Researchers identify novel drug combinations to combat Lyme persister cells

Wednesday, June 22, 2016

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In a study entitled "A Drug Combination Screen Identifies Drugs Active against Amoxicillin-Induced Round Bodies of *In Vitro* Borrelia burgdorferi Persisters from an FDA Drug Library," Feng and colleagues hypothesize that when Borrelia burgdorferi, the Lyme bacterium, is confronted with certain stressors, such as starvation or exposure to antibiotics, the spirochete can transform into a "round body" or "persister" form. When examined *in vitro*, these forms appear to be resistant to customary first-line antibiotics used to treat Lyme disease.

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"It is most likely that a single drug may not effectively kill all bacterial populations including morphological variants," states *Feng.* [2] The authors found, "*In vitro*, B. burgdorferi developed increasing antibiotic tolerance as morphology changed from typical spirochetal form in log phase growth to variant round body and microcolony forms in stationary phase."

Based on their *in vitro* studies, the authors identified novel drug combinations they believe are effective in combatting round body persisters. "These morphological variants of B. burgdorferi have different antibiotic susceptibilities, and our recent study showed that some drug combinations are more effective against aggregated B. burgdorferi persisters than single drugs." [2]

Combination treatment which included daptomycin was found to be the most effective in their *in vitro* studies. "Daptomycin plus doxycycline and cefoperazone eradicated the most resistant microcolony form of B. burgdorferi persisters, and did not yield viable spirochetes upon subculturing," reports Feng, "suggesting durable killing that was not achieved by any other two or three drug combinations." [3]

Feng and colleagues describe a persister model to identify additional drugs that did not show good activity in the previous drug screens against the stationary phase of B. burgdorferi. [2] Microscopic examination showed that 96% of the B. burgdorferi spirochetes could be induced into round bodies by amoxicillin in a 5-day-old culture after 3 days with 50 mg/ml amoxicillin. The 6-day or older cultures could not be induced to morph into round body forms completely (<80%) with even 100 mg/ml amoxicillin. [2]

Using their amoxicillin-induced round body model, the researchers identified new drug candidates that may be successful in treating ongoing LD symptoms that do not respond to first-line antibiotic therapies.

“We identified 23 drug candidates that have higher activity against the round bodies of B. burgdorferi than either amoxicillin or doxycycline,” reports Feng and colleagues. [2]

Their amoxicillin-induced round body model validated the success of daptomycin and clofazimine shown to be effective against stationary phase B. burgdorferi persisters. [2] Their model also found artemisinin, ciprofloxacin, nifuroxime, fosfomycin, chlortetracycline, sulfacetamide, sulfamethoxypyridazine and sulfathiozole to be effective. [2]

It is unclear which, if any, antibiotics or combinations would be effective until further *in vitro* and *in vivo* research is completed. Currently, artemisinin, ciprofloxacin, daptomycin and clofazimine are commercially available for other indications.

• *Daptomycin* is an intravenous antibiotic used in the treatment of systemic and life-threatening infections caused by Gram-positive organisms.

• *Clofazimine* is used in combination with rifampicin and dapsone as a multi-drug therapy for the treatment of leprosy. It is no longer commercially available in the United States.

• *Nifuroxime* is a topical nitrofuran with antifungal properties available in a number of countries worldwide.

• *Fosfomycin* (marketed in the US under MONUROL) is a synthetic, broad spectrum, bactericidal antibiotic for oral administration indicated only for the treatment of uncomplicated urinary tract infections in women due to susceptible strains of Escherichia coli and Enterococcus faecalis.

• *Chlortetracycline* is a tetracycline antibiotic for use in beef cattle, non-lactating dairy cattle, and sheep.

• *Sulfacetamide* is a 10% topical lotion approved for the treatment of acne and seborrheic dermatitis.

• *Sulfamethoxypyridazine* is a sulfonamide antibacterial prescribed for vaginal irritation, and severe acute thrush.

• *Sulfathiazole* is a short-acting sulfa drug used until less toxic alternatives were discovered. It is still occasionally used, sometimes in aquariums.

It remains unclear as to how important round body forms are *in vivo*. Feng and colleagues note that round bodies have been described in human infections including brain tissue, [4] but their significance remains unclear. [5] “Some have suggested that these round body forms might be a protective mechanism to overcome adverse environmental conditions,” states Feng. “These round bodies appear to have both lower metabolism and greater resistance to antibiotic treatment.”

Developing novel treatment regimens for Lyme disease takes much time, effort and is a costly endeavor. These *in vitro* studies have introduced novel approaches to therapy that are worthy of further studies.

References:

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