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Editorial

Damage control—The goal posts have not only shifted but we are playing on another field

For decades we have been fascinated and frustrated by the complexity of postinjury inflammatory response and our limited ability to provide an explanation through the principles of immunology. Basic science discoveries provided little direction for therapeutic interventions, which has seen trauma scientists and practicing surgeons moving further apart. Measuring interleukins from batched samples of polytrauma patients' sera and retrospectively correlating with the already recovered or dead individuals' outcomes has not lead to any targeted or patient specific therapy [1]. The association between the early postinjury concentrations of IL-6 (the ubiquitous non-specific proinflammatory cytokine) and systemic inflammatory response related complications after polytrauma has provided an attractive but clinically unproven link that popularised damage control surgery especially in the musculoskeletal system [2].

Three recent discoveries and concepts are shaping the way we understand response to injury and surgery today. None of these concepts are new and they have already withstood at least a decade of scientific challenge. They are gradually solidifying a view of postinjury inflammatory response with potential for advanced therapeutic strategies. The concepts are overlapping, mutually complementary and provide a logical framework.

The first overarching concept has challenged the self and non-self (SNS) fundamental principle of the immune system. While the SNS principle is simple and seemingly straightforward it fails to explain many physiological situations in medicine (lactation, puberty, childbearing) and offers no explanation for the seemingly "septic" state of the non-infected blunt polytrauma patients without any open wounds or surgical interventions. Martzinger proposed a new theory for the fundamental principle of the (innate) immune system [3]. Retaining some of the basics of the SNS and response to infections her principles are based on the intact versus injured/stressed/dangerous self. Our innate immune system (antigen presenting cells) responds to the self in danger rather than the non-self. This explains how certain microorganisms are "non-pathogenic", such as why some of the living donor transplants do better even with major histocompatibility complex (MHC) mismatch than cadaver kidneys with MHC match. Most importantly, the injured self provides a perfect explanation for polytrauma patients' systemic inflammatory response syndrome (SIRS), which is primarily driven by the danger signals (the building blocks and organelles released from injured cells) recognised by innate immune cells' toll-like receptors. Most of our knowledge of cellular and humoral functions of later steps of the inflammatory response is still applicable but the crux of the process has been refreshed.

The second key discovery involves the application of this principle scientifically to trauma care. Hauser's work identified that structural and functional elements of mitochondria instigate a florid inflammatory response and end organ damage in animal models and in clinical scenarios [4]. Mitochondria (ancient bacterium endosymbioid in our cells) have their own double stranded circular bacterium type DNA, which is recognised as a danger signal when exposed to the innate immune system. To date mitochondrial DNA (mtDNA) is one of the most frequently investigated and probably one of the best described danger associated molecular patterns (DAMPs). We know that higher concentrations and longer presence in the circulation is associated with worse outcomes [5]. It is both a marker and the instigator of sterile postinjury inflammation. MtDNA after trauma is released by cell necrosis and also by an active process when even intact functioning mitochondria can be expelled from stressed cells responding to major trauma [6]. Basically, mitochondria and their products can turn as an enemy within our body ("Trojan horse" analogy), while they are supposed to be our essential organelles in energy homeostasis in heightened catabolic state of polytrauma.

Trauma research has lead other surgical groups to investigate DAMPs and describe previously exclusively infection-associated pathomechanisms like neutrophil extracellular trap (NET) formation, which happens as part of the sterile inflammatory response to injury [7]. The framework of NETs is basically extracellular DNA (DAMP), which is now described in the pathomechanism of a wide range of rheumatological conditions, heart disease, stroke and cancer.

Danger molecules and NETs offer attractive prognostic and therapeutic opportunities. The elimination of cell free DNA and NETs with naturally existing DNase can control the inflammatory process at the very beginning. It has been applied successfully in neonatal respiratory distress and in cystic fibrosis. Blocking toll-like receptors is also a therapeutic option to harness overzealous postinjury inflammation.

Should the presence and the magnitude of these DAMPs in polytrauma patients' circulation guide the timing of our interventions? Based on the third major discovery, very unlikely. This simplifies the care for the injured.

The large multicentre effort to describe the genomic response to severe injury (Glue grant) provided us with valuable new insights into trauma care [8]. A large prospective cohort of traumatic shock patients with severe tissue injury were resuscitated in a standardised

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fashion and had blood samples at set time points from injury to 28 days. These studies practically ruled out the possibility of the frequently feared “second hit”, which was the conceptual driver of damage control orthopaedics. Genes influencing postinjury inflammation are completely up or down-regulated in response to major injury and literally cannot get worse due to a surgical intervention. This leaves inadequate resuscitation as responsible for clinical deterioration and requiring abbreviated surgery. As long as a patient is properly resuscitated and their homeostasis preserved, the magnitude of surgery, the length of the surgery in the initial phase cannot be a negative factor to optimal recovery. Early total care in judiciously resuscitated patients has been proven to lead better outcomes [9,10]. Obviously these principles do not apply to “in extremis”, dying patients but very much to those responding to resuscitation and do not deteriorate during surgical care.

Polytrauma is a disease with unique clinical presentations but the pathophysiological processes underneath are applicable to less acute clinical conditions in surgery and medicine. The principles of haemostatic resuscitation, massive transfusion ratios, and damage control surgery were described in an environment in which the underlying science was not well understood. In the light of the present understanding there is a much greater role for early total care and a lesser role for damage control surgery than was previously the case.

References

[1] Easton R, Balogh ZJ. Peri-operative changes in serum immune markers after trauma: a systematic review. Injury 2014;45:934–41.
[2] Giannoudis PV, Harwood PJ, Loughenbury P, Van Griensven M, Krettek C, Pape HC. Correlation between IL-6 levels and the systemic inflammatory response score: can an IL-6 cutoff predict a SIRS state? J Trauma 2008;65:646–52.
[3] Matzinger P. The danger model: a renewed sense of self. Science 2002;296:301–5.
[4] Zhang Q, Raoof M, Chen Y, Sumi Y, Sursal T, Junger W, et al. Circulating mitochondrial DAMPs cause inflammatory responses to injury. Nature 2010;464:104–7.
[5] Simmons JD, Lee YL, Mulekar S, Kuck JL, Brevard SB, Gonzalez RP, et al. Elevated levels of plasma mitochondrial DNA DAMPs are linked to clinical outcome in severely injured human subjects. Ann Surg 2013;258:591–6.
[6] McIlroy DJ, Bigland M, White AE, Hardy BM, Lott N, Smith DW, et al. Cell necrosis-independent sustained mitochondrial and nuclear DNA release following trauma surgery. J Trauma Acute Care Surg 2015;78:282–8.
[7] McIlroy DJ, Jarnicki AG, Au GG, Lott N, Smith DW, Hansbro PM, et al. Mitochondrial DNA neutrophil extracellular traps are formed after trauma and subsequent surgery. J Crit Care 2014;29:1133.
[8] Cuenca AG, Maier RV, Cuschieri J, Moore EE, Moldawer LL, Tompkins RG. Inflammation and host response to injury, large scale collaborative research program. The Glue Grant experience: characterizing the post injury genomic response. Eur J Trauma Emerg Surg 2011;37:549–58.
[9] Nahm NJ, Vallier HA. Timing of definitive treatment of femoral shaft fractures in patients with multiple injuries: a systematic review of randomized and nonrandomized trials. J Trauma Acute Care Surg 2012;73:1046–63.
[10] Harvin JA, Kao LS, Liang MK, Adams SD, McNutt MK, Love JD, et al. Decreasing the use of damage control laparotomy in trauma: a quality improvement project. J Am Coll Surg 2017;225:200–9.

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