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Can Synergy Resolve Biofilm Infection Problem?

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Editorial

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Editorial

Biofilm Infection, Anti-biofilm Peptides, Synergy between Anti biofilm Peptides and Small-Molecule Antibiotics

Bacteria exist in two states, planktonic, freely existing in bulk solution, and biofilm, attached as a unit to a surface. Thus, bacterial infection can occur in either or both states. Biofilm infection has posed a major threat to healthcare due to lack of available antibiotics with potent anti-biofilm activity. Not only difficult to treat, it also presents high reoccurring rates, not even to mention biofilm problems caused by the infamous "superbugs" strains, adding another layer of complication in treatment and prevention in community, hospital, as well as other setting.

Nature owns an interesting set of balance rules that when it allows one organism to be on the offensive, it will also allow another organism to have resources to be on the defensive. This analogy applies well to antimicrobial peptides, a class of naturally occurring peptides produced by organisms across multiple kingdoms to defend the host against the invading pathogen. Researchers have discovered a new property of antimicrobial peptides: anti-biofilm activity. This is of particular interest to the public due to biofilm problems described earlier. Anti-biofilm peptides offer great alternatives to develop the next generation anti-biofilm agents. Today, there are 221 naturally occurring and synthetic anti biofilm peptides identified according to BaAMP database, presenting a good arsenal against biofilm infection and providing a wide selection for anti-biofilm drug development [1].

Recently, researchers have turned their attention to potential synergistic effect between anti-biofilm peptides and small-molecule antibiotics, due to various successful synergistic studies of antimicrobial peptides and conventional antibiotics. Dr. R.E.W. Hancock and his teams at the University of British Columbia have published several of their studies on peptide-antibiotic synergy against a spectrum of pathogens in recent years in both bacterial and *in vivo* models, demonstrating the potential to use this strategy to combat biofilm [2-4].

Will this Really Work?

To date, most anti-biofilm peptides show micro molar to submicromolar ranges of anti-biofilm activity. Although as promising candidates, most researchers still face hurdles in implementing peptide-based anti-biofilm agents due to high cost as well as poor *in vivo* pharmacodynamics and pharmacokinetic performance. Many researchers resolve to synergy, peptidomimetics or other approaches. While all of these are valid, the questions we should really ask ourselves are: Are we really studying the right class (es) of antimicrobial peptides against biofilm? Is there still unknown class (es) of naturally occurring anti-biofilm peptides that we have not discovered? Most anti-biofilm peptides discovered so far originate from antibacterial peptides in nature. Although it makes sense for nature to design its own peptide library with multifunctional roles (e.g., LL-37), we have yet to find a class of peptides that specifically target biofilm without demonstrating any antibacterial activity (i.e.,>1024 μg/ml) or any other activity. Due to prominent biofilm problem, it would make sense for host organisms to design a class of biomolecules to treat solely biofilm infection [5].

Alternatively, peptide-peptide synergy could also be explored as another potential strategy. Hanson MA, et al. claimed that antimicrobial peptides do not work in a mixture in their *Drosophila* model [6], but it is still unclear whether this is true for anti-biofilm peptides, or true that we have discovered all possible synergistic anti-biofilm combination in nature, or true for all organisms. Since humans do not produce small-molecule antibiotics, it is not convincing to exclude all synergy possibilities of host biomolecules, be that peptide-peptide, peptide-small protein, or others. In addition, multiple research communities have greatly advanced our knowledge and technology in immunotherapy and thus provide rationales to pursue studying synergistic effect between immunotherapeutic and anti-biofilm compounds against biofilm.

What about conventional small-molecule antibiotics? To date, most pharmaceutical and industrial effort have been focused on optimizing activity against planktonic bacteria. Due to extremely high level of difficulty to treat biofilm infection using conventional antibiotics, most researches have been halted from revisiting antibiotics against biofilm. However, tens of thousands of antibiotic candidates, precursors and pro-drugs or not, have been discarded during the drug development processes, and it takes a significant amount of thinking and time commitment to design these compounds and related derivatives. While reusing currently available drugs for other treatment seems to be a very viable and convincing option, some discarded candidates may exhibit unexpected high anti-biofilm activity with low toxicity. Interestingly, some researchers have caught this idea and started to revisit polymer-based and peptide-based antibiotics [7].

What about correct method(s) to identify anti-biofilm compound(s)? So far, crystal violet-based staining assay is the most widely used screening method, but it is known for quantifying all biomass adhered to the infected surface or substrate, without the capability to identify dead, metabolically active, or dormant biofilm-state bacterial cells. In addition, most high-throughput screening assays have been developed to identify biofilm inhibitory activity, but only few on biofilm eradication, not even to mention biofilm dispersion activity. Lack of different types of anti-biofilm screening methods seriously limits the identification of potential anti-biofilm candidates with different types of anti-biofilm activity and undermines true anti-biofilm concentration values. On top of all these, one final problem to face is: how high-throughput can we reach to identify anti-biofilm compound(s)? Robotic platforms seem to help, but not widely available and financially affordable. Until these problems can be resolved, we still have a long journey toward effective anti-biofilm treatment.

Complication in Commercialization

Formulation problems with peptides and small-molecule antibiotics are well known among drug development communities. A lot of effort has been dedicated to formulate peptides and small-molecule antibiotics individually. However, only few studies have been attempted to formulate peptide and small molecule in combination. Including both peptide and small molecule in formulation requires careful consideration of two molecules with very different physical and chemical characteristics. Even if successful, whether these molecules will show concentration-dependent self-quenching or antagonistic effect, undesired side effect, inefficient drug release, or inadequate pharmacodynamics and pharmacokinetic profiles remains to be determined. Even after resolving all of above problems, will segregating two different molecules in the same formulation be necessary to improve controlled releases in patients remains as another determining factor. All these will need to be addressed prior to commercializing this synergy strategy against biofilm.

Concluding Remark

The general public mostly perceive bacterial infection as regular planktonic bacterial infection. Unless interested, most people lack the knowledge to distinguish between biofilm and planktonic, or mixed bacterial infection. In fact, I have encountered many cases where people know much more on cancer and aging than biofilm infection. We have a mission to address and educate the general public to face these problems. Conducting synergy studies is a good strategy to find solutions to overcome these problems among many others but will still require careful interpretation to reach a conclusion.

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