



unbiased bioinformatics approach can yield useful therapeutic targets to enhance nerve regeneration (8). However, the current data on both ATF3 (21) and Hsp27 (8) show only modest improvements in the rate of axonal regeneration in short-term, short-distance nerve regeneration. Therefore, translation into a clinically useful target awaits confirmation in models of long-distance nerve repair in large animals. One thing that would be extremely interesting to investigate is whether overexpression of both ATF3 and Hsp27 in the same animal has an additive or synergistic effect in enhancing the rate of peripheral nerve regeneration. The group led by Clifford Woolf is at the forefront of this research and has the mice needed to examine this issue at hand. Combining their prior work with ATF3 (21) and current work on Hsp27 (8) should be a logical next step. Once a proof-of-concept demonstration with overexpression of both ATF3 and Hsp27 is shown to be a feasible solution, drug-screening assays for small molecules that may mimic their activities may lead to actual improvements in peripheral nerve regeneration.

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Do MDL-1⁺ cells play a broad role in acute inflammation?

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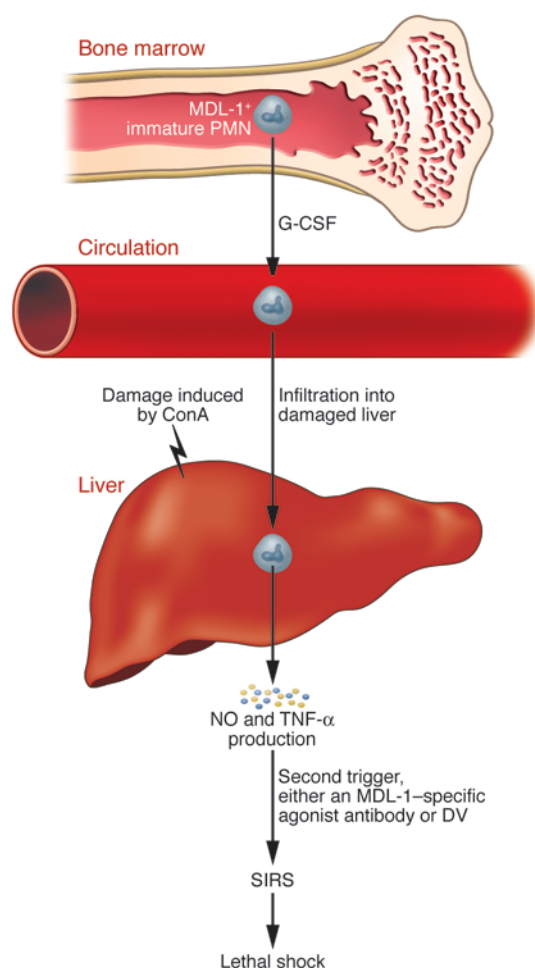
Dengue virus (DV) reacts with myeloid DAP12-associating lectin-1 (MDL-1) on immature polymorphonuclear leukocytes. Interaction of DV with MDL-1⁺ cells triggers systemic inflammatory response syndrome (SIRS) and dengue shock syndrome (DSS), with subsequent multi-organ failure. In this issue of the JCI, Cheung et al. find that sterile acute liver injury in mice is associated with the accumulation of MDL-1⁺ cells and that triggering of these cells by DV or an MDL-1-specific agonist antibody leads to SIRS, shock, and death. These findings may have broad mechanistic and therapeutic implications for the development of SIRS, sepsis, and shock in humans exposed to a wide array of infectious and non-infectious conditions.

injury, or chemical-induced injury (1). In some instances, the localized response to infection or sterile tissue damage becomes progressive, escalating to systemic inflammatory response syndrome (SIRS), a condition that can progress to shock, multi-organ failure, and death (2). The production of proinflammatory cytokines and ROS by activated myeloid lineage cells, especially polymorphonuclear leukocytes (PMNs) and macrophages, is a key component of SIRS. However, the cascade of events that causes SIRS to progress to shock, defined clinically as systemic hypotension, is not well defined. Myeloid lineage cell produc-

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Localized activation of the innate immune system is critical for host defenses against invasive pathogens and for repairing tissues damaged by trauma, ischemia/reperfusion

**Figure 1**

Proposed pathways that are MDL-1 dependent and lead to SIRS, liver injury, and lethal shock in the setting of ConA-induced acute liver injury. In this scheme, release of both PMNs and MDL-1⁺ cells occurs in the bone marrow, under the influence of G-CSF (6). Upon entry into the bloodstream, MDL-1⁺ cells and PMNs traffic into the liver, which has been injured by injection of ConA. ConA initiates inflammation that damages the liver and sets the stage for accumulation of both PMNs and MDL-1⁺ cells. This damage is both PMN- and CD4⁺ T cell-dependent (17). As Cheung et al. describe (6), MDL-1⁺ cells produce NO and TNF- α , which injure the liver and also initiate SIRS and lead to multi-organ failure. This chain of events, which leads to the death of mice, can be greatly attenuated by use of neutralizing antibodies specific for MDL-1 or nitric oxide synthase, or antibodies specific for G-CSF. Also, NO scavengers greatly reduce lethality in this model (6).

tion of TNF- α and NO, which mediate vascular changes that lead to capillary leakage and pathologic vasodilation, is thought to have an important role in the progression of SIRS to shock. However, roles for activation products of complement proteins and acute-phase proteins have also been identified. Further definition of the cellular and molecular mechanisms involved in the progression of SIRS to shock could provide new approaches for therapeutic intervention.

Dengue shock syndrome

One condition that could conceivably be treated with a therapeutic designed to prevent progression of SIRS to shock and lethality is dengue shock syndrome (DSS), a condition estimated to kill 20,000 people each year (3). DSS is a life-threatening condition that arises in some individuals infected with DV, a mosquito-borne virus endemic in tropical and subtropical areas of the world. There are four DV serotypes. Initial infection with any one of these usually results in mild disease, although in some cases DSS devel-

ops. Secondary infection with a different DV serotype is associated with a dramatically increased susceptibility to DSS.

DV can interact with myeloid DAP12-associating lectin-1 (MDL-1; also known as CLEC5A), a C-type lectin expressed by myeloid cells (4), leading to production of proinflammatory cytokines such as TNF- α (5). Blocking DV interaction with MDL-1 reduces vascular leakage and shock in a mouse model of DSS (5). In this issue of the *JCI*, Cheung and colleagues provide new insights into the characteristics of MDL-1⁺ myeloid cells and their function in inflammation (6). These data could lead to new approaches for treating multiple conditions characterized by the progression of SIRS to shock and not just DSS.

MDL-1⁺ cells in sterile inflammation

The work presented by Cheung et al. in this issue of the *JCI* (6) extends the role of MDL-1⁺ cells, which appear to be immature PMNs. The data indicate that MDL-1⁺ cells participate in sterile injury-induced acute

inflammatory responses resulting in SIRS and the subsequent development of shock and lethality. The authors used the concanavalin A (ConA) model of sterile acute liver injury and found that ConA-induced liver injury was associated with a dramatic increase in G-CSF levels in the liver and serum and that this growth factor induced release of MDL-1⁺ cells from the bone marrow into the blood (Figure 1). These cells trafficked to the liver, where they produced TNF- α and NO, triggering organ damage, SIRS, shock, and lethality. In this study (6), a second trigger (either an MDL-1-specific agonist antibody or DV) was required to cause progression to SIRS, shock, and lethality. Cheung and colleagues went on to define the signaling pathways in MDL-1⁺ cells that regulate NO and TNF- α production, which might prove useful therapeutic targets for preventing the progression of SIRS to shock and lethality. Further, as in the mouse model of DSS (5), infusion of a blocking antibody specific for MDL-1 abolished the adverse consequences of ConA



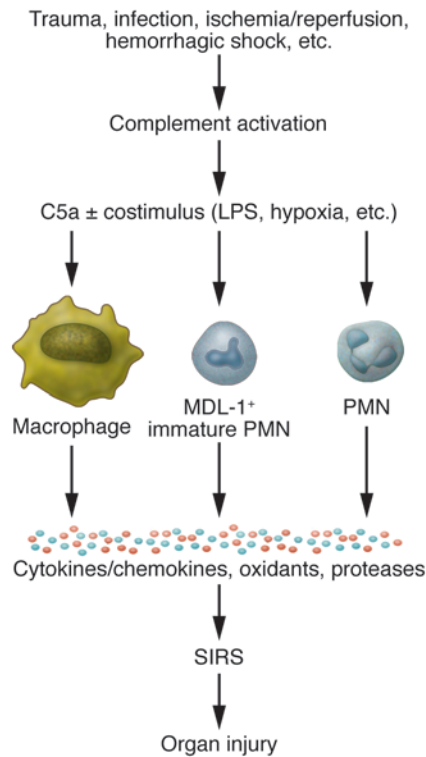
treatment (6), providing an additional potential therapeutic strategy for preventing the triggering of shock.

Fate of hematopoietic cells exiting the bone marrow

Cheung and colleagues show that G-CSF is critical for the release of MDL-1⁺ cells from the bone marrow into the blood (6). They also found that infusion of G-CSF into mice increased the number of MDL-1⁺ cells accumulating in the injured liver, suggesting that G-CSF has a role in promoting cell trafficking to sites of injury. G-CSF and CXC chemokines (such as IL-8 and CXCL4) are also known to cause proliferation of PMN precursors (and perhaps MDL-1⁺ cells) in the bone marrow, resulting in expanded numbers of PMNs released into the blood (7). PMNs spend only a few days in the blood stream (8) and then, by mechanisms described below, transmigrate into tissues/organs. The PMN life span is short due to the tendency of these cells in tissues to undergo apoptosis, which seems to prevent excessive buildup of PMNs in tissues, thereby limiting the extent of PMN-dependent tissue injury (9). To what extent these features of PMNs apply to MDL-1⁺ cells is unknown. If MDL-1⁺ cells are also subject to apoptosis once in tissues, this could represent a way to moderate their role in pro-inflammatory events.

Fate of leukocytes in the vascular compartment

Much is known about PMN trafficking, and it is possible that MDL-1⁺ cells behave like PMNs after they are released from the bone marrow. The bloodstream serves as a highway to deliver leukocytes to tissues and organs, where they form a defensive shield against microorganisms and assist in the repair of tissue damage such as that occurring after ischemia/reperfusion or as a result of trauma. Leukocytes express various adhesion-promoting factors on their cell surfaces (e.g., β_2 integrins such as CD11b/CD18) that facilitate cell adhesion to the endothelium. Activated endothelial cells also express adhesion-promoting molecules (e.g., E- and P-selectin and ICAM-1) that facilitate leukocyte adhesion (10). By this duality, leukocytes ultimately transmigrate into tissues, where they enhance the local innate immune system. Under conditions of excessive PMN buildup and unregulated activation of these recruited leukocytes in tissues, cells and matrix proteins may be damaged (Figure 2).



Complement, PMNs, MDL-1⁺ cells (?), and inflammation

The complement system is a major player in the innate immune system, causing tissue recruitment of PMNs via C5a (an 8-kDa peptide derived from complement component 5 [C5]) and its receptor, C5aR (11). It seems likely that, if MDL-1⁺ cells express C5aR, they will be similarly responsive to C5a. The C5a/C5aR axis is usually protective, allowing PMN recruitment to sites of bacterial infection and to damaged/destroyed tissue, as in myocardial ischemia (12). The recruited PMNs and macrophages will remove bacteria and tissue debris. Protective effects of C5a occur as long as its levels are carefully regulated, leading to enhanced innate immune responses (phagocytosis, chemotaxis, ROS production) in macrophages and PMNs. Another example of C5a's protective effects relates to containment of bacteria during experimental pneumonia, which requires availability of C5aR, presumably on PMNs (13). The excessive C5a production that occurs in experimental sepsis (cecal perforation) and accompanying engagement of C5aR (14) result in dysregulated MAPK signaling pathways (15) and loss of resistance to gut-derived bacteria, which become blood-borne (16). In the cecal perforation model, innate immune functions

Figure 2

Role of C5a in events leading to SIRS and organ injury in a variety of conditions. A common feature of these conditions associated with organ injury is complement activation, which leads to generation of the powerful anaphylatoxin C5a. C5a is highly proinflammatory and interacts with its receptors (C5aR and C5L2) on macrophages and PMNs, resulting in activation of innate immune responses such as phagocytosis, chemotaxis, and formation of ROS and reactive nitrogen species (RNS). When a co-stimulus such as LPS is present, the phagocyte responses are magnified. Via production and release of cytokines/chemokines, oxidants (ROS, RNS), and proteases, SIRS often develops and is frequently associated with multi-organ failure. It seems likely that, being immature PMNs, MDL-1⁺ cells may follow PMNs that accumulate in organs/tissues under conditions described above.

(chemotaxis, phagocytosis) of PMNs were compromised. It is likely that the same innate immune functions in MDL-1⁺ cells would also be impaired during sepsis.

Work to be done

Cheung et al. (6) are to be commended for their work, which sets the stage for a much broader series of studies to define the roles of MDL-1⁺ cells in infectious and noninfectious disorders. Important questions include: (a) What are the natural noninfectious ligands for MDL-1? (b) What is the evidence that MDL-1⁺ cells participate in the protective effects of innate immunity? (c) Do MDL-1⁺ cells express C5aR and respond to C5a in ways similar to PMNs? (d) Is the recruitment pathway of MDL-1⁺ cells to tissues similar to the recruitment of PMNs? (e) In general, do MDL-1⁺ cells accumulate in tissues in parallel to PMNs in acute inflammatory responses?

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The long and the short of aberrant ciliogenesis in Huntington disease

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Huntington disease (HD) is a dominantly inherited neurodegenerative disorder that is caused by a mutant huntingtin (*HTT*) gene encoding a version of the Htt protein with an expanded polyglutamine stretch. Although the *HTT* gene was discovered more than 18 years ago, the functions of normal Htt and the mechanisms by which mutant Htt causes disease are not well defined. In this issue of the *JCI*, Keryer et al. uncovered a novel function for normal Htt in ciliogenesis and report that mutant Htt causes hypermorphic ciliogenesis and ciliary dysfunction. These observations suggest that it is now critical to understand the extent to which ciliary dysfunction contributes to the different symptoms of HD and to determine whether therapeutic strategies designed to normalize ciliary function can ameliorate the disease.

Huntington disease (HD) is an autosomal-dominant disorder caused by expansion of a CAG repeat in the first exon of the huntingtin (*HTT*) gene (1). This repeat encodes an expanded stretch of polyglutamine residues at the amino terminus of the Htt protein. HD is predominantly an adult-onset disorder that is characterized by progressive neuronal cell death primarily in the striatum and deep layers of the cortex. Clinically, it is characterized by motor, cognitive, and neuropsychiatric abnormalities that cause a progressive loss of functional capacity and reduced life span (2). There are currently no effective treatments for

this devastating neurodegenerative disease. This stems largely from an incomplete understanding of the cellular and molecular mechanisms by which mutant Htt causes disease.

Evidence obtained from cell culture and animal model studies supports the hypothesis that the polyglutamine expansion in mutant Htt confers on the protein both a toxic gain of function and a partial loss of normal function (3). More than 100 Htt-interacting proteins have been identified, implicating Htt as a participant in a diverse array of cellular processes (4). One of the most predominant of these processes is microtubule-based transport of vesicles and organelles. The role of Htt in intracellular transport is mediated by its direct interaction with the dynein intermediate chain within the dynein microtubule

motor complex (5) and by an indirect interaction with dynein via its association with a complex containing huntingtin-associated protein 1 (HAP1) and dynactin (6). In the presence of mutant Htt, dynein function is compromised, perturbing vesicle and organelle transport along microtubules.

In this issue of the *JCI*, Keryer and colleagues have linked the function of Htt in intracellular transport to ciliogenesis (7). As mutant Htt was found to cause hypermorphic ciliogenesis and ciliary dysfunction, it is possible that several symptoms of HD might be caused, at least in part, by ciliary dysfunction.

Cilia and ciliopathies

Primary cilia are single hair-like protrusions 1–5 μm in length that are present on virtually all cells, including neurons and glia (8, 9). Primary cilia are nonmotile and have a microtubule skeleton consisting of nine microtubule pairs (9 + 0 axoneme), whereas motile secondary cilia have the same outer nine microtubule pairs, but include inner and outer dynein arms and a pair of central microtubules (9 + 2 axoneme) (Figure 1). Primary cilia in mammalian neurons are derived from a centriole within the centrosome and are located on the soma or proximal portion of the apical dendrite. They are thought to be involved

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