Making Macrophages Eat Cancer

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Science **341**, 41 (2013);
DOI: 10.1126/science.1241716

Science (print ISSN 0036-8075; online ISSN 1095-9203) is published weekly, except the last week in December, by the American Association for the Advancement of Science, 1200 New York Avenue NW, Washington, DC 20005.

the burst sources to be at large, cosmological distances. But this scenario is complicated by the possible residence of the sources within host galaxies that could contribute appreciably to the plasma budget. The source itself or its local environment may also be relevant.

Any of these complications would mandate a closer distance than if the intergalactic medium were solely responsible. The most extreme near-sited explanation would invoke a source whose emission process itself involves or mimics the plasma dispersion effect. Although contrived, this possibility cannot be excluded at present.

The observations by Thornton *et al*. provide an additional clue that favors a far-sited picture. The asymmetry of one of the pulses is easiest to explain if the scattering plasma is neither unduly close to the source nor close to Earth, which argues against the extreme near-sited explanation (see the figure). An extragalactic interpretation seems secure, but exact source distances are not known. Redshifts of 0.5 to 1 are indicated if the intergalactic medium dominates dispersion, but sources residing in galactic centers could be much closer. Determining distances is important for analyzing source energetics and estimating event rates. Translating the deduced daily rate of 10^4 radio bursts to a per-galaxy rate scales as the inverse cube of the distance, which makes any comparison highly uncertain.

The method used for identifying transient sources when sources are not well localized is to find counterparts at other wavelengths. The story of GRBs provides some lessons. Initial localizations were very poor, there was no distance information, and bursts did not repeat. Not until more than 20 years after their discovery were GRBs known to have originated from cosmological sources. Until GRB afterglows were localized in the x-ray, optical, and radio bands, speculation ranged all the way from the solar system (Oort cloud comets) to cosmological supernovae. Although the plasma dispersion of the radio bursts indicates an extragalactic origin, localization on the sky remains problematic. The single-dish telescope used for their discovery localizes to about 0.25°, far too large to find a smoking gun in, say, a particular galaxy among the large number contained in the field of view.

The future is extremely promising for time-domain astronomy. Extragalactic radio bursts are a disruptive discovery that will alter the usage and construction of radio telescopes for surveying the cosmos. Few radio bursts have been seen so far because radio observations have lacked either the necessary time resolution or the large field of view needed to sample large fractions of the sky.

Increasing the detection rate requires telescopes with much larger fields of view, such as those now being deployed and planned at low frequencies (*4*–*7*). New technologies for multiple-pixel systems on reflector antennas will make the Square Kilometre Array and its precursors important time-domain telescopes (*8*–*10*). Currently, any repeating bursts could be localized with the Jansky Very Large Array or the Very Long Baseline Array. Arc-second positioning will result from these interferometric arrays combined with high-bandwidth digital processing to apply detection algorithms. This big-data aspect of blind radio transient surveys is a necessary part of operations for both existing and future telescopes, especially the latter. The mystery of the radio bursts will be solved and, with a sufficiently large sample, these bursts will provide an important tool for probing ionized gas, including magnetic fields, in host galaxies, the intergalactic medium, and the cosmic web.

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10.1126/science.1240618

IMMUNOLOGY

Making Macrophages Eat Cancer

Antibody-based therapies to treat cancer may get a boost from an adjuvant that prevents cancer cells from escaping engulfment by macrophages.

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A growing number of approaches to treating cancer, including antibodies, vaccines, and cell therapy, harness the immune system to seek and destroy cancer cells (*1*–*3*). Antibody-mediated immunotherapies have the potential to treat a large proportion of cancers. For decades, monoclonal antibodies have been used to directly target tumors (*4*, *5*). However, cancer cells can develop resistance to antibodies and tumor regression may not persist in some patients. On page 88 of this issue, Weiskopf *et al.* (*6*) describe an antibody-mediated tumor immunotherapy in mice that overcomes the resistance of cancer cells to antibodies.

Antibodies can combat disease by aiding the action of macrophages. These immune cells engulf or "eat" diseased cells in a process called phagocytosis, which is mediated by engagement of the constant fragment (Fc) of antibodies with Fc receptors on the surface of macrophages (see the figure). However, tumors subvert normal immune control mechanisms to escape the attention of immune cells (*7*), including macrophages. One such mechanism involves CD47, a protein expressed by normal cells. CD47 interacts with a receptor on macrophages called signal-regulatory protein α (SIRPα). This leads to the transmission of a "don't eat me" signal to macrophages, which then leave normal cells alone (*8*). Expression of CD47 by cancer cells renders them resistant to macrophages, even when the cancer cells are coated with an antibody. Because macrophages often occur in large numbers in tumors, they are ideally placed to act against cancer cells if the "don't eat me" signal is switched off.

One therapeutic strategy is to block the "don't eat me" signal with a monoclonal antibody against CD47 (*9*). However, binding of anti-CD47 antibodies to normal cells can produce adverse side effects, and their large size can impede their penetrance of tumors. To overcome these limitations, Weiskopf *et al*. synthesized a soluble form of SIRPα monomers that block the interaction of CD47 with SIRPα expressed by mac-

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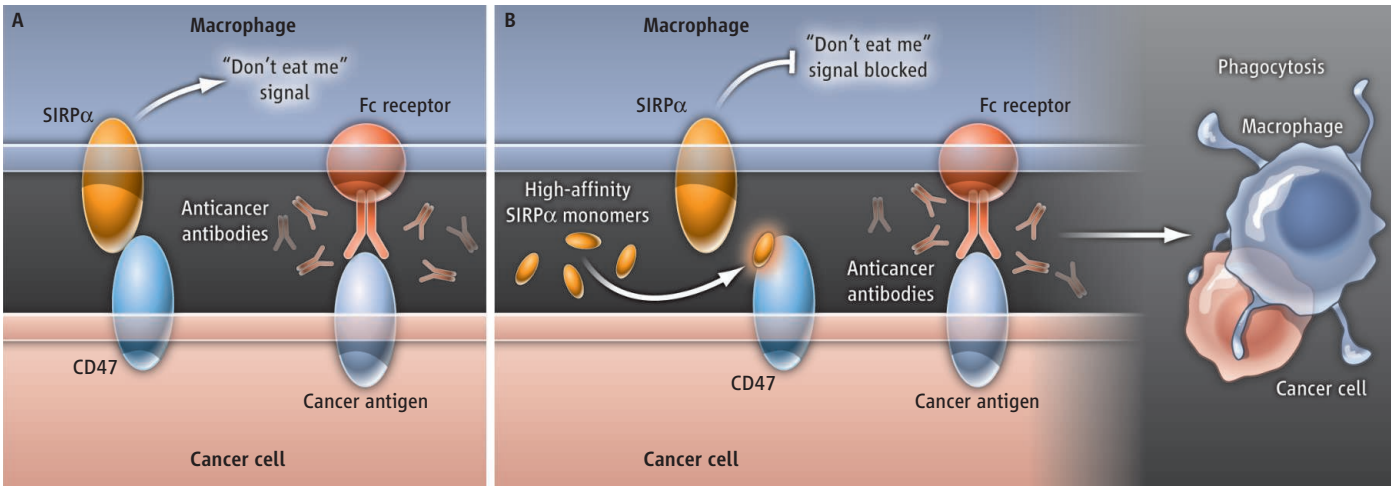

Macrophages, unleashed. (**A**) Cancer cells can be eliminated either directly by immune cells (not shown) or indirectly by antibodies that bind to antigens expressed by cancer cells, but many tumor cells escape destruction and continue to proliferate. Binding of CD47 on cancer cells to SIRPα on macrophages transmits a "don't eat me" signal to the macrophage, and the cancer cell evades destruction. (**B**) High-affinity soluble SIRPα monomers, when administered with antibodies, block CD47-SIRPα interaction, thereby preventing the "don't eat me" signal and allowing the macrophage to engulf the cancer cell.

rophages. This soluble SIRPα (~14 kD) is much smaller than anti-CD47 antibodies. By screening a library of mutant forms of SIRPα, the authors identified variants (FD6 and CV1) with affinities 50,000-fold greater than that of natural SIRPα.

The crystal structure of FD6 bound to CD47 revealed that the interaction would likely block the "don't eat me" signal. Indeed, Weiskopf *et al*. showed that monomeric high-affinity SIRPα increased the engulfment of antibody-coated cancer cells by macrophages in vitro. Remarkably, when CV1 was given to mice in combination with the monoclonal antibodies rituximab or trastuzumab (used to treat lymphoma and breast cancer, respectively), tumor growth was reduced or eliminated entirely.

The immunodeficient mice used by Weiskopf *et al*. express a SIRPα allele that binds to human CD47, which enables in vivo evaluation of human CD47 blockade by high-affinity SIRPα. The high-affinity soluble SIRPα can bind to mouse CD47 and thus the animal model allows not only the engraftment of human tumors, but also the evaluation of efficacy and toxicity due to CD47 expression on normal mouse cells. Interestingly, chronic anemia was noted in both mice and cynomolgus macaques (which express a CD47 ortholog that is nearly identical to human CD47), but only when the SIRPα variant (CV1) contained a region that could bind to the Fc receptor. Thus, separating CD47 blockade from Fc receptor engagement appears to be a safer anticancer strategy. One important limitation of the animal model is that the immunodeficient mice lack many types of immune cells, including regulatory and effector T cells, B cells, and natural killer cells; and it is unclear whether this approach to therapy will succeed in immune-competent mice or patients. Further, the immunodeficient mice used by Weiskopf *et al*. lack endogenous antibodies, and it is unknown how safe or immunogenic this approach would be in humans, particularly those possessing autoimmune antibodies.

Weiskopf *et al*. did observe a marked increase in macrophage-mediated phagocytosis of cancer cells and/or inhibition of tumor growth in the mouse model, irrespective of the type of cancer or therapeutic monoclonal antibody used. Therefore, the high-affinity SIRPα molecules may be useful to treat many types of cancer for which therapeutic antibodies currently have limited effects.

Antibodies can act on tumors in a number of ways, from blocking growth factors to recruiting immune cells that attack cancer cells (*10*). Although macrophages have some anticancer activity, the study by Weiskopf *et al*. suggests that their potential has been underestimated and that harnessing their phagocytic capabilities with antibodies and monomeric SIRPα is a substantial improvement

Advances in generating antibodies for treating malignant disease include the humanization of antibodies and optimization of their binding to Fc receptors (*11*, *12*). Weiskopf *et al.* build on these improvements to realize a much greater potential of antibodies. Direct coupling of drugs and toxins to antibodies has also provided better targeting of cytotoxic agents against cancer (*13*), although some side effects still occur. Perhaps the SIRPα strategy described by Weiskopf *et al.* will enable macrophages to destroy cancer without the use of toxins.

This approach could also be used in combination with immunotherapies that boost the activity of immune cells other than macrophages. One method is to also block the so-called checkpoint molecules—cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) and programmed death 1 (PD-1)—that inhibit T cells of the immune system (*3*). Combining SIRPα and antitumor antibodies with checkpoint blockade may liberate multiple components of immunity, including macrophages and T cells, in a united assault on cancer. More than 100 antibodies are in current clinical use against cancer. It is likely that a combination of tumor immunology, structural chemistry, and genetic engineering will dramatically revolutionize cancer treatment.

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Acknowledgments: M.H.K. and M.J.S. are supported by the National Health and Medical Research Council of Australia.

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10.1126/science.1241716