An Evolving Understanding of the Pathophysiology of Acne

Current thinking in treating acne and the role of nanotechnology in developing future therapies and delivery techniques.

BY ADAM FRIEDMAN, MD

While our understanding of the pathophysiology of acne is still incomplete, it’s definitely grown considerably in the last 10 years or so. And with this, there’s been somewhat of a shift from thinking of our treatment of acne as a “treatment” but rather as a “regimen.” Acne pathophysiology is multi-factorial—it includes inflammation, hyperkeratinization of the follicular ostia, P. acnes, and even hormones—so the one-size-fits-all cookie-cutter approach to treating every patient with acne no longer exists. When treating acne, you have to think about not just the morphology, the distribution, but also the individual patients—that’s where diet and comorbidities come into play.

Another change over the last several years in treating acne has developed as a result of our understanding of how treatments work and why we are using certain medications to treat acne, such as oral antibiotics. We are currently facing a medical crisis of epidemic proportion with multi-drug resistant bacteria as a result of overuse of antibiotics in the US. We know using bactericidal (or more likely static) doses of these antibiotics to treat acne increases that risk, and we have found that it’s not actually killing bacteria that makes a difference; rather the anti-inflammatory effects of antibiotics was helping. You get these anti-inflammatory effects with sub-antimicrobial doses. In understanding this, the way we actually use antibiotics has changed considerably.

THE ROLE OF INFLAMMATION IN ACNE

There’s been a great deal of research and excitement in the area of acne as an inflammatory disease and in serving as a model for understanding other disease states, as well. Historically, we thought of the pathophysiology in terms of the initiating event being hyperkeratinization or blockage of the follicular unit, forming the microcomedone—a lesion from which visible acne emerges with the development of comedonal (“non-inflammatory”) and/or inflammatory lesions (inflammation initiated and propagated by the genome of strains of P. acnes). However, research published over the past decade has provided information about inflammatory mechanisms that warrant us reconsidering the traditional model of pathogenesis, this concept of inflammatory vs non-inflammatory acne, and therefore treatment as

PRACTICAL POINTER

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well. This significant shift in gears occurred after a group of researchers from England published their findings in a 2003 article in *Journal of Investigational Dermatology* showing that, in fact, in non-lesional skin in acne patients, there was evidence of peri-follicular inflammation, macrophages, and the expression of IL-1b, which is very important because that cytokine actually stimulates sebum production as well as follicular epithelium turnover.¹

This paradigm shift from thinking it’s not plugging, but rather baseline inflammation even before the formation of what was once described as a non-inflammatory acne lesion has guided a whole host of new papers and research endeavors and, of course, hopefully therapeutics.

Since then, there’s been a lot of excitement about toll-like receptors (TLR)—pattern recognition receptors that recognize elements specifically on the *P. acnes* cell wall and instigate an immune response. It is believed that this interaction is central to the elicitation of innate immune response early in the process of acne lesion formation, playing a major role in this concept of early preclinical inflammation. And, in fact, retinoids—probably one of the best topical agents we have—down-regulate TLR2, in addition to a broad range of biological activities giving further insight into their efficacy.

But that isn’t the whole story. Recently Jenny Kim and colleagues at UCLA showed that it’s not just TLR2, especially with respect to IL-1b production, but it’s the inflammasome.² Think of the inflammasome as a collection or complex of proteins linked together. This includes caspases as well as NOD-like receptors and pattern-recognition receptors that recognize specific bacterial elements as well as initiate damage response. The researchers found that those same macrophages that that research group saw back in 2003 around the follicular unit actually expressed a specific nod-like receptor that then instigates IL-1b. This is revolutionary because now we may have a target — IL-1b. If we can design therapeutics that target this pre-lesional inflammation, we may be able to treat acne before it’s even clinically there. This can help prevent residual effects of acne, including inflammatory processes, scarring, residual macular erythema, and dyschromia is patients with darker skin types, all of which can be very disabling from a cosmetic standpoint and from a physical standpoint as well. And we don’t have great treatments for these—there are some, but not many. Identifying these kind of preclinical markers that we maybe can interfere with current therapeutics or new agents is very important.

**FUTURE THERAPEUTICS**

The innovation we’ve been seeing in acne therapeutics is not really with respect to new active ingredients, although there are some in the pipeline, but more in delivery. A classic example is that we are now able to deliver two medications that couldn’t be brought together—a retinoid and benzoyl peroxide are now in the same product in EpiDuo. Another is Aczone, which allows for effective delivery of the established antibiotic dapsone, now solubilized and deliverable in a unique vehicle. The innovation has also been utilizing vehicles that reduce adverse events or bystander events of the active products, as many, if not most, acne drugs can be irritating to patients and therefore limit patient compliance.

The trend now is developing vehicles that will really limit this irritation, and maybe make dosing regimens more palatable. At the center of this innovation is nanotechnology, the science of the really really small (one billionth of a meter). Nanotechnology can play an essential role in refining the topical delivery of anti-acne agents by enhancing their dermal localization with a concomitant reduction in their side effects. Pointing is the capability to direct the drug-loaded system to the site of attention. Controlled drug release and subsequent biodegradation are important for developing successful formulations. Research has demonstrated that the size of the particle can influence, for example, the depth of penetration in the pilosebaceous unit, allowing one to specifically target the site of interest. Therefore, it’s possible to design a particle that has a product—benzoyl peroxide, a retinoid, or maybe even both together—to specifically target the pilosebaceous unit and release the payload over time, increasing tolerability. We’ve already seen a little bit of those with Retin A Micro, for example. Sustained delivery allows fewer applications, easier application, and higher benefit without the adverse events.

Across the world, many established products are being put in various forms of nanomaterials—liposomes, nano-emulsions, etc, which is allowing for innovations not just with respect to delivery vehicles, but newer agents, including the following.

Researchers at UCSD have been looking at lauric acid, which is derived from coconuts, and comparing it to

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benzoyl peroxide—its ability to kill *P. acnes* and its role as an immunomodulator. The difficulty is lauric acid is very difficult to deliver in its native form because it’s not hydrophilic and cannot really be put it in a good vehicle. But when encapsulated in a liposome, it’s much easier to deliver and it’s much more effective, as seen in an animal model of inflammatory acne.²,⁴

Another example is chitosan nanoparticles, which I’ve researched along with a group from UCLA. Chitosan is derived from chitin, which is found in the exoskeletons of crustaceans. Nanoparticles synthesized with chitosan and alginate demonstrated a direct cidal effect in vitro against *P. acnes*. Using electron microscopy (EM) imaging, we found chitosan-alginate nanoparticles induced the disruption of the *P. acnes* cell membrane, providing a mechanism for the bactericidal effect. The chitosan-alginate nanoparticles also exhibited anti-inflammatory properties as they inhibited *P. acnes*-induced inflammatory cytokine production in human monocytes and keratinocytes. Utilizing the observed activity with the drug delivery element of nanomaterials, we encapsulated benzoyl peroxide in the chitosan-alginate nanoparticles and demonstrated superior antimicrobial activity against *P. acnes* compared with benzoyl peroxide alone while demonstrating less toxicity to eukaryotic cells. Together, these data suggest the potential utility of topical delivery of chitosan-alginate nanoparticle-encapsulated drug therapy for the treatment of dermatologic conditions with infectious and inflammatory components. How it imparts this anti-inflammatory effect is unclear, but the evidence is definitely there.⁵

Nanotechnology is also being researched for its ability to deliver the undeliverable—nitric oxide. Nitric oxide is a biomolecule that is very simple, very small, somewhat innocuous, but extraordinarily important in biology. It modulates blood vessels, wound healing, melanogenesis, and serves as a key player of innate immune defense. We know what it does, but the difficulty is delivery. It’s so reactive that generally its site of action is just microns from its site of generation. And because it interacts with oxygen, hemoglobin, etc., it really doesn’t last that long.

Nanotechnology is enabling us to deliver it over sustained time periods at physiological or super physiological concentrations.⁶ While there are numerous potential applications in dermatology,⁷ let’s focus on acne vulgaris. It’s no surprise we already generate nitric oxide to fight acne. We have nitrite and nitrate in our sweat and when that comes to the surface, either the acidity of the skin or bacterial commensal organisms convert that nitrite into nitric oxide. Nitric oxide kills *P. acnes* very effectively through multiple mechanisms, being directly cytotoxic as well as inhibiting key cellular machinery for cell growth and survival. Nitric oxide can also function as a potent anti-inflammatory, inhibiting the production of key inflammatory cytokines such as IL-6 and IL-1β (Data presented at the 2014 AAD). Recently it’s been shown that nitric oxide could inhibit the production of androgens, which is really important in managing the hormonal element of acne. So really it can hit acne from every angle, not only in killing *P. acnes* and inhibiting inflammation, but also ultimately preventing sebum production.

Lastly, Dr. Rox Anderson and colleagues are investigating the use of gold nanoparticles to take the major player of acne out of the equation—the sebaceous gland. The strategy in theory is simple, to design a light-absorbing material, force it into the gland, then once the gland is made to absorb light, do selective photothermalism—the same principles that were developed for hair removal. A nano is allowing for this to become a reality. Once applied, the gold nanoparticles were found in human subjects to enter hair follicle, and subsequently excited with an external light source, resulting in selective ablation of the sebaceous gland. And through this data, he brings up a very good point: Do we need sebaceous glands? Dr. Anderson and researchers in Europe have started clinical trials and are so far seeing very good results.

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### References