Healing without inflammation?

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ISCHEMIA FOLLOWED BY REPERFUSION, traumatic injury, muscle unloading followed by reloading, or many other types of injury result in a vigorous inflammatory response followed by eventual healing or ultimate demise of the damaged tissue. The inflammatory response is characterized by neutrophil infiltration, which is often associated with significant additional tissue damage beyond the injury inflicted by the ischemia itself (4). This phenomenon is known as reperfusion injury.

Muscle unloading, a phenomenon that would occur during periods of enforced inactivity, such as prolonged bedrest or microgravity as encountered during space travel, results in a classical inflammatory response (8). Blocking the neutrophilic phase by neutrophil depletion or by blocking neutrophil-endothelial adhesion molecules ameliorates tissue damage in response to ischemia-reperfusion injury and similar insults (1, 9). However, previous studies have raised concern that blocking the (deleterious) inflammatory response may also block the (beneficial) healing response.

The paper by Frenette et al. (3) in this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology addresses this important issue. In a model of hindlimb unloading followed by reloading, the authors show that mice lacking E- and P-selectin have reduced neutrophil recruitment, indicative of a reduced inflammatory response, yet intact monocyte recruitment, indicative of intact healing of the injury, in the reloaded muscles. Monocytes possess a recruitment pathway dependent on $\alpha_{4}\beta_{1}$ integrin on the monocyte and VCAM-1 on the endothelial cells (2), which is not available to neutrophils, or is at least much less important in neutrophils. This pathway of adhesion can apparently engage in the absence of E- and P-selectin.

Selectins are currently being explored as drug targets for inflammatory diseases. Recently, antibodies to selectins were developed and humanized, including antibodies blocking more than one selectin. A humanized version of an L-selectin antibody (DREG-55) is in a phase II multicenter, double-blind, placebo-controlled trial designed to enroll up to 84 subjects who have sustained multiple trauma with injuries involving two or more organ systems. The same antibody is also being tested in psoriatic patients. A recombinant truncated form of a PSGL-1-Ig fusion protein showed promise as a selectin inhibitor (6) aimed at P- and L-selectin in many responses. In clinical trials, this molecule shows good affinity and pharmacokinetics, but it must be produced in mammalian cells that have to be cotransfected with cDNAs encoding for the enzymes fucosyl transferase and core2 GlcNAc transferase, which makes production of even moderate amounts needed for clinical trials very expensive. A few small molecule inhibitors of selectins, so-called glycomimetics, have been developed, notably for E-selectin (5). However, there are few preclinical disease models that are E-selectin-dependent (7), so that the therapeutic benefit of E-selectin blockade alone is not easily tested. Inhibitors of E- and P-selectin are not available for pharmacological use at this time.

A common concern with selectin inhibition is the possibility that healing of the injured tissues would be blocked along with the infiltration of inflammatory cells. The study by Frenette et al. shows that this need not be the case. At least in this one model of skeletal muscle unloading followed by reloading, the absence of P- and E-selectins inhibits inflammation, but not monocyte recruitment associated with the healing response. This finding suggests that the two responses can be dissociated, at least in skeletal muscle injury.

What does this mean physiologically? Frenette’s findings suggest that it may be possible to block the inflammatory response, for example by interventions aimed at blocking selectin function, without blocking the healing response. Although pharmacological blocking studies were not conducted in the present study, the results suggest that such studies could yield favorable results. Monocyte recruitment through the $\alpha_{4}\beta_{1}$ integrin pathway or other pathways not studied in the current investigation, appears to be robust enough to bypass the requirement for selectins. Monocytes express functional ligands for P- and E-selectins, but these are apparently not required for their recruitment to recovering skeletal muscle. The current study therefore encourages the exploration of selectin-blocking therapies in skeletal muscle unloading followed by re-loading.

REFERENCES


