IMMUNOLOGY

Dispensable But Not Irrelevant

Heart injury triggers the release of monocytes from an unexpected reservoir, the spleen.

Ting Jia[1] and Eric G. Pamer[1,2]

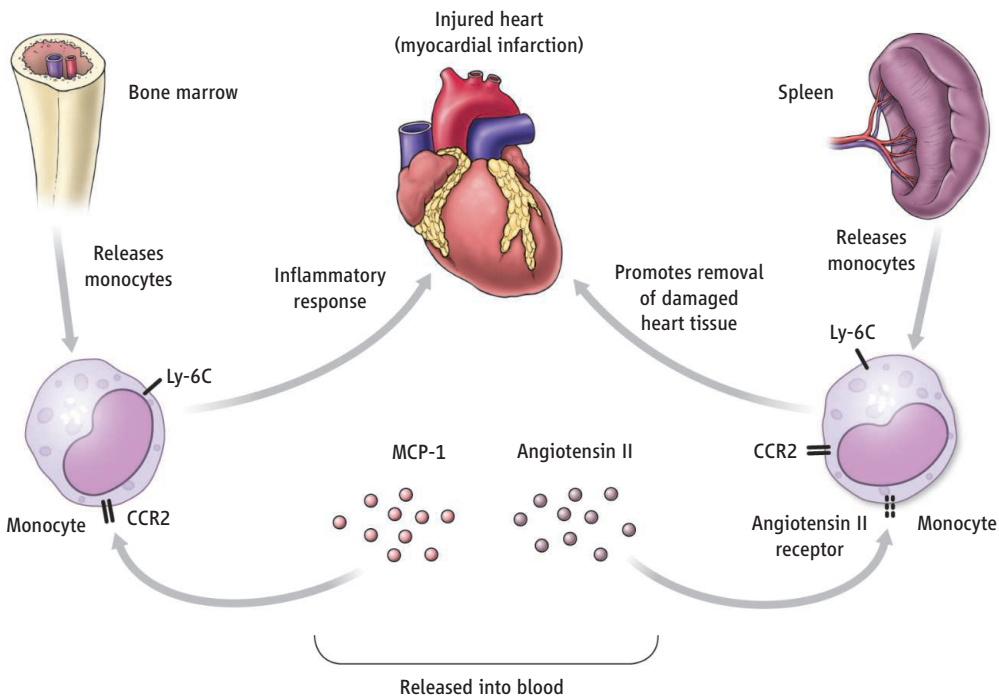
In the left upper quadrant of the abdomen lies the spleen, functioning in two major capacities—filtering and storing blood cells, and acting as an immune tissue, where antibody synthesis occurs and certain pathogens are eliminated. Yet the spleen lacks the gravitas of neighboring organs because we can survive without it, albeit with some inconveniences. Its surgical removal causes modest increases in circulating white blood cells and platelets, diminished responsiveness to certain vaccines, and increased susceptibility to infection with certain bacteria and protozoa. But on page 612 in this issue, the organ gains some new respect, as Swirski *et al*. (*1*) show that in the mouse, the spleen serves as a reservoir for immune cells (monocytes) that function in repairing the heart after myocardial infarction.

Circulating monocytes were postulated by Florence Sabin and Charles Doan, over 80 years ago, to play an important role in defense against infection (*2*), and recent work has confirmed this (*3*). Indeed, monocytes are essential for immune defense against potentially lethal microbial pathogens (*4*). Clearance of microbial infection requires dispatching monocytes from their reservoir, thought to be the bone marrow, in adequate numbers toward the site of infection. Monocytes are guided to their proper destination by chemokines, inflammatory cytokines, and adhesion molecules (*3*). But how adequate numbers of monocytes are mustered for their mission is less well understood. Swirski *et al*. demonstrate that after induction of inflammation—in their case, by myocardial infarction in mouse—monocytes rapidly exit the spleen, enter the bloodstream, and infiltrate the inflamed myocardium to remodel damaged tissue.

Circulating monocytes are a heterogeneous population (*5*), and in humans, can be divided into at least two subsets: one that expresses a high amount of the surface protein CD14 and no CD16, and a more mature subset that expresses a lower amount of CD14 and higher amount of CD16. The latter subset shares similarities with tissue macrophages, which are derived from monocytes. In mice, circulating monocytes also can be divided into subsets on the basis of chemokine receptor expression and the presence of the Ly-6C surface protein (*3*). One subset of murine monocytes (Ly-6C^{high}) expresses high amounts of the CCR2 chemokine receptor and the surface protein Ly-6C, and has been implicated in inflammatory responses. The second murine monocyte subset expresses a high amount of the chemokine receptor CX3CR1 and a low amount of Ly-6C (Ly-6C^{low}) and is similar to macrophages.

Although Ly-6C^{high} monocytes contribute to antimicrobial defense, they have also been implicated in the pathogenesis of atherosclerosis (hardening of the arteries). High blood cholesterol increases the frequency both of circulating monocytes and those that infiltrate lesions (plaques) in arterial walls (*6*). Furthermore, mice in which the CCR2 chemokine receptor or its major ligand, monocyte chemotactic protein-1 [(MCP-1); also called CCL2] are genetically deleted have markedly reduced atherosclerosis (*7*, *8*). Recruitment of monocytes to plaques depends on CCR2-mediated signaling, perhaps in response to MCP-1 produced by cells within the arterial wall. Ly-6C^{high} monocytes lacking CCR2 that are "adoptively transferred" into recipient mice do not traffic as efficiently into plaques of hypercholesterolemic mice as do CCR2-expressing Ly-6C^{high} monocytes (*6*, *9*). Although the most obvious explanation for this is that monocytes use CCR2-mediated signals to enter the arterial wall, it is also possible that CCR2-deficient monocytes return to the bone marrow and become trapped there, because CCR2 is required for monocytes to emigrate from the bone marrow (*10*, *11*). Adoptive transfer studies with Ly-6C^{high} monocytes have shown that they rapidly return to bone marrow in the absence of active recruitment to sites of inflammation (*12*).

Monocytes have also been implicated in the repair of damaged myocardium after myocardial infarction (*13*). In this scenario, Ly-6C^{high} monocytes are first to infiltrate damaged heart tissue and contribute to the



Calling up the reserves. In response to heart injury (myocardial infarction), specific subsets of monocytes are recruited from the bone marrow and spleen to remove and repair damaged tissue.

CREDIT: C. BICKEL/*SCIENCE*

[1]Immunology Program, Sloan-Kettering Institute, New York, NY 10065, USA. [2]Infectious Diseases Service, Memorial Hospital, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA. E-mail: pamere@mskcc.org

fragmentation and recycling of necrotic and apoptotic tissues, whereas Ly-6C^{low} monocytes arrive at the scene later to promote revascularization and collagen deposition. Recruitment of Ly-6C^{high} monocytes to damaged myocardium is dramatically diminished in CCR2-deficient mice. Swirski *et al*. used the mouse myocardial infarction model to further characterize Ly-6C^{high} monocyte recruitment and identified the subcapsular red pulp of the spleen as a major source of recruited monocytes. Interestingly, angiotensin II, a circulating peptide that regulates vascular tone and blood pressure, promotes CCR2-independent emigration of splenic Ly-6C^{high} monocytes into the circulation.

Corticosteroid administration and vigorous physical exertion both result in abrupt increases in the number of circulating white blood cells, including monocytes. It has been assumed in these circumstances that white blood cells are released from endothelial surfaces. The finding by Swirski *et al*. that an increase in the circulating concentration of angiotensin II after myocardial infarction induces the dimerization of the angiotensin receptor on Ly-6C^{high} monocytes reveals a novel mechanism to boost circulating white blood cells in times of stress.

The findings by Swirski *et al*. raise questions about whether other types of stress or injury draw upon the spleen's reserve of monocytes as well. In the meantime, although the study does not make the spleen any less dispensable for mammalian survival, it does make this easily dismissed immune system organ seem a bit more purposeful and deserving of recognition.

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COMPUTER SCIENCE

Is Your Computer Secure?

Security must be built in to software from the outset rather than added on later.

Frederick R. Chang

Cybersecurity is a pressing global issue today and increasingly affects all of us. According to a recent estimate, each U.S. adult had a 66% chance of experiencing at least one data exposure in 2008 and a 30% chance of experiencing multiple such exposures (*1*). A key motivator for cyber attackers is financial gain; a study of the underground economy observed advertisements for over $276 million in total "goods" (such as stolen credit card information) during a recent 1-year period (*2*). The annual cost to companies due to intellectual property theft and repair after data breaches has been estimated at over $1 trillion globally (*3*). Yet, in a study of consumer's personal computers, only 37% had up-to-date anti-malicious software (malware) protection; of those, 23% had active malware infections (*4*). What are the key cybersecurity dangers today, and how can they be addressed?

Computers can be infected merely by surfing the Web. By attacking a single Web site, attackers can potentially infect the computers of all visitors to that site. Using a technique known as SQL (Structured Query Language) injection, an attacker can insert malicious code into the database associated with the Web site. If the victim's browser is vulnerable, that malicious content is transmitted to the victim's computer. Using another technique, cross-site scripting, the software toolkit known as "Mpack" recently caused considerable damage (*5*). Users visiting legitimate Web sites were invisibly redirected to a server that downloaded malicious software onto the user's machine. Various types of malware can be downloaded to the victim's machine in this way, including keyloggers (which steal account and password information), rootkits (which hide the presence and activity of malicious software), and software enlisting the computer in a botnet.

Botnets are responsible for attacks including spam, phishing, distributed denial of service, data harvesting, click fraud, and password cracking. A bot is a computer that has been infected such that it can be remotely controlled; a botnet is a large network of bots. Up to 25% of the world's network-connected computers may be part of a botnet (*6*). In 2008, the botnet Srizbi sent out an estimated 60 billion spam messages per day—about 50% of the world's total (*7*). At the end of 2008, Srizbi's impact was much reduced when a suspect Web hosting company was cut off from the Internet. The botnet made a comeback, but in early 2009 a software patch was released that could remove the Srizbi software from client computers.

Another recent botnet, Storm, was estimated to have infected 1 million to 5 million computers; each infected computer sent out an average of 1200 spam messages an hour (*8*), generating healthy revenue for the botnet owners (*9*). Storm successfully evaded antivirus protection, had a decentralized control structure that made it difficult to shut down, and had a built-in self-defense mechanism (it launched denial of service attacks against researchers trying to access and study it). Storm also made sophisticated use of social engineering techniques: It was highly effective at inducing people to take action (such as to download and execute files), thereby infecting their computers with malware.

Social engineering here refers to manipulating a computer user to take an action with undesired consequences, such as downloading a file containing malware, clicking on a link that takes them to a fraudulent Web site, or divulging confidential information. Many users are easily manipulated in this way. In a study (*10*), university computer science students were sent an e-mail explaining that the system password database had been compromised and that they should reply with their password so that they could be validated in the database. No such database compromise had in fact occurred. The students were advised that they should never reveal their passwords to anybody, yet 41% of the students sent their passwords. Most were suspicious, changing their passwords in the 2 weeks after the study, but very few reported the incident (*10*).

In another study, a credit union hired a security firm to perform a social engineering "penetration test" on itself. When

Department of Computer Sciences, The University of Texas at Austin, Austin, TX 78712, USA. E-mail: chang@cs.utexas.edu