EDITORIAL 10.1111/1469-0691.12066

Dangerous liaisons—our expanding appreciation of microbial synergism

S. J. Cutler

School of Health & Bioscience, University of East London, London, UK

E-mail: s.cutler@uel.ac.uk

Article published online: 18 October 2012

The ancient paradigm that one microorganism causes one infection that has become entrenched within our fundamental understanding of microbiology since the time of Robert Koch is now being repeatedly challenged. For well over a decade now, this dogma has been contested, with expansion in our conceptualization of how microorganisms multiply *in situ*, often growing in biofilms rather than in the planktonic cultures with which we make our laboratory predictions on how these organisms might respond to various therapeutic interventions. These are often not growing as a pure culture, but instead employ variegated interactions between both similar and unrelated microorganisms within this diverse heterogeneous population. The review by Wolcott and Costerton provides a valuable overview of our current understanding of these polymicrobial communities that has helped our understanding of the challenges of managing infections, particularly those associated with indwelling devices and complex microbial communities [1]. The application of metagenomic approaches has helped us to unravel some of the intricacies by which these communities recruit further microorganisms and work collectively, utilizing a 'distributive genome' to provide a recalcitrant population resistant to their surrounding forces [1]. Appreciation of these polymicrobial communities and their enhanced abilities to persist, withstanding both host immune interventions and therapeutic strategies, will improve our appreciation of these communities and evaluation of innovative intervention strategies. We are further indebted to the contributions of Bill Costerton, who sadly passed away during the final stages of the preparation of this review.

Although microbial superinfections have been recognized since the early 19th century, the multiplicity of factors that exacerbate their development remain poorly understood. The review by Jon McCullers opens up another dimension of the consequences of multiple infections. Within this thought-provoking review, he debates the clinical outcome following infection with influenza virus, comparing and contrasting the potential for secondary bacterial infections with pandemic strains that are newly associated with their human hosts, as compared with seasonal strains that have become adapted to infection of their human hosts [2]. Within his review, he highlights the limitation of our current data capture that makes it impossible to disentangle those cases resulting from pandemic and from seasonal strains. Without this level of detail, giving both typing information and geographical data, it is impossible to draw more detailed conclusions regarding strain type and location, and their propensity to predispose individuals to greater risk of secondary infections, increasing the severity following this scenario. Further limitations arise from the capture of mortality statistics as compared with the probably greater burden of non-lethal infections that, in many cases, are not reported [2]. This review offers many as yet poorly investigated possibilities of how one infection might influence the potential for succumbing to another, with particularly severe adverse outcomes for the human host. One such example is the apparent correlation of viral neuraminidase activity and the likelihood of succumbing to secondary bacterial infection [2].

Our appreciation of microbial interactions is further emerging beyond the above interactions between separate entities such as those seen within biofilms and co-infections, with a growing realization that organisms themselves can be infected with other agents that might influence their virulence, longevity, nutritional capabilities, or response to potential intervention strategies. Some *Leishmania* parasites also harbour a cytoplasmic RNA virus (*Leishmania* RNA virus) that can influence the upregulation of inflammatory cascades and thus impact on the pathological consequences of infection [3]. Unsurprisingly, co-infection with human immunodeficiency virus enhances the susceptibility to leishmaniasis by 1000-fold, which, coupled with the bias towards a Th2 response, has severe consequences for disease progression [3]. This has resulted in an upsurge of complicated atypical infections that are challenging to manage with currently available arsenals. Potential targets to tip the balance in favour of the human host to control and eventually eliminate these parasites are excellently reviewed by Hartley and coworkers, who highlight the need to tailor the immunomodulatory therapeutic regimes appropriately to the type of leishmaniasis [3].

The last of our reviews is focused on intrinsic 'nested' co-infections, such as the *Leishmania* RNA virus example above, namely the finding that significant proportions of the Onchocercidae are themselves infected with *Wolbachia* species. Members of the Onchocercidae family include the cause of notable human filarial infections, such as lymphatic filariasis (elephantiasis)

and onchocerciasis (river blindness). Collectively, these infections afflict up to 180 million people residing within endemic zones [4]. The impact of these infections extends beyond human infection to include a range of infections of veterinary importance among both livestock and companion animals. With the exception of the filariae causing *Loa loa* filariasis, those that infect humans are all themselves harbouring *Wolbachia*. This apparently synergistic arrangement enables enhanced establishment of the filariae within their human host through the ability of *Wolbachia* to exacerbate the proinflammatory response, thus helping the nematodes to successfully reach their target locations. Furthermore, the presence of *Wolbachia* is correlated with recruitment of neutrophils rather than a filaricidal eosinophilic host response, so *Wolbachia* appears to enhance the survival of these nematodes within the human host [4]. The inappropriate neutrophil response has been associated with subsequent pathology of corneal inflammation in cases of onchocerciasis [4].

This synergistic union between multiple pathogens opens potential new therapeutic options that target one member of this union, thus tipping the balance towards the demise of its 'partner in crime'. Indeed, doxycycline has been used in this way for the management of both lymphatic filariasis and onchocerciasis. Novel therapeutic agents, such as corallopyronin A and berberin, are both under evaluation for their ability to inhibit RNA synthesis and cytokinesis, respectively, of *Wolbachia* (reviewed by Bouchery *et al.* [4]). The complexity of interactions of these parasites extends beyond those associated with *Wolbachia* alone, and involves dynamic interactions with the host's innate and adaptive immune responses.

Collectively, these reviews underscore our need to adopt a more holistic approach to our consideration of infection, incorporating the role of both extrinsic and intrinsic co-infections that can modulate, and indeed influence, the immunological cross-talk with the immune system of the host.

References

1. Wolcott R, Costerton JW, Raoult D, Cutler SJ. The polymicrobial nature of biofilm infection. *Clin Microbiol Infect* 2013; 19: 107–112.
2. McCullers JA. Do specific virus–bacteria pairings drive clinical outcomes of pneumonia? *Clin Microbiol Infect* 2013; 19: 113–118.
3. Hartley M-A, Kohl K, Ronet C, Fasel N. The therapeutic potential of immune cross-talk in leishmaniasis. *Clin Microbiol Infect* 2013; 19: 119–130.
4. Bouchery T, Lefoulon E, Karadjian G, Nieguitsila A, Martin C. The symbiotic role of *Wolbachia* in Onchocercidae and its impact on filariasis. *Clin Microbiol Infect* 2013; 19: 131–140.