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editorial focus

Insulin-like growth factor-I: a traffic control device on the road to tissue recovery

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STRESSES ASSOCIATED WITH TRAUMA, infection, and burns have a common denominator. There occurs with the onset of these stresses a set of temporally phased and coordinated responses that involve innate assessment of the magnitude of the "event," redirection of metabolism, coordinated homeostatic rebalancing of the internal milieu, and, finally, if all goes well, recovery. Interestingly, what might appear to be a quite localized site of trauma can force systemic responses that severely affect the prognosis for recovery. Beisel (1) stated that the severity of the host response was largely proportional to the severity of the threat. Similarly, Sir John Hammond (7, 8) was the first to crystallize the theory of metabolic rate-dependant prioritizing of nutrient partitioning between tissues and it is applicable to stress scenarios. Our lab expanded this vision with the superimposition of what we termed the "endocrine-immune gradient" on Hammond's model, wherein the coordinated push and pull of growth factors and cytokines, driven by the response to stress, served to limit the use of nutrients for growth and to make available those same nutrients for immune defense and tissue stabilizing events. This was especially important when food intake was low because of stress-induced hypophagia and cachexia (5). What is so interesting in all of this is that at the core of these host responses lie perhaps only a few key regulators critical to these physiological mechanisms by having the capacity to "morph" in functionality from one phase into another and insulin-like growth factor-I (IGF-I) appears to be one of these key morphing effectors.

Large numbers of investigations have made statistical correlations between some aspect of IGF-I (content or mRNA level) and a given state of pathology for the purpose of implying some cause and effect relationship between IGF-I and the studied condition. However, far fewer investigations have dealt with a structured dissection of biochemical pathways involving IGF-I to explain just how IGF-I plays its regulatory role. Considering IGF-I's rather ubiquitous distribution among various tissues and cells, as well as differing concentrations throughout a variety of normal and pathological situations, this can be a daunting task. Where this can be delineated, a far greater appreciation and understanding of how a once thought of generalized growth factor can have specific multiple signaling capabilities can be realized. In one instance the key to its participation may be its decreased expression and concentration, whereas in another situation, the effect may reside in the increased expression and additional presence of this "growth factor." Again, regarding stress and the endocrine-immune gradient, several functions of IGF-I are often observed within the context of making nutrients more or less available to tissues and in turn increasing or decreasing the anabolic character of metabolism. Collectively, IGF-I (along with its binding protein milieu and signal transduction pathway) plays a strong leading role in setting the priority through which tissues are impacted by the onset and recovery from and in particular with degrees of fine tuning existing in the intricate interplay between signal transduction elements. For example, maintenance of systemic anabolic metabolism via liver-derived circulating IGF-I and its binding proteins (2) becomes a secondary concern to a young animal where site-specific increases in IGF-I may be a primary focus to establish the healing process (9, 10).

Recent data suggest that many aspects of recovery from stress may be facilitated, hastened, and improved with a timely action imparted by a temporally precise delivery of IGF-I to a site-specific location (9, 10). However, in taking the basic science from the laboratory setting to the clinic, we are certainly challenged with regard to how to accomplish this delivery of IGF-I to a target and not further complicate matters because of what are termed negative side effects of IGF-I. Systemic administration by injection, implant, or microencapsulation has limitations associated with the development of hypoglycemia and pharmacokinetic distribution to the target (6, 13, 14). Similarly, because of the associations with feedback on growth hormone secretion, systemic delivery can impact somatotropic axis compromising actions of growth hormone that also participate in homeostatic balance (4). Several of these issues complicating the use of IGF-I as a burn healing effector are surmounted in the results of research reported in this issue of the *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* (3), where a novel delivery of IGF-I to tissues is summarized and discussed in terms of how IGF-I regulates tissue healing through its effects on specific signal transduction elements that participate in reducing apoptosis, modulating (downregulating) the in-

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flammatory phase of burn trauma, and increasing tissue regeneration capacity.

In a series of papers from this laboratory authored by Jeschke et al. (11, 12), reports demonstrated successes in the delivery of IGF-I to the site of thermal injury using liposome-mediated IGF-I gene transfer protocol (11, 12). This nonviral vectored approach has advantages over other delivery techniques, not the least of which are the capacity for site-specific application and the transient nature of the transgenic overly expressed product. Although still in a rather infant stage of development, liposome-mediated gene transfer overcomes additional apparent stumbling blocks associated with the potential for downregulation of expression over time, overexpression resulting in systemic increases in this metabolically active peptide, and problems associated with undesirable clonal expansion of unwanted or unnecessary cell types and functions.

The current study unravels some of the mystery of how IGF-I discriminates among biochemical processes to arrive at a situation that facilitates the repair of tissues injured in thermal trauma. Specifically, these researchers have shown that the expression of IGF-I at the burn injury site works through two principal biochemical pathway adjustments. First, the IGF-I appears to select against proapoptotic processes normally associated with the inflammatory cascade. In this regard nuclear factor (NF)-κB components consistent with anti-apoptotic stabilization processes mediated by the expression of DNA binding factors such as activation protein (AP)-1 are favored along with the suppression of death domain effectors in the Bax and caspase-3 pathways.

Extrapolating just a bit, it appears that this liposome-mediated process may be more of a facilitator of normalization than a pharmacological driver of homeostatic restoration. As these authors point out, a significant feature of this gene process is not that it can just increase a localized production of IGF-I; it more appropriately extends the time period for restoration by expanding the window of opportunity for the positive NF-κB processes to unfold and assist in tissue rebuilding. So, here we come full circle again, and with the stress of these traumatic biochemical events ameliorated, native IGF-I once again returns to its the role as. . .a traffic control device?

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