SciMedCentral

Journal of Immunology & Clinical Research

Editorial

Contusions, Blood Leakage, and the Immune Response

Marta Lishnevsky and Alan R. Schenkel*

Department of Microbiology, Immunology, and Pathology Colorado State University 1682 Campus Delivery Fort Collins, USA

***Corresponding author**

Alan R. Schenkel, Department of Microbiology, Immunology, and Pathology Colorado State University 1682 Campus Delivery Fort Collins, CO 80523 USA, Tel: 970-491-2926, E-mail: alan.schenkel@colostate.edu

Submitted: 25 July 2013

Accepted: 14 August 2013

Published: 18 August 2013

Contusion to organs, in the absence of infectious agents, is a rare example of "sterile damage." This sets up an inflammatory response that is similar but different to the response to pathogens. From there, there must be a healing response to remodel and repair the wound site. This is a vital but somewhat neglected field of immunology. Concussions and spinal cord injuries are becoming highly visible to the public due to the popularity of sports like professional American football, snowboarding, and mixed martial arts. Recent studies on Damage Associated Molecular Patterns (DAMPs) have brought much needed immunological interest in the subject. The immunological aspects of wound healing are medically important.

All organs can have traumatic but sterile contusion injuries. Most models of contusion use an engineered mechanical impactor to strike the target organ, for example a mechanical impactor to simulate traumatic brain [1], spinal cord [2], lung [3], skeletal muscle [4,5] injuries in anesthetized mice or rats. Similar systems have been used in larger animals, such as miniature pigs [6], rabbits [7], and monkeys [8]. Evaluation in human subjects remains difficult. Most basic physiological studies rely traditionally on epidemiological surveys [9] or observations of select populations such as children [10] or occupational risk in adults [11]. Advanced non-invasive imaging techniques [12,13] or sonography [14,15] may make understanding of the situation in human physiology more feasible. Further, modeling the dynamics of fluids, like blood pools, is being developed at the nexus of math and biomedical engineering [16].

There have been many recent studies looking at the cells of the innate immune response after contusion, such as macrophages [17,18] and neutrophils [19,20]. Mitochondrial derived DAMPs can also activate γδ T cells [21]. In general, these responses are organ specific, but resident macrophages, followed by the influx of monocytes, neutrophils, and T lymphocytes all appear to play critical roles during the acute damage and repair/fibrosis phases. Of particular interest are the different activation phenotypes of T lymphocytes and macrophages. Surprisingly, in the CNS, one study found beneficial contributions to healing from the adaptive arm such as T Helper 1 lymphocytes [22]. Another found detrimental contributions by regulatory T lymphocytes [23]. One might have predicted the opposite, given the normal roles played by these cell types. Do certain subtypes of M1/M2a/M2b/M2c influence this process in different ways and in different organs [24]? For example, the study by Kumar, et al., suggests that M1 activation of microglial cells is detrimental to healing in CNS [17].

DAMPS are molecules released by damaged cells and organs. There is a growing list of DAMPS that includes the family of S100 proteins found in neutrophil, eosinophil, and mast cell granules, defensins, and components of extracellular matrix (fibronectin, hyaluronate, and heparin sulfate proteoglycans). DAMPS are recognized by members of the Toll-like receptor family, in particular TLRs 1-4 and TLRs 7-9 [25-28]. Other receptors include CD36, Receptor of Advanced Glycation End products (RAGE), Advanced Glycation End product receptors (AGE-Rs 1-3), and the purinogenic receptors P2Ys 1, 2, 4, 6, 11-14, and P2Xs 1-7. For further reading, we recommend an excellent recent review of DAMPs and their receptors in the airway by Van Crombruggen et al. [28].

In addition to damage to organ-specific cells, there is localized vasculature rupture. Components of blood also act as DAMPs. The immune response to repair the damaged vasculature, organ architecture, and removal of the clotted blood and dead cells can be quite complex in different tissues. Additionally, fibrinolysis activates many different cell types. Vascular endothelial cells produce tissue plasminogen activator (tPA) and many organ specific cells produce urokinase-like plasminogen activator (uPA) found in plasma. tPA and uPA activate plasmin to degrade fibrin into fibrin degradation products (FDPs) [29,30]. Fibrinogen, fibrin, and potentially, FDPs, can bind to TLR2 and TLR4 [30,31], as well as VLDL-R [32], VE-cadherin [33], and the integrins Mac-1 [34] and αvβ3 [35].

Red blood cells and hemoglobin can also be considered DAMPs. After blood vessel rupture, the red blood cells exit, die, and release their hemoglobin. Macrophages phagocytose and degrade the hemoglobin into hemosiderin and billiverdin [36,37]. Extravasated red blood cells and iron in the microenvironment can induce M2 phenotype in macrophages [38]. Hemosiderin is an exclusively intercellular iron-storage complex that consists of ferritin, denatured ferritin, and additional components. It is found in macrophages in areas of hemorrhage [36,37]. Unlike pro-inflammatory M1 macrophages that take up iron slowly and sequester it to make it unavailable to pathogens, alternatively activated M2 macrophages upregulate scavenger receptors (CD163). CD163 receptors allow for rapid iron uptake, and they

enable M2 macrophages to express a ferritin^{low}/ferroportin^{high} phenotype that enables a robust iron donation to the immediate microenvironment [38]. M2 phenotype is also known to secrete anti-inflammatory mediators through the heme-oxygenase-dependent heme catabolism, and is suspected of donating iron to fibroblasts for collagen synthesis, thus contributing further to collagen deposition and fibrosis [38].

Many contusion studies look at the acute phase of the response to contusion, within hours or a few days. However, there is some evidence that chronic sterile damage can lead to fibrosis in tissues such as muscle [39], spinal cord [40], heart [41], and lung (manuscript submitted). In the lung, components of the pro-coagulant and anti-coagulant pathways, such as Tissue Factor upregulation, decreased anticoagulant Protein C, and thrombin generation can lead to fibrosis when chronically activated [42]. It is currently thought that pulmonary clot formation and activation of protease activated receptors PAR1 and PAR2, are early events that leads to a fibrotic cascade. Pulmonary microhemorrhages quickly lead to interstitial and alveolar fibrin deposition. Although in vitro studies have shown that the endothelium maintains an anti-thrombotic and pro-fibrinolytic profile, in vivo studies indicate that the situation is more complex, and varies with the activation status and concentration of active receptors and cytokine concentrations [43]. It is possible that repetitive chronic injury could dysregulate the balance towards procoagulant and anti-fibrinolytic state, where repetitive post-hemorrhage fibrin deposition could feed into PAR activation and Transforming Growth Factor β pro-repair activity. Alveolar/interstitial fibrin deposition contributes to provisional matrix formation which gets replaced by collagen in as little as 7 days [44].

In summary, signals from DAMPs and blood components, in the absence of infectious agents, lead to a variation of the "inflammatory" programming to control wound repair and remodeling. It is just now being understood how different subtypes of cells, such as M1 and M2 macrophages, influence this process. Further, the growing number of DAMPs should be further expanded by including the blood components, like fibrin and red blood cells, which are clearly a part of a contusion process. Finally, determining how acute damage is controlled versus chronic or repetitive contusion and bleeding will affect studies looking at healing from sterile injuries.

ACKNOWLEDGMENTS

The authors would like to thanks Jamie S. Schenkel for critical reading of the manuscript.

REFERENCES

1. Dixon CE, Kline AE. Controlled cortical impact injury model. In Animal models of acute neurological injuries. Chen J, Xu XM, Xu ZC, Zhang JH, edn. 2009; Humana Press, New York, Totowa, NJ. 385-391.
2. Erbayraktar Z, GÃ¶kmen N, YÄ±lmaz O, Erbayraktar S. Experimental traumatic spinal cord injury. Methods Mol Biol. 2013; 982: 103-112.
3. Hoth JJ, Wells JD, Brownlee NA, Hiltbold EM, Meredith JW, McCall CE, et al. Toll-like receptor 4-dependent responses to lung injury in a murine model of pulmonary contusion. Shock. 2009; 31: 376-381.
4. Curl WW, Smith BP, Marr A, Rosencrance E, Holden M, Smith TL. The effect of contusion and cryotherapy on skeletal muscle microcirculation. J Sports Med Phys Fitness. 1997; 37: 279-286.
5. McBrier NM, Neuberger T, Okita N, Webb A, Sharkey N. Reliability and validity of a novel muscle contusion device. J Athl Train. 2009; 44: 275-278.
6. Jones CF, Lee JH, Kwon BK, Cripton PA. Development of a large-animal model to measure dynamic cerebrospinal fluid pressure during spinal cord injury: Laboratory investigation. J Neurosurg Spine. 2012; 16: 624-635.
7. Nie C, Chen SH. Pathological changes in rabbit retina and its relationship with glutamic Acid after injuries from high-speed bullets. Yan Ke Xue Bao. 2011; 26: 239-243.
8. Suresh Babu R, Sunandhini RL, Sridevi D, Periasamy P, Namasivayam A. Locomotor behavior of bonnet monkeys after spinal contusion injury: footprint study. Synapse. 2012; 66: 509-521.
9. Mauer AC, Khazanov NA, Levenkova N, Tian S, Barbour EM, Khalida C, et al. Impact of sex, age, race, ethnicity and aspirin use on bleeding symptoms in healthy adults. J Thromb Haemost. 2011; 9: 100-108.
10. Dunstan FD, Guildea ZE, Kontos K, Kemp AM, Sibert JR. A scoring system for bruise patterns: a tool for identifying abuse. Arch Dis Child. 2002; 86: 330-333.
11. Alamgir H, Yu S. Epidemiology of occupational injury among cleaners in the healthcare sector. Occup Med (Lond). 2008; 58: 393-399.
12. Oikonomou A, Prassopoulos P. CT imaging of blunt chest trauma. Insights Imaging. 2011; 2: 281-295.
13. Prieto-Valderrey F, Muñiz-Montes JR, López-García JA, Villegas-Del Ojo J, Málaga-Gil J, Galván-García R. Utility of diffusion-weighted magnetic resonance imaging in severe focal traumatic brain injuries. Med Intensiva. 2013; 37: 375-382.
14. Guillodo Y, Bouttier R, Saraux A. Value of sonography combined with clinical assessment to evaluate muscle injury severity in athletes. J Athl Train. 2011; 46: 500-504.
15. Hayashi D, Hamilton B, Guermazi A, de Villiers R, Crema MD, Roemer FW. Traumatic injuries of thigh and calf muscles in athletes: role and clinical relevance of MR imaging and ultrasound. Insights Imaging. 2012; 3: 591-601.
16. Stam B, Gemert MJ, Leeuwen TG, Aalders MC. How the blood pool properties at onset affect the temporal behavior of simulated bruises. Med Biol Eng Comput. 2012; 50: 165-171.
17. Kumar A, Stoica BA, Sabirzhanov B, Burns MP, Faden AI, Loane DJ. Traumatic brain injury in aged animals increases lesion size and chronically alters microglial/macrophage classical and alternative activation states. Neurobiol Aging. 2013; 34: 1397-1411.
18. Tidball JG. Mechanisms of muscle injury, repair, and regeneration. Compr Physiol. 2011; 1: 2029-62.
19. Suresh MV, Yu B, Machado-Aranda D, Bender MD, Ochoa-Frongia L, Helinski JD, et al. Role of macrophage chemoattractant protein-1 in acute inflammation after lung contusion. Am J Respir Cell Mol Biol. 2012; 46: 797-806.
20. Perl M, Kieninger M, Huber-Lang MS, Gross HJ, Bachem MG, Braumüller S, et al. Divergent effects of activated neutrophils on inflammation, Kupffer cell/splenocyte activation, and lung injury following blunt chest trauma. Shock. 2012; 37: 210-218.
21. Schwacha MG, Rani M, Zhang Q, Nunez-Cantu O, Cap AP. Mitochondrial damage-associated molecular patterns activate Î³Î´ T-cells. Innate Immun. 2013; .
22. Ishii H, Jin X, Ueno M, Tanabe S, Kubo T, Serada S, et al. Adoptive transfer of Th1-conditioned lymphocytes promotes axonal remodeling and functional recovery after spinal cord injury. Cell Death Dis. 2012; 3: e363.
23. Kipnis J, Mizrahi T, Hauben E, Shaked I, Shevach E, Schwartz M. Neuroprotective autoimmunity: naturally occurring CD4+CD25+

regulatory T cells suppress the ability to withstand injury to the central nervous system. Proc Natl Acad Sci U S A. 2002; 99: 15620-15625.

24. Gordon S. Alternative activation of macrophages. Nat Rev Immunol. 2003; 3: 23-35.

25. Hoth JJ, Hudson WP, Brownlee NA, Yoza BK, Hiltbold EM, Meredith JW, et al. Toll-like receptor 2 participates in the response to lung injury in a murine model of pulmonary contusion. Shock. 2007; 28: 447-452.

26. Cavassani KA, Ishii M, Wen H, Schaller MA, Lincoln PM, Lukacs NW, et al. TLR3 is an endogenous sensor of tissue necrosis during acute inflammatory events. J Exp Med. 2008; 205: 2609-2621.

27. Gill R, Ruan X, Menzel CL, Namkoong S, Loughran P, Hackam DJ, et al. Systemic inflammation and liver injury following hemorrhagic shock and peripheral tissue trauma involve functional TLR9 signaling on bone marrow-derived cells and parenchymal cells. 2011; Shock. 35: 164-170.

28. Van Crombruggen K, Jacob F, Zhang N, Bachert C. Damage-associated molecular patterns and their receptors in upper airway pathologies. Cell Mol Life Sci. 2013; .

29. Flemmig M, Melzig MF. Serine-proteases as plasminogen activators in terms of fibrinolysis. J Pharm Pharmacol. 2012; 64: 1025-1039.

30. Ward JR, Dower SK, Whyte MK, Buttle DJ, Sabroe I. Potentiation of TLR4 signalling by plasmin activity. Biochem Biophys Res Commun. 2006; 341: 299-303.

31. Motojima M, Matsusaka T, Kon V, Ichikawa I. Fibrinogen that appears in Bowman's space of proteinuric kidneys in vivo activates podocyte Toll-like receptors 2 and 4 in vitro. Nephron Exp Nephrol. 2010; 114: e39-47.

32. Yakovlev S, Mikhailenko I, Cao C, Zhang L, Strickland DK, Medved L. Identification of VLDLR as a novel endothelial cell receptor for fibrin that modulates fibrin-dependent transendothelial migration of leukocytes. Blood. 2012; 119: 637-644.

33. Bach TL, Barsigian C, Yaen CH, Martinez J. Endothelial cell VE-cadherin functions as a receptor for the beta15-42 sequence of fibrin. J Biol Chem. 1998; 273: 30719-30728.

34. Barrera V, Skorokhod OA, Baci D, Gremo G, Arese P, Schwarzer E. Host fibrinogen stably bound to hemozoin rapidly activates monocytes via TLR-4 and CD11b/CD18-integrin: a new paradigm of hemozoin action. Blood. 2011; 117: 5674-5682.

35. Xu Q, Chen X, Fu B, Ye Y, Yu L, Wang J, et al. Integrin alphavbeta3-RGDS interaction mediates fibrin-induced morphological changes of glomerular endothelial cells. Kidney Int. 1999; 56: 1413-1422.

36. Hanzlick R, Delaney K. Pulmonary hemosiderin in deceased infants: baseline data for further study of infant mortality. Am. J. Forensic Med. Pathol. 2000; 21: 319-322.

37. Schluckebier DA, Cool CD, Henry TE, Martin A, Wahe JW. Pulmonary siderophages and unexpected infant death. Am J Forensic Med Pathol. 2002; 23: 360-363.

38. Gaetano C, Massimo L, Alberto M. Control of iron homeostasis as a key component of macrophage polarization. Haematologica. 2010; 95: 1801-1803.

39. Sato K, Li Y, Foster W, Fukushima K, Badlani N, Adachi N, et al. Improvement of muscle healing through enhancement of muscle regeneration and prevention of fibrosis. Muscle Nerve. 2003; 28: 365-372.

40. Zhang SX, Huang F, Gates M, White J, Holmberg EG. Histological repair of damaged spinal cord tissue from chronic contusion injury of rat: a LM observation. Histol Histopathol. 2011; 26: 45-58.

41. Doty DB, Anderson AE, Rose EF, Go RT, Chiu CL, Ehrenhaft JL. Cardiac trauma: Clinical and experimental correlations of myocardial contusion. Ann Surg. 1974; 180: 452-460.

42. Idell S. Coagulation, fibrinolysis, and fibrin deposition in acute lung injury. Crit Care Med. 2003; 31: S213-20.

43. Cines DB, Pollak ES, Buck CA, Loscalzo J, Zimmerman GA, McEver RP, et al. Endothelial cells in physiology and in the pathophysiology of vascular disorders. Blood. 1998; 91: 3527-3561.

44. Swaisgood CM, French EL, Noga C, Simon RH, Ploplis VA. The development of bleomycin-induced pulmonary fibrosis in mice deficient for components of the fibrinolytic system. Am J Pathol. 2000; 157: 177-187.

Cite this article

Lishnevsky M, Schenkel AR (2013) Contusions, Blood Leakage, and the Immune Response. J Immunol Clin Res 1: 1010.