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EXPERIMENTAL ARTHRITIS

Addressing inflamed joints with peptides

Why does arthritic inflammation affect joints, when the aberrant immune response is systemic? A new approach to targeting the inflamed vasculature offers to exploit—and perhaps characterize—this enigmatic specificity. Taking inspiration from efforts to inhibit tumor angiogenesis, Kamal Moudgil and colleagues have identified peptides that home to the vasculature of inflamed joints in an animal model of arthritis. What is more, as the authors report in *Proceedings of the National Academy of Sciences*, one peptide is also anti-inflammatory *in vivo*.

Erkki Ruoslahti (a coauthor of the new study) has, over the past 15 years, "pioneered the concept of vascular 'address molecules,'" says Moudgil. Ruoslahti's work showed that tumors have specialized vasculatures with unique endothelial markers. Realizing that the same approach might identify unique attributes of the synovial vasculature was the start, Moudgil adds, of "a very fruitful and productive collaboration."

Adjuvant arthritis, resembling human rheumatoid arthritis, is induced in the arthritis-susceptible Lewis rat strain using heat-killed *Mycobacterium tuberculosis*. To find the 'molecular address' of inflamed vessels in these rats, the team began with bacteriophage displaying random peptides—a 'phage peptide-display library'. The advantage of this approach, explains Moudgil, is "there is no *a priori* bias in defining the target molecules."

Phage were initially screened for avidity for joint tissue by incubation with synovial tissue from inflamed rat joints. Those with endothelial specificity were identified by isolating cells expressing the endothelial marker CD31; bound phage were recovered and amplified using *Escherichia coli*. Enriched phage were injected into arthritic Lewis rats, and synovial and control tissues were excised. Phage recovered from synovia were injected into equivalent rats, and synovial specificity was increased through repeat rounds of *in vivo* selection. Individual phage from the resultant pool were cloned and their peptide-coding inserts sequenced; cognate peptides were synthesized, and two were chosen for further study. Finally, the peptides were delivered intravenously to Lewis rats either upon, or just after, the onset of arthritis, and clinical signs of disease were monitored.

"We identified two phage-encoded peptides—NQR and ADK—that homed preferentially to arthritic joints," says Moudgil. "They showed specificity for binding to vascular endothelial cells, and they did not bind uninflamed tissue." Furthermore, he continues, "treatment of arthritic rats with NQR, but not ADK, attenuated the disease process." Angiogenesis and leukocyte migration into the joint were inhibited by NQR, partly explaining its anti-inflammatory effect. The elusive 'molecular address' to which the joint-homing peptides bind is as yet unknown, but is not the αVβ3 integrin that binds the 'well-known' peptide RGD, which was used as a positive, non-joint-specific control.

"Inflammation and angiogenesis are two tightly linked processes," begins Marie-Christophe Boissier (University of Paris 13, France) who is an expert in efforts to target the vasculature in rheumatoid arthritis. "Vessels are a key factor for inflammation in arthritis and good candidates for anti-arthritic treatment," she continues, adding: "what is interesting in this paper is that one of the peptides is clinically anti-inflammatory *in vivo*, and does not involve αVβ3 for signaling."

Short peptides are unlikely to become a useful therapy alone, but could be coupled to macromolecules. They could be exploited for targeted delivery of anti-arthritic drugs or imaging agents to the joints. If their ligand can be identified (a goal of Moudgil and colleagues) they could be used to design targeted biologic treatments such as antibodies. "This finding might help us identify an inflammation-specific biomarker," notes Moudgil. For Boissier, an interesting next step would be "to evaluate these peptides in other models of arthritis."

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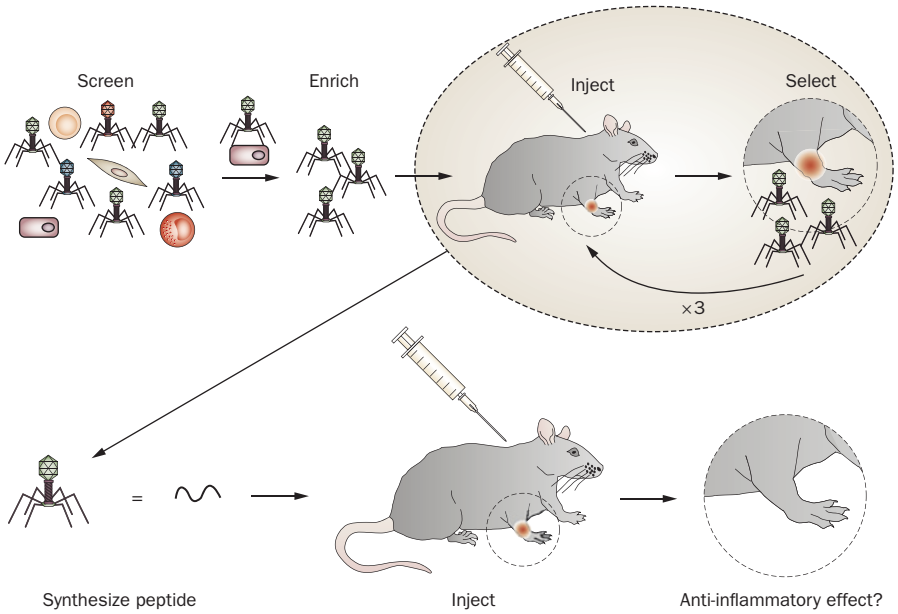

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