Myxobacteria: natural pharmaceutical factories

Juana Diez1, Javier P Martinez2, Jordi Mestres3, Florenz Sasse4, Ronald Frank4 and Andreas Meyerhans2*

Abstract

Myxobacteria are amongst the top producers of natural products. The diversity and unique structural properties of their secondary metabolites is what make these social microbes highly attractive for drug discovery. Screening of products derived from these bacteria has revealed a puzzling amount of hits against infectious and non-infectious human diseases. Preying mainly on other bacteria and fungi, why would these ancient hunters manufacture compounds beneficial for us? The answer may be the targeting of shared processes and structural features conserved throughout evolution.

Keywords: Myxobacteria, Natural products, Drug discovery, Chemical space

Commentary

Natural products from plants and microbes have played a pivotal role in drug discovery for more than a century [1-3]. In recent years, myxobacteria have matched fungi, actinomycetes as well as some species of the genus Bacillus as top producers of microbial secondary metabolites [4-6]. More importantly, screening campaigns have revealed a large proportion of the myxobacteria secondary metabolism to have activities against human diseases such as cancer, bacterial and viral infections [6-8].

Myxobacteria are a group of proteobacteria which reside mainly in soil [9,10]. These social microbes move by an axonal cellular motion called gliding [11,12], and although cells grow independently, they form collective swarms to prey and generate transient structures, called fruiting bodies (Figure 1), when resources are scarce [13]. During cooperative feeding, individual cells organize in waves which travel in a rippling-like motion [12,14]. As waves of cells collide, they aggregate in mounds that grow in size forming fruiting bodies that can harbor about 10^5 individuals. Cells within these structures become myxospores. Sporulation is triggered by signaling at the cell-cell contact surface when nutrients are available, and the myxospores germinate to eventually develop new swarms [11]. To control these processes, myxobacteria have evolved a unique mechanism of extracellular and intracellular signals, including diverse proteins and small metabolites [15].

The chemical space of the myxobacteria metabolome is rare both in diversity and biological activities [5,16,17]. Their secondary metabolites present structural elements not commonly produced by other microbes such as unusual hybrids of polyketides and non-ribosomally made peptides [5,18]. In fact, around 40% of the described myxobacterial compounds represent novel chemical structures [9]. Furthermore, most small molecules from myxobacteria are not glycosylated as opposed to products derived from actinomycetes [19] and they target molecules that are often not targeted by metabolites from other microbes. Examples include inhibitors of mitochondrial respiration and eukaryotic protein synthesis, carboxylase and polymerase inhibitors and molecules that affect microtubule assembly [17]. Although the reasons why myxobacteria display such a large array of secondary metabolites are still not well understood, it has been argued that they confer a competitive advantage in the soil environment and are used to modulate cell-cell interactions within the population [20], to protect ecological niches in their competitive environment [17], and used as weapons for predation [13].

This level of chemical complexity requires an equally complex regulatory network to function, altogether enhancing the survival and competitiveness of both the individual and the population [10]. This is reflected in the genetic space employed by myxobacteria for their secondary metabolism. One of the largest bacterial genome reported to date belongs to the myxobacterium Sorangium cellulosum with around 20 secondary metabolite loci and probably more to be discovered [15]. Another well studied myxobacterium, Myxococcus xanthus, has
around 18 secondary metabolite gene clusters accounting for around 9% of its genome [21] which is more than some species of actinomycetes with around 6% of genome coverage for secondary metabolite loci [22,23]. Given this large space on the level of the genome, the known diversity between different myxobacteria and the vast number of different bacterial strains available in various collections, there seems to be an immense room for exploration and exploitation.

The amount of different small molecules from myxobacteria targeting other soil bacteria and fungi, around 29% and 54% respectively, and their higher production rates during exponential growth seems to reinforce the idea of a broad use of secondary metabolites for hunting [13,17]. Any predatory microorganism would benefit greatly from such a diverse armament but why would a large amount of these metabolites be active against human diseases and pathogens? An attractive explanation is that many of these products target shared processes or structural features conserved throughout evolution [24-26]. For example, the LSm1-7 protein complex in mammalian cells was shown to be required for efficient hepatitis C virus (HCV) translation and replication [25]. The Brome mosaic virus (BMV), a plant virus that can replicate in yeast, utilizes the respective yeast homologues for the same processes [27-29]. Likewise, the bacteriophage Qß, a plus-strand RNA virus as HCV and BMV, requires Hfq, the homologue of LSm1 in bacteria for its expansion [30]. Thus there is a functional conservation of cellular and viral regulatory elements across kingdoms and virus groups that may be exploited for antiviral drug development. Indeed, a recent screen against processing body proteins that include the LSm1-7 complex revealed several hits from a myxobacterial metabolite library that overlapped with antiviral activities (Martinez et al., unpublished). To learn more about the bioactivity profile of these potent compounds, systematic testing in a broad panel of bioassays as offered by e.g. academic consortia such as EU-OPENSENCREEN would be strategically worthwhile. However, to develop a metabolite hit into an applicable pharmaceutical compound is not an easy task, especially given the complexity of their natural product chemistry, side effects and poor bioavailability. Therefore, to make better use of nature’s pharmaceutical factories, new technologies such as engineering of microorganisms to synthesize complex molecular structures, in silico tools to predict the target profile and anticipate potential side effects of those metabolites, and targeted delivery strategies for example via nanoparticles are under the spotlight and will play an increasing role in the future [31-35].

Competing interests
The authors declare that they have no competing interests.

Acknowledgements
The authors of this article are supported by grants from the Spanish Ministry of Science and Innovation (BFU2010-26669 to JD, SAF2010-21336 to AM, BIO2011-26669 to JM and the Spanish Instituto de Salud Carlos III. The EU-OPENSENCREEN preparatory phase project receives funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 261861.

Author details
1Molecular Virology Group, Department of Experimental and Health Sciences, Universitat Pompeu Fabra, Barcelona, Spain. 2ICREA Infection Biology Group, Department of Experimental and Health Sciences, Universitat Pompeu Fabra, Barcelona, Spain. 3Chernogenomics Laboratory, Research Program on Biomedical Informatics (GRIB), IIMM-Hospital del Mar Research Institute and Universitat Pompeu Fabra, Barcelona, Spain. 4Department of Chemical Biology, Helmholtz Centre for Infection Research, Braunschweig, Germany.

Received: 24 March 2012 Accepted: 30 April 2012
Published: 30 April 2012

References
1. Davies J, Ryan KS: Introducing the parvome: bioactive compounds in the microbial world. ACS Chem Biol 2012, 7(2):252–259.
2. Mitra BB, Tiwari VK: Natural products: an evolving role in future drug discovery. Eur J Med Chem 2011, 46(10):4769–4807.
3. Newman DJ, Cragg GM: Natural products as sources of new drugs over the 30 years from 1981 to 2010. J Nat Prod 2012, 75(3):311–335.
4. Arguelles-Arias A, Ongena M, Halimi B, Lara Y, Brans A, Joris B, Fickers P, Bacillus amyloliquefaciens GA1 as a source of potent antibiotics and other secondary metabolites for biocontrol of plant pathogens. Microb Cell Fact 2009, 8:63.
5. Bode HB, Muller R: Analysis of myxobacterial secondary metabolism goes molecular. J Ind Microbiol Biotechnol 2006, 33(7):577–588.
6. Weissman KJ, Muller R: Myxobacterial secondary metabolites: bioactivities and modes-of-action. Nat Prod Rep 2010, 27(8):1276–1295.
7. Gentzsch J, Hinkelmann B, Kaderali L, Irschik H, Jansen R, Sasse F, Frank R, Pietschmann T. Hepatitis C virus complete life cycle screen for identification of small molecules with pro- or antiviral activity. Antiviral Res 2011, 89(1):S16–S18.

8. Nickelet I, Zender S, Sasse F, Geffers R, Brandes G, Sorensen I, Steinmetz H. Kubicka S, Carelon G, Neerincx D, et al. Argyrin A reveals a critical role for the tumor suppressor protein p27(kip1) in mediating antitumor activities in response to proteasome inhibition. Cancer Cell 2008, 14(1):23–35.

9. Reichenbach H. Myxobacteria, producers of novel bioactive substances. J Ind Microbiol Biotechnol 2001, 27(3):149–156.

10. Velicer GJ, Vos M. Sociobiology of the myxobacteria. Ann Rev Microbiol 2009, 63:599–623.

11. Kaiser D. Coupling cell movement to multicellular development in myxobacteria. Nat Rev 2003, 1(1):45–54.

12. Nan B, Chen J, Neu KC, Berry RM, Oster G, Zsupman DR. Myxobacteria gliding motility requires cytoskeleton rotation powered by proton motive force. Proc Natl Acad Sci USA 2011, 108(6):2498–2503.

13. Xiao Y, Wei X, Ebright R, Wall D. Antibiotic production by myxobacteria plays a role in predation. J Bacteriol 2011, 193(18):4626–4633.

14. Berleman JE, Kirby JR. Deciphering the hunting strategy of a bacterial wolfpack. FEMS Microbiol Rev 2009, 33(5):942–957.

15. Schneker S, Perlovich G, Kaiser O, Gerth K, Alci A, Altman EG, Bartels D, Bekel T, Beyer S, Bode E, et al. Complete genome sequence of the myxobacterium Sorangium cellulosum. Nat Biotechnol 2007, 25(11):1281–1283.

16. Bon RS, Waldmann H. Bioactivity-guided navigation of chemical space. Acc Chem Res 2010, 43(8):1103–1114.

17. Weissman JS, Muller R. A brief tour of myxobacterial secondary metabolism. Bioorg Med Chem 2009, 17(6):2121–2136.

18. Süsskowsk B, Kunze B, Muller R. Multiple hybrid polyketide synthase-non-ribosomal peptide synthetase gene clusters in the myxobacterium Stigmatella aurantiaca. Gene 2001, 275(2):233–240.

19. Xia J, Fischer C, Remsing LL, Rohr J. Modification of post-PKS tailoring steps through combinatorial biosynthesis. Nat Prod Rep 2002, 19(5):542–580.

20. Davies J, Spiegelman GB, Yim G. The world of subinhibitory antibiotic concentrations. Curr Opin Microbiol 2006, 9(5):495–499.

21. Bode HB, Muller R. The impact of bacterial genomics on natural product research. Angew Chem Int Ed 2005, 44(26):4828–4846.

22. Bentley SD, Chater KF, Cerdeno-Tarraga AM, Challis GL, Thomson NR, James KD, Harris DE, Quail MA, Kieser H, Harper D, et al. Complete genome sequence of the model actinomycete Streptomyces coelicolor A3(2). Nature 2002, 417(6885):141–147.

23. Ikeda H, Ishikawa J, Harnamoto A, Shinose M, Kikuchi H, Shibata T, Sakai Y, Hattori M, Oshima S. Complete genome sequence and comparative analysis of the industrial microorganism Streptomyces avermitilis. Nat Biotechnol 2003, 21(5):526–531.

24. Hong J. Role of natural product diversity in chemical biology. Curr Opin Chem Biol 2011, 15(3):350–354.

25. Scheller N, Min A, Galas DP, Chari A, Gimenez-Barcons M, Noueiry A, Fischer U, Meyerhans A, Diez J. Translation and replication of hepatitis C virus genomic RNA depends on ancient cellular proteins that control mRNA fates. Proc Natl Acad Sci USA 2009, 106(32):13517–13522.

26. Schneider K, Kromer JO, Wittmann C, Alves-Rodrigues I, Meyerhans A, Diez J, Heinle E. Metabolite profiling studies in Saccharomycetes cerevisiae: an assisting tool to prioritize host targets for antiviral drug screening. Microb Cell Fact 2010, 9:12.

27. Diez J, Ishikawa M, Kaido M, Ahlquist P. Identification and characterization of a host protein required for efficient template selection in viral RNA replication. Proc Natl Acad Sci USA 2000, 97(8):3913–3918.

28. Mas A, Alves-Rodrigues I, Noueiry A, Ahlquist P, Diez J. Host deactivation-dependent mRNA deacapping factors are required for a key step in brome mosaic virus RNA replication. J Virol 2006, 80(1):246–251.

29. Noueiry AO, Diez J, Falk SP, Chen J, Ahlquist P. Yeast Lsm1p-Pbp1p/Pat1p deacapping-dependent mRNA-decapping factors are required for brome mosaic virus genomic RNA translation. Mol Cell Biol 2003, 23(12):4094–4106.

30. de Fernandez MT, Franca E, Loyang L, August JT. Factor fraction required for the synthesis of bacteriophage Qbeta-RNA. Nature 1968, 219(5154):588–590.

31. Andexer JN, Kendrew SG, Nur-e-Alam M, Lázos D, Foster TA, Zimmermann A, Warneck TD, Suthar D, Coates NJ, Koehn FE, et al. Biosynthesis of the immunosuppressants FK506, FK520, and rapamycin involves a previously undescribed family of enzymes acting on chorismate. Proc Natl Acad Sci USA 2011, 108(12):4776–4781.