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Celebrating the career and legacy of Professor Pascale Cossart

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1 **EDITORIAL: CELEBRATING THE CAREER AND LEGACY OF PROFESSOR**
2 **PASCALE COSSART**

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9
10 It is an enormous pleasure and honour for me to contribute this editorial to introduce the
11 special issue that we have assembled to honour the numerous, unique and outstanding
12 scientific achievements of Pascale Cossart and her group. Pascale Cossart, a distinguished
13 Professor at the Institut Pasteur in Paris, France, has been a worldwide leader in the study of
14 fundamental processes in molecular and cellular microbiology and host pathogen interactions
15 for more than 30 years. Using mainly *Listeria monocytogenes*, but also *Rickettsia conorii*, as
16 models she has made several seminal findings in the field of infection biology, cell biology
17 and epigenetics. Her work on fundamental RNA biology and bacterial regulation, and more
18 recently the discovery of a new antibiotic resistance mechanism that is called ribosome
19 splitting, are examples of her elegant contributions to the field.

20
21 In this Special issue of *Molecular Microbiology*, colleagues, former students, postdoctoral
22 fellows and friends of Pascale Cossart have gathered together to contribute reviews and
23 articles in the area of her major research interests. The special issue starts with a personal
24 tribute to Pascale Cossart, contributed by *Werner Goebel*, a longstanding colleague and
25 competitor who traces many of the ground-breaking findings made by Pascale Cossart and her
26 group.

27
28 *Listeria monocytogenes* is reported in all textbooks as an intracellular pathogen that replicates
29 in the cytosol of human cells after its escape from the vacuole. However, recently this
30 paradigm was challenged by observations that *L. monocytogenes* can also adopt a vacuolar
31 lifestyle when persisting within cells (Kortebi *et al.*, 2017). As another example,
32 *Mycobacterium tuberculosis*, which was thought for a long time to be a strictly intra-vacuolar
33 pathogen, was recently shown to rupture the phagosome and to contact the cytosol of the
34 phagocytes it infects (Russell, 2016, Simeone *et al.*, 2009). This discovery was very important
35 to better understand former unsolved steps of the disease process, as it is associated with
36 altered intracellular signalling. In particular, this knowledge is important for the development

37 of vaccines, a priority for tuberculosis research (Groschel *et al.*, 2017). Thus a strict
38 distinction between vacuolar and cytosolic intracellular pathogens is not evident. Similarly,
39 the strict distinction between extracellular and intracellular pathogens does not hold true
40 anymore. In a very interesting opinion article *Arturo Casadevall and Ferric Fang* show that
41 new findings blur the boundaries between extracellular and intracellular pathogens and they
42 discuss the benefits and caveats arising from the intracellular pathogen concept.

43

44 Today, multidrug resistant bacteria are a worldwide public health threat with increasing
45 mortality and tremendous costs. Thus multidisciplinary research efforts are of utmost
46 importance to better understand resistance emergence, persistence, dissemination and to find
47 new, effective drugs. In an illustration of how the knowledge of ancient civilisations might
48 help to solve this modern problem, *Julian Davis* and *Shekooh Behroozian* provide insights on
49 how to use native environmental resources for extraction of natural products, so called
50 medicinals. In particular, they present a personal view on the antimicrobial properties of clay
51 minerals and propose that these underexplored natural resources may provide an alternative
52 means to fight pathogens resistant to commonly used drugs.

53

54 Another fascinating approach to fight antibiotic resistance is proposed by *Jörg Vogel* who
55 provides new ideas on how species-specific programmable RNA antibiotics could be
56 developed. Indeed, broad-spectrum antibiotics are killing many bacteria present in and on our
57 body, including both beneficial as well as pathogenic ones. Thus, the possibility of selective
58 killing of pathogenic and/or multidrug resistant bacteria is very appealing, and might lead to
59 microbiome editing for health. While proposing different ways to use short antisense
60 oligonucleotides as antimicrobials, he also highlights the caveats including specificity,
61 delivery, resistance and persistence.

62

63 Antibiotics are mainly seen as drugs to treat bacterial infections by inhibiting bacterial growth
64 or killing them. However, as most antibiotics are naturally produced by soil organisms, their
65 primary ecological function in the environment may be different. *Pishchany Gleb* and
66 *Roberto Kolter* consider possible ecological roles of antibiotics and discuss their alternative
67 functions at sub-inhibitory concentrations, such as the modulation of gene expression or
68 biofilm formation, their influence on the stability of RNA molecules, and effects on bacterial
69 evolution by increasing mutagenesis rates and horizontal gene transfer through conjugation.
70 They argue that it is important to start studying the importance of these molecules in the

71 context of multispecies communities and in environmental conditions to understand how
72 antibiotics might affect microbial communities and to expand our knowledge on these other,
73 understudied effects of antibiotics.

74

75 *Fernando Baquero, Val Fernandez-Lanza, Melodie Duval and Teresa Coque* consider another
76 idea that puts the environment into the focus of antibiotic resistance, namely the impact of
77 gene – environment interactions on the acquisition of antibiotic resistance determinants, the
78 ecogenetics of antibiotic resistance. As a specific example of how the ecology of an organism
79 may shape the acquisition of antibiotic resistance, they examine *L. monocytogenes*, as it is
80 intriguing that these bacteria have retained susceptibility to the key antimicrobials used to
81 treat infections. This is even more surprising as *L. monocytogenes* is found ubiquitous in the
82 environment and in a large spectrum of animals and plants. The authors discuss the impacts of
83 global ecology, population size, genome structure, environmental stresses, and suggest that
84 the many biocide and heavy metal resistance genes that are present in the *L. monocytogenes*
85 genome may also play a role.

86

87 *Cameron Parson, Sangmi Lee and Sophia Kathariou* discuss these heavy metal resistance
88 genes in *L. monocytogenes* and other Gram-positive bacteria further. They give a
89 comprehensive update on the plasmid- and chromosomal-borne cadmium and arsenic
90 resistance genes, and discuss their importance for environmental persistence. They suggest
91 that the food-processing environment exerts a major selection pressure for cadmium
92 resistance in *L. monocytogenes*, however many natural *Listeria* isolates are also highly
93 resistant to several toxic metals. Thus, further studies will help to understand the ecological
94 and evolutionary factors that drive acquisition, spread and diversification of the genomic
95 elements conferring heavy metal resistance.

96

97 Two important new concepts in RNA biology have been discovered by the group of Pascale
98 Cossart that are highlighted in the two following articles. *Pierre Mandin* and *Jörgen*
99 *Johansson* give a short overview on how bacteria sense temperature changes and the impact
100 this might have on virulence. For many years it was known that bacteria can sense
101 temperature changes, and that in pathogenic bacteria virulence gene expression is often
102 correlated with the transition from the environment (low temperature) to the human host
103 (37°C). An example of temperature-regulated virulence gene expression the PrfA
104 thermosensor of *L. monocytogenes* is described and compared to other bacterial

105 thermosensors. *Alejandro Toledo-Arana* and *Iñigo Lasa* discuss additional regulatory
106 concepts by giving a masterly account of the advances made and new insights gained through
107 the implementation of high-throughput methods for RNA profiling. Through genome-wide
108 transcriptional profiling massive amount of antisense transcription, as well as conditional
109 transcriptional termination and non-contiguous operons, have been discovered. Furthermore,
110 the authors highlight riboswitch-dependent regulation of antisense RNA and overlapping
111 transcription between neighbouring genes and present the related excludon concept, a new
112 paradigm of regulation based on overlapping transcription.

113

114 Another rapidly expanding area of gene regulation studies was initiated by the discovery and
115 characterization of small noncoding regulatory RNAs. Many of these control bacterial
116 pathogenicity and the adaptation of bacteria to environmental stresses and to their hosts
117 (*Oliva et al., 2015*). *Jens Georg, David Lalaouna, Shengwei Hou, Steffen Lott, Isabelle*
118 *Caldelari, Stefano Marzi, Wolfgang Hess* and *Pascale Romby* present a comprehensive and
119 exciting overview on how targets of small RNAs can be identified, a still very challenging
120 task. They show how by combining powerful computational approaches with experimental
121 approaches the full extent of small RNA-dependent regulatory networks can be elucidated.

122

123 Peptidoglycan is an essential molecule for bacteria that maintains their shape, cell integrity
124 and provides a protective function against changing environmental conditions. Furthermore,
125 peptidoglycan can be altered within the host to impair responses triggered by pattern
126 recognition receptors (*Pucciarelli & Garcia-del Portillo, 2018*). Peptidoglycan is also studied
127 as a target to control bacterial infections. However, these studies are rarely undertaken in
128 natural environments but under laboratory conditions. Until now our knowledge on
129 peptidoglycan stems mainly from few model bacteria, and intracellular bacteria have only
130 been studied very recently. *Francisco Garcia-del-Portillo* provides an illuminating account of
131 recent advances on probing peptidoglycan synthesis and assembly within eukaryotic host
132 cells, with a particular focus on the enzymes involved in peptidoglycan metabolism in the
133 context of symbiotic growth and persistent infection. He gives a detailed description of the
134 enzymatic machinery identified mainly in *Escherichia coli* and of peptidoglycan recycling
135 utilized by bacterial pathogens to evade immune defences. Furthermore, the current
136 techniques that are used for analysis and isolation of cell wall muropeptides are described and
137 examples of intracellular bacteria that have been analysed with these methods are
138 summarised.

139

140 Peptidoglycan is also one of the three major constituents of the *L. monocytogenes* cell wall,
141 along with anionic teichoic acid polymers and wall-associated and wall-anchored proteins.
142 Polymeric teichoic acid is divided into wall teichoic-acid, which is directly conjugated to the
143 peptidoglycan, and lipoteichoic acid, which is tethered to the plasma membrane. The *Listeria*
144 teichoic acid polymers have important functions such as regulating bacterial growth, ion-
145 homeostasis, biofilm formation, interaction with bacteriophages, host cell invasion and
146 virulence. The *L. monocytogenes* serotyping scheme classifies strains into different serotypes.
147 It recognizes structural and compositional changes on the cell wall surface and led to the
148 discovery of strains belonging to specific serovars, which cause most human infections. In
149 their MicroReview *Eric Sumrall, Anja Keller, Yang Shen and Martin Loessner* provide a
150 comprehensive update on the synthesis, structural variability and function of teichoic acids in
151 the genus *Listeria*. They discuss the impacts of teichoic acid decorations on serotype-specific
152 designations, on phage resistance and virulence *via* wall-associated virulence proteins. They
153 propose that the chemical synthesis of teichoic acids could be used for vaccine development.
154 These engineered, teichoic acid-based vaccines could fully exploit their immunogenic
155 potential and might represent a new strategy to fight infections with Gram-positive bacteria.

156

157 In the following article, *Eric Sumrall, Christopher Schefer, Jeanine Rismonod, Angelika*
158 *Gründling, Martin Loessner and Yang Shen* present new research results on the function of
159 teichoic acids in virulence of *L. monocytogenes*. They show that two different
160 glycosyltransferases are required for the galactosylation of lipoteichoic acid (LTA) and wall
161 teichoic acid (WTA), respectively. Thus *L. monocytogenes* encodes two surface-acting
162 galactosyltransferases with distinct substrate specificities, which have an impact on the cell
163 surface modification and InlB (an important virulence factor for invasion of eukaryotic cells)
164 retention and function. The demonstration that modification of WTA alone is critical for InlB
165 localization is interesting in that LTA and WTA are often referred to in the literature with
166 minimal functional distinction. This study clearly indicates that these surface moieties have
167 important functional differences, and leads one to wonder what other functions might be
168 solely attributed to WTA *versus* LTA, or *vice versa*. Another important surface structure is
169 pili. They have a pivotal role in the colonization of specific host tissues in many pathogenic
170 bacteria. *Frederico Iovino, Priyanka Nannapaneni, Brigitta Henriques-Normark and Staffan*
171 *Normark* provide a state-of-the art overview of the recent findings of type 1 pilus and its
172 adhesive tip protein RrgA from *Streptococcus pneumoniae*. The type 1 pilus is an important

173 yet less studied surface associated virulence determinant of pneumococcal surface proteins,
174 and thus the presentation of biochemical, structural and host pathogen interaction studies
175 showing the impact of type 1 pilus in colonization and pathogenicity are very timely.
176 Pneumococcal type 1 pili seem to confer a competitive advantage for nasopharyngeal
177 colonization of humans, and the RrgA tip protein might be a good addition to the group of
178 proteins used for the pneumococcal vaccine.

179

180 How did these different bacterial cell envelopes evolve? In particular, how did monoderm and
181 diderm bacteria evolve? In the penultimate article of this issue *Daniela Megrian, Najwa Taib,*
182 *Jerzy Witwinowski, Christophe Beloin* and *Simonetta Gribaldo* address the important question
183 of cell envelope diversity across the bacterial domain. Based on the existence of diderm
184 bacteria among the generally monoderm Firmicutes, the division of Gram-positive
185 (monoderm) and Gram-negative (diderm bacteria) is discussed. Using an in depth and
186 comprehensive phylogenomic analyses, together with results from a new experimental model,
187 *Veillonella parvula*, a diderm Firmicute, the authors propose that the diderm envelope is
188 ancestral within the Firmicutes and the monoderm envelope evolved multiple times through
189 loss of the outer membrane. This provocative hypothesis will stimulate discussions and
190 further studies to understand bacterial cell envelope evolution. Finally, *Megan de Ste Croix,*
191 *Jonathan Holmes, Joseph Wanford, Richard Moxon, Marco Oggioni, and Christopher Bayliss*
192 discuss the role of bottlenecks in the evolution of diversity-generating mechanisms of
193 microbes during bacterial transmission and infection. They provide an authoritative summary
194 of progress in the field and challenges for future studies.

195

196 This collection of articles reflects many of the areas of research to which Pascale Cossart has
197 contributed, highlighting and building upon her outstanding findings over the last decades.
198 We are confident that these contributions and ideas will inspire young researchers to embrace
199 the upcoming challenges of the New Microbiology (Cossart, 2018).

200

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