Clin Orthop Relat Res (2014) 472:393–395 / DOI 10.1007/s11999-013-3404-x

Clinical Orthopaedics and Related Research®
A Publication of The Association of Bone and Joint Surgeons®

Published online: 3 December 2013

Editor's Spotlight/Take 5

Editor's Spotlight/Take 5: Osteogenic Gene Expression Correlates With Development of Heterotopic Ossification in War Wounds

Seth S. Leopold MD

When a basic science paper floats across the radar of a clinician, or clinician-scientist, it often creates some tension: Read it, or pass?

Attend clinic, pay taxes, or read about osteogenic gene expression? If there is only time for two, I sense the paper, seemingly remote from our next patient or next operation, will go on the back burner. As clinicians and clinician-scientists, we can be excused for being somewhat choosy about basic research. Time is always tight; we want to read science, but prefer to read the science that can potentially "break out" and offer clinical solutions.

The work by Dr. Jonathan A. Forsberg (Fig. 1) and colleagues strikes me as worth the attention of even the busiest of clinicians for three reasons:

1. *The paper is a carefully selected, thoughtfully crafted human model.* The authors are looking for the genes that drive the formation of ectopic ossification in war wounds; their samples come not from animals injured in experiments, but rather from injured service members at the initial and final débridements of high-energy penetrating wounds. We must learn what we can from injured service members in order to improve their care, as well as other patients who sustain severe trauma.
2. *The findings are specific, biologically plausible, and clearly presented.* The investigators identified 13 genes with dramatically upregulated expressions in patients who eventually developed heterotopic ossification. Those genes, including genes involved with the coding of cartilage matrix, tissue remodeling, and

Fig. 1 Dr. Forsberg, above, and colleagues consider heterotopic ossification as one of the most significant barriers to functional mobility, independence, and quality of life for wounded service members.

Note from the Editor-in-Chief: In ''Editor's Spotlight,'' *one of our editors provides brief commentary on a paper we believe is especially important and worthy of general interest. Following the explanation of our choice, we present* ''Take Five,'' *in which the editor goes behind the discovery with a one-on-one interview with an author of the article featured in* ''Editor's Spotlight.''

The authors certify that they, or any members of their immediate family, have no commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc) that might pose a conflict of interest in connection with the submitted article.
All ICMJE Conflict of Interest Forms for authors and *Clinical Orthopaedics and Related Research*® editors and board members are on file with the publication and can be viewed on request.
The opinions expressed are those of the writers, and do not reflect the opinion or policy of *CORR*® or the Association of Bone and Joint Surgeons®.
This comment refers to the article available at: http://dx.doi.org/10.1007/s11999-013-3325-8.

S. S. Leopold MD (✉)
Clinical Orthopaedics and Related Research, 1600 Spruce Street, Philadelphia, PA 19013, USA
e-mail: sleopold@clinOrthop.org

Editor's Spotlight/Take 5

calcification of cartilage, have a high degree of biological plausibility for the problem at hand.

3. *Human model + clear findings = High potential for diagnostic and therapeutic applicability*. Risk stratification identifying patients who will likely form heterotopic bone and molecular mechanisms in order to block the expression of genes that caused it, seems like a plausible next step. This strikes me as genuine translational research — the kind of paper we all want to read.

I hope you enjoy reading the *Take 5* interview with Dr. Jonathan Forsberg as much as I enjoyed conducting it, and by all means after you read it, do explore the fine paper that he and his team published in *Clinical Orthopaedics and Related Research®*. Even if you are busy.

Take 5 Interview with Jonathan A. Forsberg MD Senior Author of "Osteogenic Gene Expression Correlates With Development of Heterotopic Ossification in War Wounds"

Seth S. Leopold MD: *Congratulations on a wonderful study. Why is it so important to study heterotopic ossification?*

Jonathan A. Forsberg MD: Thank you, Dr. Leopold. Early on, during the beginning of the conflicts in Iraq and Afghanistan, we were surprised to find that the majority of casualties developed heterotopic ossification. We now believe this is due to the unique physiologic insult dealt by the blast wave, in particular from improvised explosive devices. This results in an exaggerated and distinctive systemic inflammatory response, which then influences the local wound environment. Since the usual means of primary prophylaxis (radiotherapy or nonsteroidal antiinflammatory drugs) were generally felt to be contraindicated in the acute postinjury setting, and had not been evaluated in these types of patients, we had few options other than surgical excision of mature lesions. Later on, we discovered just how problematic heterotopic ossification was, particularly in amputees who rely on a consistent and durable soft tissue envelope to support a prosthesis. It became clear that heterotopic ossification was one of the single most important barriers to functional mobility, independence, and I believe, quality of life in this patient population.

Dr. Leopold: *To what degree do you think that the genetic findings in your model — one that involved serious, high-energy trauma — might apply to heterotopic ossification in other settings, such as around the elbow, or after lower extremity arthroplasty?*

Dr. Forsberg: This is the real question. We have an opportunity to translate our findings into everyday orthopaedics. One of our goals is to identify early cellular and molecular changes within the tissue — ideally at a time during which primary prophylaxis would still be effective [2]. The present study supports the use of gene expression at the mRNA level for this purpose. However, one of the most exciting prospects involves the use of Raman spectroscopy, which is a noninvasive tool that could even be used intraoperatively [1]. Still, the variability of the human inflammatory system is difficult to quantify. A more thorough understanding of this variability from a molecular signaling and proteomics standpoint may be necessary to allow for more personalized assessments. This knowledge would allow surgeons to act preemptively and suppress an exaggerated inflammatory response before it begins [4]. By doing so, we may be able to mitigate certain downstream complications, such as heterotopic ossification.

Dr. Leopold: *Your paper suggests the obvious next step of trying to predict which patients will develop heterotopic ossification based on their gene expression profiles. How close are you to accomplishing this?*

Dr. Forsberg: We are very close. One of our main focuses is the development of clinical decision support tools for the orthopaedic surgeon. In addition to developing them "in house," we have also partnered with the public and

Editor's Spotlight/Take 5

private sector to make use of more powerful analytical techniques. This type of support is absolutely essential as we move toward the molecular gene expression/proteomics approaches I mentioned above. In the past decade, we have collected thousands of specimens from wounded service members to help answer this question, but long-term success depends upon identifying a surrogate patient population within the civilian sector in which to conduct external validation studies.

Dr. Leopold: *Another area of opportunity, still more exciting, would be to prevent heterotopic ossification from developing in the extremities of injured patients. What are the next steps you expect to take in this direction?*

Dr. Forsberg: The role of the blast overpressure exposure must be evaluated more thoroughly since its effect on systemic inflammation is unique. We have been successful in modeling blast-related heterotopic ossification in the laboratory, and those results should be available shortly. We are also fortunate to receive funding from the U.S. Navy Bureau of Medicine and Surgery Advance Medical Development Program, as well as the Defense Health Program's Peer Reviewed Orthopaedic Research Program to evaluate several novel means of primary prophylaxis. If successful, one or more of these may achieve the desired end of primary prevention. On the clinical side, we are enrolling patients in a FDA randomized clinical trial investigating whether celecoxib is effective in decreasing the prevalence and/or severity of heterotopic ossification in combat casualties [3].

Dr. Leopold: *If you would not mind, talk a little bit about the experience of engaging wounded service members. Unrelated to the basic science of heterotopic ossification, what did you learn from your time with them?*

Dr. Forsberg: Thank you for asking this question. Caring for wounded service members is extraordinarily difficult at times, always humbling, and unbelievably rewarding. Combat casualty care is a team effort, fueled by expertise from all surgical subspecialties, anesthesia/pain management, infectious disease, social work, prosthetics, psychiatry and rehabilitation. In the last decade of war, we have learned firsthand that the human body (and spirit) is extraordinarily resilient. Nevertheless, the devastating nature of these injuries affects not only the patients, but also everyone who provides care to them, which includes clinicians and surgeons, but most importantly, their families. These injuries also tax our abilities as clinician scientists to come up with meaningful solutions as we strive to improve functional outcomes. I am constantly impressed and humbled by my colleagues' ability to adapt and innovate even in seemingly impossible situations. From a research standpoint, I believe that combat casualties should be considered a vulnerable patient population, and we have gone to great lengths to ensure our study designs and recruitment practices reflect this.

Thank you, once again, for the opportunity to share our work.

References

1. Crane NJ, Polfer E, Elster EA, Potter BK, Forsberg JA. Raman spectroscopic analysis of combat-related heterotopic ossification development. *Bone*. 2013;57:335–342.
2. Davis TA, O'Brien FP, Anam K, Grijalva S, Potter BK, Elster EA. Heterotopic ossification in complex orthopaedic combat wounds: quantification and characterization of osteogenic precursor cell activity in traumatized muscle. *J Bone Joint Surg*. 2011;93:1122–1131.
3. Forsberg JA ed. Prophylaxis of heterotopic ossification in wartime penetrating injuries: A randomized clinical trial. Available at: http://www.clinicaltrials.gov. Accessed November 1, 2013.
4. Hawksworth JS, Graybill JC, Brown TS, Wallace SM, Davis TA, Tadaki DK, Elster EA. Lymphocyte modulation with FTY720 improves hemorrhagic shock survival in swine. *PLoS ONE*. 2012;7:e34224.