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Antimicrobial Peptide Elicitors (APEs) and Inhibitors (APIs): Challenges and Opportunities in Personalized Medicine

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Abstract

Antimicrobial Peptide Elicitors (APEs) and inhibitors (APIs) are physical (class I), chemical (class II) or biological agents (class III) that either up- or downregulate human antimicrobial peptide expression respectively. The up- or downregulation of antimicrobial peptides (APs) is related to the origin and/or severity of several diseases, including tuberculosis, HIV/AIDS, cancer and psoriasis among others which lead to opportunities for drug design. The development of these "first in class" molecules in the so-called "host-directed therapy", together with companion diagnosticsoffer unique opportunities to increase efficacy and minimizing toxicity in future clinical settings. In this context, APIs and APEs could help in current treatment schemes with reduced risk of side effectsor in new schemes as e.g. MDR-TB clinical trials. The efficacy and safety of APEs and APIs remain to be demonstrated in the clinic, but this new class of molecules holds great opportunities to personalized medicine.

Keywords: Antimicrobial peptide elicitor; Beta defensin; Cathelicidin; DEFB1; LL-37; Cancer; Diabetes; HIV/AIDS; Psoriasis; Personalized medicine

Abbreviations: 1KGP: 1000 Genomes Project; DEFB1: Human Beta Defensin 1 Gene; ENCODE: Encyclopedia of DNA Elements; hBD-1: Human β-Defensin-1 Peptide; MDR-TB: Multi-Drug Resistant TB; rSNP: Regulatory SNP: Single Nucleotide Polymorphism; T1R: Type 1 Reaction; TB: Tuberculosis

Introduction

Antimicrobial Peptide Elicitors (APEs) and inhibitors (APIs) are physical (class I), chemical (class II) or biological agents (class III) that up or down regulate human anti-microbial peptide expression respectively [1]. The up or down regulation of anti-microbial peptides (APs) are related in origin and/or severity to several diseases [1-3], which leads to opportunities for drug design and development of this first in class molecules in the so-called "host-directed therapy" Nylen, F 2017. In this context, APIs and APEs could help in current treatment schemes with reduced risk of side effects, or in new schemes as e.g. MDR-TB clinical trials.

Challenges and opportunities

APEs and APIs in the future clinical setting: Even when a submitted patent Prado 2013 Innate Immun and a cell assay for high-throughput screening (HTS) has been published to discover APEs Nylen 2004 and 2017 these methods have a limitation in that they attempt to represent all human ethnic variants with just one promoter from one cell line from only one donor. These assays are useful to discover effective APEs for the donor but not necessarily for other patients, even if from the same ethnic background or family. Furthermore, we do not know the extent to which the different responses among cell lines are due to the disease status *per se* or because those cell lines come from genetically different individuals Prado 2013 Innate Immun.

In recent years, we have been able to making predictions by generating in silico representative promoters of determinate ethnic origin based on the most frequent alleles of each SNP and to predict which signalling routes are not altered by regulatory SNPs (rSNPs). After that, propose the APE/API that could be more effective in that target population, also with future application in N=1 clinical trials (Flores Saiffe Farias A, Chavez Alvarez R, Prado Montes de Oca E, in preparation). Also due to the advantages of performing the customized regulatory SNP prediction (rSNP) with in silico analysis (based on the *in-vitro*

evidence ENCODE and 1000 Genomes Project among other initiatives other projects) of the promoters of patients and/or a target ethnic group Flores Saiffe 2015, there is a unique oppurtunity unthinkable years ago) to develop simultaneously both lead molecules and their companion diagnostics as y "pharmacogenomics" panels. Most potential drugs fail in Phase II trials, and at least 50% of these are due to lack of efficacy and 25% due to toxicity Plenge 2013. The in silico prediction of that efficacy and toxicity can now be determined before the design of a clinical trial and more easily explained by SNPs (and other genetic variants) functionality, originated by interindividual or inter-ethnic genetic differences. Our above mentioned software together with additional databases, methods and software to predict drug side effects Niu 2015, Toropov 2014, Zhang 2015 could pave the way to the effective application of APEs/APIs in the clinic with personalized medicine as the background rationale.

A novel indirect approach: The use of APEs and APIs is promising and innovative because it is theoretically more difficult for a pathogen to develop a way to overcome these agents, because in most cases they are not antimicrobial per se but act indirectly up on a) induction, b) upregulation or c) downregulation of antimicrobial peptides Prado 2013, Innate Immun. These can be novel molecules or well-known molecules such as vitamin C with novel role as an APE Cruz Díaz 2015. APEs could be useful in the treatment of diseases caused or modified by AP deficiencies such as shigellosis, Crohn's disease, HIV/AIDS, atopic dermatitis, lepromatous leprosy and cancer, among others Prado 2013 Innate Immun. In the case of leprosy, for example, the challenge is to find specific and mild inhibitors as APIs that combat T_{h1} inflammatory response of type 1 reactions (T1R) without compromising the host immune system or use APIs for hepcidin combination with APEs for both cathelicidin and defensins [11]. Alternatively, in tuberculosis (TB) research, there could be an opportunity to test APEs of DEFB1(hBD-1 peptide), DEFB4 (hBD-2) and CAMP genes (LL-37) in clinical trials of multidrug resistant variant tuberculosis (MDR-TB), because there is a need and justification to try novel approaches when in the past other drugs/therapeutic schemes have fail Khusro A, 2016.

Conclusion

APIs and APEs could help in current treatment schemes with reduced risk of side effects or as completely new approaches as e.g. MDR-TB. The efficacy and safety of APEs and APIs remain to be demonstrated in the clinic setting, but this new class of molecules with their companion diagnostics, even with great challenges to overcome, holds great promise for the future of personalized medicine.

Acknowledgement

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Conflict of Interest

Dr. Prado Montes de Oca and collaborators are pursuing two patents related to the methods for the enzymatic synthesis, purification of a novel API and APEs as well as their applications.

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