et al., 2017) (Rule B). The biofilm barrier and this network are also interdependent, where the extracellular matrix is produced by the bacteria and the bacteria are regulated by the conditions created by the extracellular matrix (Rule C). Bacterial communities, such as can be found in biofilms, can therefore also be considered as multicellular, as these also conform to the rules of an autopoietic system (Fig. 1a). A biofilm is composed of bacteria as first order autopoietic subunits, and the biofilm itself can then be considered to be a second order autiopoietic system. Biofilms as multicellular and biofilms as autopoietic units is not a new concept when viewed in the context of autopoiesis (Luisi, 2003).

Bacterial "multicellularity" is different from eukaryotic multicellularity in two striking ways: it can be transient and patchy (Claessen et al., 2014). It can be transient, as many bacteria exist in a multicellular state such as filaments can also grow in a single celled state (as mentioned previously). Multicellularity in bacteria can also be patchy, because not all members of a bacterial autopoietic system have to be of the same species, which is the case in many biofilms (Stewart and Franklin, 2008). The patchy nature of biofilms is promoted by the electrical signalling of bacteria within the biofilm that non-specifically attracts bacteria from outside the biofilm, but also by the micro-environments created by the consumption of nutrients and oxygen (Humphries et al., 2017; Stewart and Franklin, 2008).

3. Mechanisms of bacterial programmed cell death

Many different types of bacterial programmed cell death have been identified, rivalling mammalian eukaryotes in diversity. Similar to eukaryotes, these systems range from very well studied to obscure.

3.1. MazEF toxin-antitoxin system mediates cell death

Almost all organisms contain genes that have been identified to inhibit cell growth when expressed. The most well studied type of these are toxin-antitoxin (TA) systems, which are widely found in both bacteria and archaea (Sevin and Barloy-Hubler, 2007). Multiple types of