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Disentangling nanonets: Human α-defensin 6 targets *C. albicans* virulence

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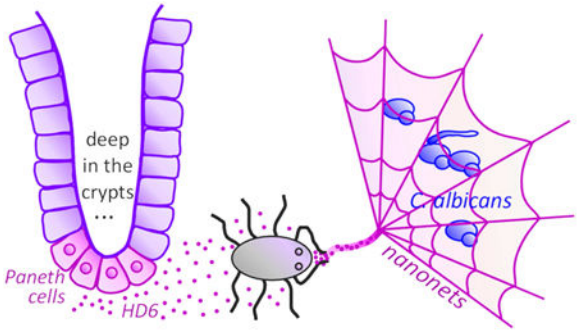
Graphical abstract



The human body employs multiple levels of physical and biochemical protection from infectious microorganisms. Nevertheless, microorganisms can subvert these defenses, colonize undesired niches, and cause a wide range of infectious diseases. Clinicians have relied on antibiotic therapy for decades in order to treat such infections when they occur. However, many microorganisms are emerging resistant to our current arsenal of antimicrobials and are challenging this treatment paradigm. New antimicrobials and anti-infective strategies are needed to infuse the clinical arsenal with new therapies. Traditional antibiotics operate as variations on the theme of cell killing. An alternative and attractive approach to developing new therapies is to target and attenuate virulence, *i.e.* to target essential steps in pathogenesis that do not influence cell viability directly. Humans naturally produce peptides termed defensins as arms of the innate immune system. New work by Nolan and coworkers reveals the anti-virulence nature of human defensin 6 (HD6), further underscoring the opportunity to consider and design anti-virulence therapies to complement cell-killing strategies.[1]

Two defensins, α-defensin 5 and 6 (HD5 and HD6) are produced in the approximately 16-foot long small intestine in adults, where nutrient absorption takes place through the intestinal epithelium following food and drink consumption.[2] In this niche, where numerous molecules are constantly in transit across the epithelium, intestinal Paneth cells secrete HD5 and HD6 along with lysozyme, for example, to attempt to prevent access to microorganisms that can cause acute food-borne illness as well as complicated systemic infections. HD5 acts molecularly to kill bacterial pathogens. HD6, on the other hand, has not been observed to exhibit antimicrobial activity, but gained attention in 2012 when it was discovered to oligomerize and assemble into “nanonets” to entangle and trap bacteria, preventing intimate

contact with epithelial cells and cell invasion.[3] The HD6 nanonets are visually striking, akin to the spider-web-like biofilm networks produced by bacteria and fungi to enmesh microbial communities. Between 2012 and 2016, HD6 was demonstrated to inhibit host-cell invasion by *Salmonella* (Chu et al 2012) and *Listeria monocytogenes*.[3,4]

Chairatana *et al.* have discovered a new biological function for HD6. HD6 prevents adhesion, invasion, and biofilm formation by the fungal pathogen, *C. albicans*.[1] Furthermore, they have provided insight into the fundamental chemical basis for its function, implicating a key phenylalanine at position 2 of the 32-residue HD6 as being crucial to intermolecular HD6 hydrophobic interactions and, thus, HD6 oligomerization. A single point variant with an alanine replacement, F2A, is unable to form higher order oligomers and is not effective at preventing adhesion to human intestinal epithelial cells or biofilm formation by *C. albicans*. The F2A variant was also ineffective when compared with HD6 in the authors' previous work examining host-cell invasion by *Listeria monocytogenes*.[4]

C. albicans biofilm formation, invasion into the intestinal epithelium, and the consequences of systemic fungal infection present a serious challenge to the host, particularly with the increase in *C. albicans* resistance to antifungal drugs. All promising anti-infective strategies warrant thorough and creative exploration capable of ultimately introducing either immune-boosting or antimicrobial or anti-virulence therapeutics. It is common to look to polymicrobial communities for design strategies that have evolved among microbes in a kind of interbacterial warfare setting to eradicate or influence neighboring microbial populations. Here we find an exciting example of a human defense system that inhibits virulence traits of *C. albicans* without cell killing. Such a strategy may help to maintain the physiologically beneficial balance of microbes in the gut microbiome while preventing the undesired consequences associated with cells that can transition to a pathogenic lifestyle and become poised to invade or colonize intestinal mucosa.

The authors suspect that a general mode of action may be at work to enable HD6 nanonets to interact with and entangle *C. albicans* as well as other microbes, including Gram-negative *Salmonella* species and the Gram-positive bacterium *Listeria monocytogenes*. This possibility brings to light the likeness of nanonets with other web-like materials involving microbes. Biofilm aficionados will note the striking similarities between electron micrographs of these host-derived nanonets and the web-like extracellular matrix materials produced by bacteria in self-entangling and often protective bacterial communities. Biofilm matrix components can vary widely among biofilm-forming organisms, but function similarly at a broad level, promoting cohesion and entanglement among resident microbes. Nanonets also resemble Neutrophil extracellular traps, referred to as NETs[5], in both physical likeness and function. NETs are composed of fibrous materials, primarily DNA from neutrophils, and serve to immobilize and contain invading microorganisms, aiding in their ultimate demise. Further work may identify specific molecular attributes that are uniquely suited to these distinct macromolecular nets and networks and may reveal more specific functional correlates beyond their general adhesive and cohesive functions. The collective discoveries by Chairatana *et al.* demonstrate for the first time that HD6 can prevent key steps in *C. albicans* pathogenesis. The anti-adhesion and anti-biofilm functions ascribed to HD6 and the sequence-specific attributes of HD6 as compared to other defensins fuel future work

to further investigate the molecular advantages of deploying HD6 nanonets in the intestinal niche to maintain a healthy microbiome and defend against pathogens.

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