WOUND HEALING

The hallmarks of cancer are also the hallmarks of wound healing

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The Hanahan and Weinberg "hallmarks of cancer" papers provide a useful structure for considering the various mechanisms driving cancer progression, and the same might be useful for wound healing. In this Review, we highlight how tissue repair and cancer share cellular and molecular processes that are regulated in a wound but misregulated in cancer. From sustained proliferative signaling and the activation of invasion and angiogenesis to the promoting role of inflammation, there are many obvious parallels through which one process can inform the other. For some hallmarks, the parallels are more obscure. We propose some new prospective hallmarks that might apply to both cancer and wound healing and discuss how wounding, as in biopsy and surgery, might positively or negatively influence cancer in the clinic.

INTRODUCTION AND BACKGROUND

For over a century, it has been noted that tumors appear to behave similar to wounds that fail to heal (*1*–*4*). In recent years, it has become clear that there are many cellular and molecular parallels indicating multiple shared mechanisms that differ only in their being well regulated during healing of a wound and dysregulated during cancer growth and metastasis (*5*, *6*). Whereas acute wound repair normally has a resolution phase, tumors behave more similar to a chronic wound, which has no resolution phase. Because of these parallels, the genomic datasets and mechanistic findings gathered from studying wound healing may provide us with potential insights into the processes that are involved in tumorigenesis and vice versa.

Hanahan and Weinberg's original and subsequently revised and expanded "hallmarks of cancer" papers (*7*, *8*) highlight the key mechanisms that appear to underpin all cancers. In this Review, we propose that many of these "hallmarks" and "enabling characteristics" may also be shared by those mechanisms that underpin healing wounds (Fig. 1). What might be a necessary and precisely activated mechanism for tissue repair is mirrored by dysregulation and failure to attenuate in a growing cancer. This way of thinking may elucidate the parallels between these two processes and suggest ways in which these research disciplines might learn from one another. We discuss which of the hallmarks most clearly extrapolate from cancers to wounds and which are less clearly true for both (Fig. 2). We also speculate on additional shared parallels to be considered prospective hallmarks or enabling characteristics and discuss what happens when cancers meet wounds in the clinic, such as during biopsy and surgery.

HALLMARKS AND ENABLING CHARACTERISTICS WITH THE CLEAREST PARALLELS

Hallmark 1: Sustaining proliferative signaling

Many early studies of cancer focused on this hallmark because, naturally, without cell proliferation, cancer cannot grow. Mutations that affect some key oncoproteins (such as Ras and Raf) result in either constitutive activation of proliferative signaling or failure of normal negative feedback mechanisms, both of which can drive uncontrolled cell proliferation without the need for mitogenic stimuli (*9*). Tissue damage, in contrast, leads to at least some tissue loss, and, generally, these missing cells need to be replaced as part of the repair process.

In a tumor, cell proliferation can appear haphazard and disorganized, but wounding triggers a coordinated and synchronized proliferative response. Classic studies of repair described proliferative zones behind the migrating epidermal leading edge (*10*, *11*). More recent investigations of wounds in mice have refined this proliferative zone and shown that it arises several hours after wounding and persists for several days; although the proliferative zone is indeed behind the immediate leading edge, it can be dynamic and encroach into the zone of migration (*12*, *13*). After the epidermal wound edges have met and migration ceases, cell proliferation spreads into the just-sealed central zone (*13*). Whereas an inability to proliferate is incompatible with repair of large skin lesions, cell division does not necessarily drive re-epithelialization; indeed, tissues that do not divide, such as the epidermis of embryonic *Drosophila melanogaster*, are perfectly capable of healing a small wound (*14*). Moreover, inhibiting cell division in murine skin wounds with mitomycin C delays but does not prevent wound re-epithelialization (*12*).

Whereas tumorigenic proliferation is caused by constitutive, intrinsic changes in mitogenic signaling, proliferation in wounds is specifically induced by tissue damage and ceases when repair is complete. Simple in vitro scratch wound assays suggest that cell division is contact inhibited in a confluent, intact sheet of cells, and this inhibition is released upon wounding (*15*, *16*). This release from contact inhibition might be sensed, in part, by the stretch receptor, piezo, which reports tension changes through Ca^{2+}-dependent phosphorylation of extracellular signal–regulated kinases 1 and 2 (ERK1/2), leading to *cyclin B* transcription, which is necessary to drive mitosis (*17*). This change in tissue mechanics will be sensed by cells experiencing reduced density as migration begins. However, classic laminar flow scratch wound studies have shown that at least some of the cell division at a cut edge is driven by increased exposure to growth signals in the media (*18*). We know some of the mitogenic signals that drive epidermal wound proliferation in vivo. For example, transcripts encoding fibroblast growth factor 7 (FGF7;

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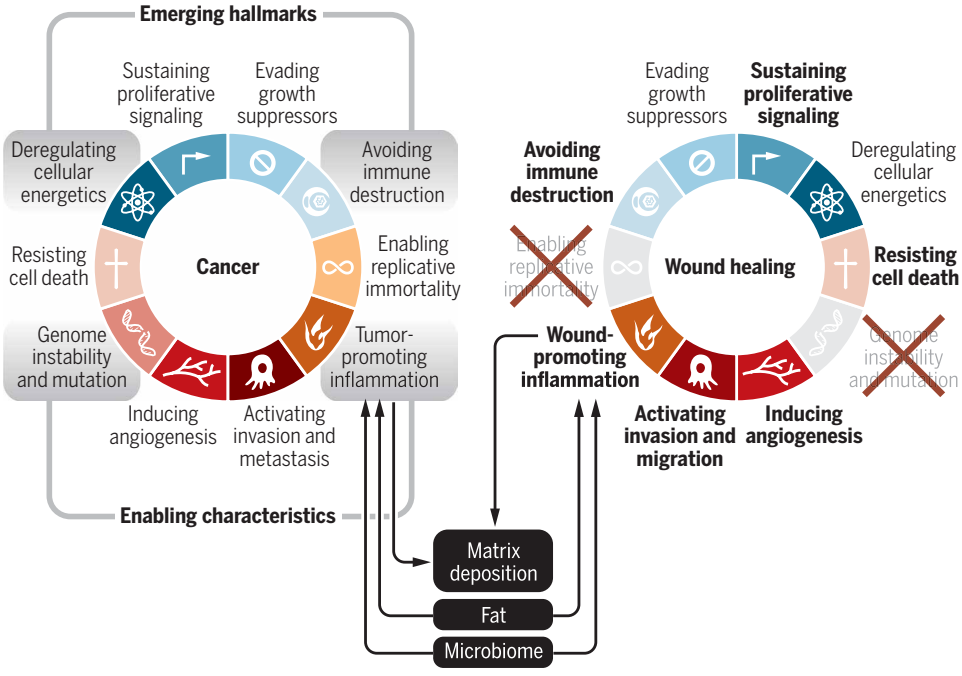

Fig. 1. The classic "Hallmarks of Cancer" circle adapted from Hanahan and Weinberg (2011) to illustrate parallels between cancer and wound healing. Many of the hallmarks and enabling characteristics of cancer are mirrored in wound healing. For some processes, the parallels are very clearly present (bold text) or absent (crossed-out text). For other processes, there are hints that there may be parallels. We propose three new prospective enabling characteristics or hallmarks (black boxes) that either contribute to or are a consequence of inflammation and may apply to both cancer and wound healing: changes in matrix deposition, fat cells, and changes in the microbiome (dysbiosis).

also known as keratinocyte growth factor) are strongly stimulated in dermal fibroblasts in a skin wound (*19*), and blocking the epidermal response to FGF7 by expressing a dominant-negative FGF2 receptor largely prevents cell divisions in the advancing wound epidermis and leads to impaired wound re-epithelialization (*20*). Other important epidermal wound growth factor signals include epidermal growth factor (EGF) and transforming growth factor–α (TGF-α) (*21*), both of which are delivered to the wound largely through the degranulation of platelets and infiltrating macrophages, and hepatocyte growth factor, which is produced by the advancing wound-edge epithelium, thus acting as an autocrine signal (*22*).

Some of these proliferation signals are present at the wound from the start; yet, the surge in proliferation is not immediate. One early indication of epidermal responsiveness conserved from flies to mammals may be an increase in, and nuclear translocation of, immediate early transcription factors including c-Fos and c-Jun and Egr1 (*23*–*25*) within hours of wounding. However, access to the DNA by these immediate early transcription factors depends on the epigenetic status of target genes in these cells. At least some of the later-activated genes have silencing histone methylation marks deposited by the polycomb family of epigenetic regulators. Upon wounding, the polycombs are repressed and the suppressive marks are removed, enabling the previously silenced genes, including that encoding the EGF receptor, to be transcriptionally activated (*26*). It is tempting to speculate that at least some of these wound-induced genes that are first epigenetically unsilenced before they can be transcribed are those that drive key cancer-associated mechanisms such as proliferation and migration and thus need fail-safe regulation.

Many epidermal wound mitogens will naturally disappear as platelets are cleared and the inflammatory response is resolved, but, very likely, there are also additional active mechanisms that shut down epidermal cell proliferation in the wound epidermis when closure is achieved. These will include the very same contact inhibition cues that the release of which, in part, drove the initial proliferative surge, as wound-edge cells re-establish contacts when they close the wound (*17*). Such mechanical cues are again detected by mechanoreceptors including piezo in a process that clearly fails to operate properly in a growing cancer [reviewed in (*27*)].

Hallmark 2: Activation of invasion (and metastasis)

Generally, cancers kill when they become invasive and metastasize, and so this has become one of the most keenly investigated of the hallmarks. Re-epithelialization during wound closure bears considerable resemblance to processes that occur in the early migratory stages of carcinoma invasion, including epithelial-to-mesenchymal transition (EMT), breaching the basement membrane (BM), and associating with nonepithelial cells. Several hundred genes are switched on in the advancing epidermal wound-edge cells, and many of these also form the transcriptional signature(s) of invasive carcinomas [reviewed in (*5*)]. For many of these genes, we still do not know their precise function in the repair process, but others have characterized roles in transient tethering, proteolysis, or the loosening of cell-cell junctions.

The invading fronts of a carcinoma usually comprise small clusters of outgrowing cells, and the advancing wound epidermal tongue is similarly limited to only one or two cell layers at the advancing tip. Wound re-epithelialization requires leading-edge basal keratinocytes and all follower cells to leave their usual BM substratum and migrate onto and across the wound provisional matrix deposited by fibroblasts. This transition requires an alteration in the integrin expression profile to accommodate the changing matrix and to enable cells to make transient adhesions for forward migration. To migrate from the BM, cells switch off the hemidesmosomal α6β4 integrins and instead express several other integrins that are not normally present in unwounded skin; these new integrins are essential for proper migration across the newly deposited provisional wound matrix, as revealed by the delayed and abnormal re-epithelialization of wounds in mice having epidermal-specific knockout of β1 integrin (*28*). Whereas integrin expression is generally confined to the basal layer in unwounded skin, all epidermal cell layers in the advancing wound edge express them (*29*), suggesting that all the cells there are active migrators; indeed, live imaging studies in repairing murine wounds indicate that there is cell shuffling between these layers and active participation in the migration process by both suprabasal and basal cells (*12*). At least one migration-specific cell-cell

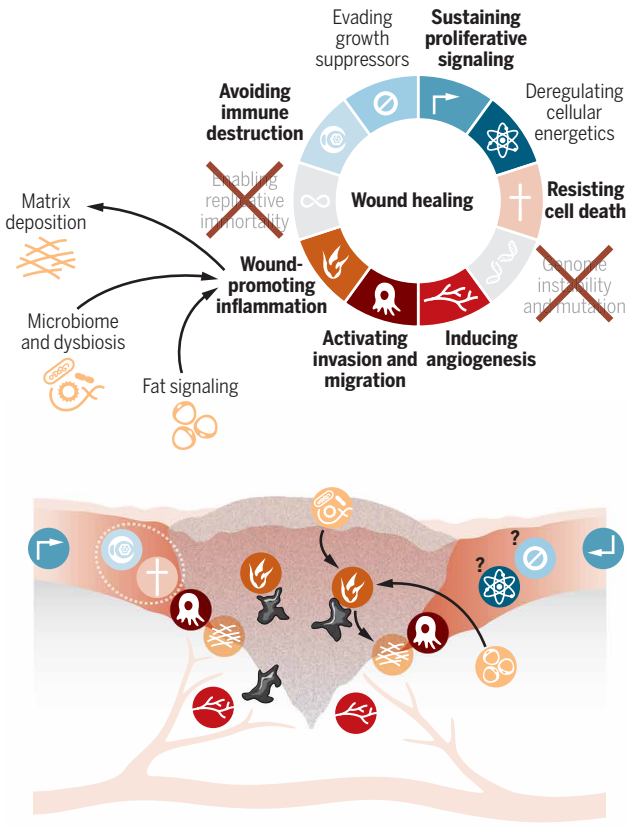

Fig. 2. How the hallmarks extrapolate to a healing wound. The contribution of the hallmarks and enabling characteristics to wound healing are mapped onto a schematic of a healing skin wound. Cell migration and proliferation drive re-epithelialization, which may also depend on altered cellular energetics. The wounded epithelium must also resist cell death and avoid damage inflicted by inflammatory cells that infiltrate the wound. Damage signals, the microbiome, and fat cells contribute to the inflammatory response, which, in turn, regulates both wound angiogenesis and matrix deposition.

and cell-matrix adhesion molecule, L1CAM, appears to be necessary and sufficient in both tissue repair and cancer contexts in the gut, being produced at colitis lesion sites and wherever colorectal cancer cells are metastasizing along the BM of nearby blood vessels (*30*).

All adhesion-mediated, traction-based cell migrations require regulation of a cell's cytoskeleton, largely actin and microtubules achieved through the regulation of Rho small guanosine triphosphatase (GTPase) switches, which, in turn, control when and where in a cell the actin-rich machineries of filopodia, lamellipodia, and contractile stress fibers assemble [reviewed in (*31*)]. In this regard, several studies have shown how Rho family small GTPases are absolutely required for wound re-epithelialization (*14*), and in many cancers, Rhos and their regulators are mutated or misregulated in other ways (*32*).

It is generally believed that carcinoma cell invasion involves EMT, the reversion through a developmental program whereby epithelial cells can convert, at least partially, toward a mesenchymal cell phenotype and then back to epithelial after the migration is complete. EMT—and the converse, mesenchymal-to-epithelial transition (MET)—occurs partially or fully to enable cells to migrate either as a loosely adherent collective or as individual cells (*33*). Frequently, E-cadherin, the linchpin component of adherens junctions linking epithelial cells together, is dysregulated in human carcinomas (*34*). Both basal and suprabasal layers of an advancing wound epidermis also exhibit considerable loosening of adhesions between neighbors, and these junctional changes extend many tens of cells back from the leading edge. It appears that increased levels of the ligand EphrinB1, and thus activation of several Eph receptor subtypes, may lead to a reduction in the amounts of components of both tight and adherens junctions, leaving wound epidermal cells more loosely linked to one another only through modified desmosomal junctions; this loosening of connections between cells then provides flexibility for the shuffling forward of cells within the advancing epidermal wound front (*35*). In developmental biology and in cancer, it is believed that EMT and MET are regulated by several transcription factors including Snail, Slug, and Twist [reviewed in (*33*, *36*)], but in wound repair, this remains a somewhat understudied area of research, although there is evidence for the involvement of at least Slug in some aspects of re-epithelialization (*37*, *38*).

As discussed above, the wound-edge epidermis must migrate across a denuded wound surface where the BM is missing. Moving over this substratum requires epidermal cells to first re-equip with the appropriate integrin matrix receptors and produce factors to enable the wound tongue to cut a pathway between the scab and the wound granulation tissue. The latter requires the increased production of several proteases, particularly matrix metalloproteinase 1 (MMP1), which may facilitate integrin-matrix adhesion dynamics by locally cleaving various extracellular matrix (ECM) and ECM-associated proteins [reviewed (*39*)].

These steps have parallels in all skin cancers during early invasive events wherein a rate-limiting step is the breakdown of the BM barrier that separates the epidermis from the underlying connective tissue. Studies in zebrafish indicate that small, naturally occurring holes in the BM act as opportunistic portals for immune cells to access the epidermis for surveillance purposes, and these openings also allow immune cells to traverse the BM in response to damage signals released by preneoplastic cancer cells (*40*). At later stages, cancer-associated fibroblasts (CAFs) have been shown in ex vivo models to stretch and soften small regions of the BM in advance of cancer cell invasion (*41*), and, subsequently, the BM beneath a growing clone of cancer cells becomes locally eroded by invadopodia-delivered MMPs that breach the barrier and enable full-blown cancer invasion (*40*, *42*).

It has become clear that other cell lineages in the cancer microenvironment can support the migration of invasive cancer cells. CAFs tunnel through matrix, apparently leading the way for invasive cancer cells (*43*). Macrophages, similarly, comigrate with invading breast cancer cells (*44*), as well as having other roles in cancer progression (see next section). Whether similar co-migratory efforts are important during wound repair has not been carefully studied but certainly during *Drosophila* wound re-epithelialization, macrophages are attracted to and associate with the advancing epidermal wound margin (*45*).

Hallmark 3: Tumor- and repair-promoting inflammation

It has long been apparent from patient studies that several cancers are a consequence of long-term, chronic inflammation (*46*) and that the presence and phenotypic state of inflammatory cells within different cancer types can substantially alter prognostic outcome (*47*). And yet, inflammation was not one of the original cancer hallmarks

but, rather, was added to the second, revised Hanahan and Weinberg listing as an enabling characteristic (*7*).

Intravital imaging studies in mice have shown the involvement of macrophages in tumor metastasis, where they help shuttle cancer cells from the primary tumor to nearby vessels, through which they disperse through the circulation to secondary sites (*47*). These studies have revealed a mutually supportive paracrine loop with cancer cell–synthesized CSF-1 (colony-stimulating factor–1) and macrophage-derived EGF together guiding the directional movement of both cell lineages toward local vessels (*48*, *49*). There is increasing evidence that neutrophils too can play a metastasis-enhancing role at the cancer site (*50*). To study much earlier stages of cancer initiation, which are difficult to observe in mice, researchers have turned to live imaging studies in translucent zebrafish, which show how surveillance by both neutrophils and macrophages can rapidly detect abnormal preneoplastic cells from as early as the single-cell stage and remain with these growing clones, supplying them with trophic signals and making the early cancer microenvironment resemble a chronic wound (*51*–*53*). The recruitment of inflammatory cells and their delivery of supportive factors are important for both tumor development and wound healing.

Wounding induces a rapid Ca^{2+} flash in leading-edge epidermal cells that spreads across the wounded epithelium as a wave, as shown in studies of worms, flies, and fish (*54*–*57*). This Ca^{2+} signal activates the nicotinamide adenine dinucleotide phosphate oxidase (NOX), Duox to generate hydrogen peroxide (H_2O_2) (*57*), which appears to be a key damage attractant drawing inflammatory cells to wounds, at least in flies and fish (*58*, *59*). In mammalian tissues, particularly those with a nonmucosal epithelium, we speculate that other NOXes may play similar functions. H_2O_2 acts as an early-damage signal responsible for drawing immune cells to wounds, and it has a similar function in the recruitment of inflammatory cells to preneoplastic cells when they first arise in tissues. These abnormal cells and their immediate neighbors release H_2O_2 pulses that appear to draw innate immune cells to them; this is a necessary attractant, demonstrated by the finding that blocking Duox in zebrafish larval tissues prevents immune cells from homing to growing clones of precancer cells (*52*). Other damage attractants, including high mobility group box 1 (HMGB1), appear also to draw leukocytes to both acute wounds and to cancer cells (*60*–*62*), and studies in zebrafish have shown that various chemokines, including those binding to the receptor CXCR2, act as attractants for neutrophils to wounds and also to clones of preneoplastic cancer cells (*51*, *63*). Despite having the capacity to engulf and kill preneoplastic cells, innate immune cells are often instead subverted into nurturing them, as indicated by genetic knockdown studies wherein the depletion of leukocytes prevents further preneoplastic growth (*51*, *52*, *64*).

Although macrophages are abundant at the wound site, they are not always essential for wound healing, as indicated by studies of embryo healing, which is effective even before leukocytic lineages first appear in tissues (*65*). Furthermore, mice null for the leukocyte-switching, ETS family transcription factor PU.1, which lack all innate immune cell lineages, are still capable of efficient wound repair up until neonatal stages; these wounds, without an inflammatory response, not only heal but do so without a scar, suggesting that fibrosis is triggered by signals from inflammatory cells [(*66*) and see below]. However, adult tissue repair does seem to depend on macrophages for efficient wound healing. Transient depletion of macrophages in mice with lineage-targetted diptheria toxin results in wound healing deficiencies that vary according to the phase of the repair process when macrophage killing is induced: Early macrophage depletion results in impaired re-epithelialization, reduction of wound granulation tissue, and decreased scar size, whereas killing of macrophages at later stages results in the failure of granulation tissue to mature and contract and eventually leads to wound hemorrhaging (*67*), suggesting a role in wound angiogenesis (see below). Genetic depletion of leukocytes in various models at various stages in cancer progression suggests a similar supportive role for neutrophils and macrophages toward cancer cells (*68*–*74*). Several of the key growth factor signals delivered to a wound by macrophages with established regulatory roles in repair also have related functions in cancer progression and vice versa.

TGF-βs 1 and 2, for example, are delivered to wounds both through degranulation of platelets and secretion by macrophages and have multiple functions, influencing several cell lineages within the wound granulation tissue, including immune cells and wound fibroblasts that drive aberrant collagen deposition, resulting in a wound scar [reviewed in (*75*)]. TGF-β1 has more complex roles in cancer, being both positively and negatively associated with tumor progression. TGF-β1 was initially described as a tumor suppressor, with mutations in the receptors TGF-βR1 and TGF-βR2 and the downstream regulators SMAD1 and SMAD4, indicating a suppressive role for TGF-β signaling in cancer. However, overexpression of TGF-β1 has also been linked to multiple cancers, including breast, lung, colon, esophageal, and pancreatic cancers, and correlates with poor prognostic outcome. This may be, in part, because of its capacity to drive tumor immune evasion (*76*). Frequently, it seems, in early-stage cancers, a high level of TGF-β is prognostically favorable, whereas in late stages, TGF-β in the microenvironment promotes tumor growth, leading to the TGF-β paradox (*77*–*80*). The TGF-β–related growth factor, activin, also has both protumorigenic activity and considerable effects in a wound repair scenario. It seems that both of these influences may be mediated by activin's activity on inflammatory cells (*81*).

The platelet-derived growth factors (PDGFs) are another family of growth signals associated with inflammation and with strong links to cancer; many malignancies are associated with overactivation of PDGF signaling (*82*), and similarly, they appear to have multiple and complex activities, both positive and negative, during tissue repair (*21*). Ectopic expression of PDGF-B in a murine model of non-healing diabetic wounds leads to faster wound closure (*83*), but PDGF released at the wound site by macrophages triggers the production of osteopontin in wound fibroblasts, which, in turn, leads to collagen deposition and scarring (*84*).

Hallmark 4: Angiogenesis

It is generally considered that tumors cannot grow beyond 1 mm in diameter without recruiting their own vascular supply, largely from pre-existing vessels in the vicinity, and, as a consequence, there has been considerable research, led by studies from the Folkman lab (*85*), into the tumor-derived angiogenic signals and how they might be dampened to block this rate-limiting step in cancer progression. Cancer-associated vessels are visibly different from normal tissue vasculature. Perhaps due to the overexpression of various angiogenic factors, they tend to be tortuous, disorganized, and leaky and remain so throughout cancer progression [reviewed in (*86*)]. Wound angiogenesis also initially consists of a complex intertwining network of

leaky capillaries, but this is only a transient condition, and the vessels rapidly acquire a pericyte layer and become fully patent after several days (*87*). Angiogenesis at the sites of tissue repair appears to be similarly rate limiting as it is for a growing cancer, and its failure is associated with chronic nonhealing wounds, whereas an inability to resolve wound vessels has been linked to overgrowing keloid scars [(*88*–*90*) and reviewed in (*91*)].

For tumor vessel growth, it is believed that the "angiogenic switch" is a complex interplay involving reduced levels of a portfolio of poorly characterized angiogenesis inhibitors, complemented by a new local source of proangiogenic signals, primarily thrombospondin and vascular endothelial growth factor (VEGF) (*92*). At least some of this proangiogenic signaling is believed to be a consequence of inflammation (*93*). In the initial laying down of vessels in embryonic tissues, macrophages are not required for the earliest stages of vessel sprouting per se, suggesting that other guidance cues are at play, but they do have a role in the subsequent remodeling and anastomosing of developing vessels (*94*). At sites of tissue damage, evidence indicates that macrophages are essential for all aspects of wound angiogenesis. This may be, in part, because of their early interactions with neutrophils, which are not present in the early embryo but generally arrive at the damage site before macrophages and are initially seen associated with vessel tips. Neutrophils appear to be inhibitory to vessel sprouting, perhaps due to the secretion of truncated VEGF receptors that compete with full-length plasma membrane receptors for binding to VEGF, and macrophages release this inhibitory signal by both dislodging the early-recruited neutrophils and acting as a local source of proangiogenic VEGF (*87*).

Whereas resolution of angiogenesis occurs during development and in healing wounds, it is misregulated in tumors. During embryogenesis, there are several transient vascular networks that must eventually be resolved. This developmental pruning is partially mediated by Wnt7a signals delivered by macrophages, which likely act by countering VEGF angiogenesis-promoting signals (*95*, *96*). Several anti-VEGF drugs are approved as cancer therapeutics, but although they have had some success, particularly in combination therapies, they are not the magic cancer blockers initially hoped for; rather, they may cause excessive pruning of tumor vessels, leading to local hypoxia, which can trigger early metastatic spread (*97*, *98*). In a wound scenario, late-stage macrophages switch from a proinflammatory phenotype and have a second contrasting role; this time driving vessel regression, but, unlike in development, Wnt7 signaling seems not to mediate this vessel-resolving instruction (*87*).

Hallmarks 5 and 6: Resisting cell death and avoiding immune cell destruction

These two hallmarks may have different underlying mechanisms in a cancer scenario, but we think that they can be considered as a continuum for the purposes of tissue repair because the signals for killing healthy cells within a healing wound come largely from the "friendly fire" of recruited inflammatory cells. At any site of malignant cancer growth, there will be numerous physiological stresses that, in healthy tissues, would trigger apoptosis. These include the signaling imbalances associated with sustained proliferative signaling, which, in turn, can lead to DNA damage, as can the cell-damaging signals from inflammatory cells. Other stresses will be the hypoxic and reduced nutrient conditions that are a consequence of a tissue outgrowing its angiogenic supply, not to mention cancer therapeutics such as chemotherapy and radiotherapy. And yet, the apoptotic switches appear subdued or even abrogated in cancer cells (*99*). This capacity to ignore proapoptotic cues is achieved in numerous ways, including, most commonly, loss of the tumor suppressor p53, which has critical DNA damage–sensing functions [reviewed in (*100*)], or increases in antiapoptotic signals, including those of the Bcl-2 family [reviewed in (*101*)]. Rather, little research has been undertaken to investigate these apoptosis-regulating pathways during tissue repair, but there is some indication that p53 plays a role in wound re-epithelialization, and, indeed, its transient shutdown can accelerate normal repair (*102*, *103*).

Cancer cells must also avoid surveillance and destruction by both the innate and adaptive arms of the immune system. One of the key mechanisms whereby cancer cells evade immune cell destruction is by increasing their production of inhibitory checkpoint molecules, and this strategy has been recently highlighted as a therapeutic Achilles heel with new anti-PD1 (programmed cell death protein 1) and anti-CTLA4 (cytotoxic T lymphocyte antigen 4) antibody treatments that expose aberrant cells to T cell–mediated killing [reviewed in (*104*)]. There is evidence that some elements of an adaptive immune response are activated in a wound repair scenario alongside the more fully studied wound inflammatory response. A local sentinel subpopulation of γδ T cells (*105*) and a transient influx of regulatory T cells (*106*) contribute to healing and are nurturing to repairing cells. The innate immune response, however, is "clumsy" in comparison to the adaptive response and nonspecific in its killing strategies.

Any tissue damage will trigger a rapid inflammatory response to counter potential infection. Inflammatory cells, particularly the early-recruited neutrophils, release microbiocidal factors such as reactive oxygen species (ROS) to eliminate pathogens, but of course these are also toxic to host tissues. To counter these inflammatory stresses, organisms have evolved a battery of cytoprotective mechanisms to limit collateral damage. Studies in mammalian and *Drosophila* wound models have uncovered several complementary signaling pathways that enable host tissues in the wound vicinity to survive in this hostile environment. The transcription factor Nrf2 is rapidly activated downstream of Ca^{2+} signals in a band of epidermal cells at the margin of the wound, and this leads to the expression of genes that encode several ROS-sequestering enzymes that shield cells from oxidative damage and permit their survival when they, otherwise, would die (*107*, *108*). In parallel with this Nrf2-dependent, ROS-sequestering shield, DNA and other repair machineries are also produced. For example, growth arrest and DNA damage–inducible 45 (GADD45), which appears to increase the access of repair machinery to damaged DNA, is produced as a consequence of inflammation. In flies and mice devoid of an inflammatory response, GADD45 expression levels did not increase in the wound epidermis (*107*, *109*). Ectopic expression of GADD45 in *Drosophila* epidermis is sufficient to protect it from ultraviolet (UV) light–induced killing even in the absence of a wound (*107*).

Hallmark 7: Deregulating cellular energetics

Research on this cancer hallmark began almost a century ago when Warburg first described how cancer cells tend to use glycolysis rather than oxidative phosphorylation to fuel their activities (*110*, *111*). Recent studies in *Drosophila* show how lactate dehydrogenase, a key enzyme in Warburg effect metabolism, is necessary and sufficient for the switch from hyperplasia to neoplasia in skin cancer models (*112*). Positron emission tomography (PET) scanning in the clinic

takes advantage of this phenomenon because cancer cells primarily using glycolysis are much more demanding of glucose than are healthy cells primarily generating energy through oxidative phosphorylation, and so radioactively tagged glucose highlights cancer cells within tissues (*113*). This altered metabolic signature can even be used to guide a surgeon's iKnife for excising the margins of a tumor (*114*).

Metabolism has only recently begun to be considered anything more than a niche topic by wound healing researchers, but new findings suggest it may be a key player in repair, much as it is in cancer. In the 1960s, T. Hunt and colleagues revealed high amounts of lactate in healing wounds and speculated that several cell lineages in wounds switch to a glycolytic pathway and that this might be important for some elements of the repair process (*115*). Gene expression studies in the regenerating *Xenopus laevis* tadpole show that many genes linked to glycolytic metabolism are locally induced here also (*116*). Single-cell transcriptomic analysis of mouse skin wounds indicates major alterations in the expression of metabolism-associated genes, with a reduction in transcripts associated with oxidative phosphorylation and a complementary increase in transcripts associated with glycolysis in subpopulations of cells at the wound edge (*117*). Studies in the regenerating zebrafish heart also show evidence for cardiomyocytes in the border zone at the edge of a wound reprogramming their metabolism, suggesting that metabolic plasticity might explain why fish cardiac tissues can repair so much more efficiently than their mammalian equivalents, because blockade of this metabolic switch impairs fish heart repair (*118*). Inflammation is instrumental in both cancer and wound healing (see above), and it may be that inflammatory cells, in part, have these pivotal roles by being key sensors of altered microenvironmental conditions, for example, hypoxia, and being the mediators of changes to metabolic signaling in other cells (*119*).

CANCER HALLMARKS THAT MIGHT NOT BE SHARED BY REPAIRING TISSUES

It would be disingenuous to presume that all cancer hallmarks have likely parallels in wound repair, although equally naive to argue that they absolutely do not. However, we think that for three of the hallmarks and enabling characteristics for cancer, the links to wound repair are likely to be slim.

Evading growth suppressors and enabling replicative immortality

These two hallmarks of cancer have no immediately obvious parallels in the tissue repair response. The closest that a wound-edge cell comes to "evading growth suppressors" is when some of the signaling pathways that enable proliferation and migration are transiently epigenetically unsilenced as discussed above, but when the wound has been repaired, they will be epigenetically silenced again (*26*) in ways that clearly fail to occur in a progressing cancer. Similarly, there is no evidence that migrating wound-edge cells would become immortal. On the contrary, epidermal and fibroblast cells at the wound margin may become senescent, and recent studies suggest that the senescence-associated secretory phenotype (SASP) includes signals that are beneficial to repair (*120*). As a counter to this, and in support of the observation that younger tissues repair better than older tissues, is the finding that mice with "hyper-long" telomeres exhibit faster skin healing than their wild-type littermates (*121*).

Genomic instability and mutation

Here, again, it does not seem likely that this enabling characteristic of cancer has any direct equivalent in a tissue repair scenario unless one considers chronic wounds with their persistent inflammation, potentially excessive viral load, and exposure to UV damage. All of these insults may result in secondary mutations, leading to neoplastic lesions in this vulnerable, exposed tissue that, for example, occurs in Marjolin's ulcers at the margins of venous leg ulcers (*122*). In the context of cell abnormalities in cancer and, possibly, of broader relevance to general tissue repair than currently understood, it has been observed that wound-edge epithelial cells in larval *Drosophila* fuse and become syncytial, but this is not associated with mutation or genomic instability (*123*).

SHARED HALLMARKS THAT ARE NOT BONA FIDE CANCER HALLMARKS (YET)

There have always been discussions about what "cancer hallmarks" are missing or might be coming in the next Hanahan and Weinberg update, and we have some suggestions below that are inspired, in part, because they have recently become extremely popular topics for cancer research and, moreover, are becoming hot topics in tissue repair research too. All three of these potential prospective hallmarks could be considered as either upstream or downstream of the established enabling characteristic of inflammation that promotes both tumor development and wound healing.

The microbiome and dysbiosis

From birth, and possibly earlier, all external-facing human epithelial tissues, including the skin and gut, are colonized by bacteria that eventually establish homeostasis and symbiotically influence the local immune cell repertoire and systemic immunity (*124*). Disturbances of the microbiota, known as dysbiosis, have been implicated directly and indirectly in cancer development with the presumption that such changes will likely affect local inflammation to drive cancer initiation and progression [(*125*) and above]. In the gut, a failure to control pathogenic microorganisms frequently leads to dysregulated inflammation and tissue damage, leading to disorders such as Crohn's or inflammatory bowel disease, both of which considerably increase the risk of bowel cancer (*126*). Established links between alterations in microbiome leading to cancer include bacterial infections, such as infection with *Heliobacter pylori*, which is associated with a large proportion of all stomach cancers (*127*), and it is now clear that many other cancers have associated microbiome signatures (*128*). *Fusobacterium nucleatum* infection is implicated in accelerating colorectal cancer, and infected cells have been shown to release proinflammatory cytokines that promote metastatic migration (*129*). More directly, it has been demonstrated that injecting bacterial toxins into gut organoids drives a signature of oncogenic mutations common to human colorectal cancer even in the absence of any inflammatory cell mediators (*130*).

Whereas alterations in the microbiome of a tissue are generally considered to be potential activators rather than inhibitors of cancer progression, there is a classic observation reported by W. Coley in the early 1900s of some patients with inoperable cancers in whom infections leading to fevers occasionally resulted in their tumors "melting" away (*131*). Although the mechanisms underpinning this phenomenon are still not entirely clear, loading the bladder with Bacillus Calmette-Guérin, an attenuated strain of *Mycobacterium*

bovis, has remained a standard treatment for bladder cancer (*132*). An understanding of how infections somehow modulate the host immune response to kill cancers is well worthy of further research.

That the wound microbiota might influence the efficiency of healing also seems plausible because infection of both wild-type and diabetic mice (which have impaired healing) tends to retard healing, and antimicrobial treatment rapidly reverses this impairment (*133*). However, there is some controversy over whether germ-free (GF) animals are more effective healers than colonized animals or, conversely, might exhibit reduced healing capacity (*134*), perhaps through a failure of the activation of Toll-like receptors that are required permissively for some aspect of the repair process. In most reports, it is clear that the inflammatory response is dampened in GF animals; for example, one study of GF mice reports that they heal their wounds faster, have increased vasculature, and repair with less scarring, which might be because of a reduced neutrophilic influx to the wound site (*135*).

Advances in high-throughput 16*S* bacterial sequencing have provided the first detailed insights into the complexity of the skin microbiome, how it varies between individuals and across anatomical sites, and some of the changes that occur after wounding (*136*). The host wound response has clearly adapted to account for these striking changes in bacterial flora, and some of this protective machinery is now coming to light in the context of bacteria invading a wound site. For example, mice lacking NOD2, which is an intracellular receptor recognizing motifs from both Gram-positive and Gram-negative bacteria, have an altered skin microbiome, favoring pathogens over commensal species, and this dysbiosis becomes exaggerated after wounding, leading to severely delayed healing (*137*). Moreover, the dysbiotic microbiome is dominant because cohousing NOD2 null mice with wild-type littermates results in the wild-type mice "catching" impaired healing (*137*).

Aberrant matrix deposition

The ECM defines the mechanical properties of all tissues and is a key element of the cancer microenvironment that can directly affect the prognostic outcome (*138*). For example, the presence of aligned, cross-linked, and stiffened collagen bundles is associated with invasive regions of breast cancers and worse outcomes for patients (*139*).

Aberrant collagen deposition in tumors may be, in part, driven by abnormal signaling in the cancer cells themselves, but it will also be affected by inflammatory and other cells in the cancer microenvironment. TGF-β is a key driver of excessive matrix deposition and is highly expressed by macrophages in the most aggressive breast cancer subtypes and at sites of increased collagen deposition (*140*). Lysyl oxidases (LOXes), which are rate limiting in the cross-linking of collagen fibers, are also frequently reported as misregulated in many tumor types and likely involved in the regulation of metastatic spread (*141*). A cross-linked, stiff matrix encourages integrin clustering and sustained phosphoinositide 3-kinase–Akt and ERK signaling, which promotes both survival and migration, and provides tracks to facilitate invasion away from the primary tumor site (*142*, *143*). In a mouse model of pancreatic cancer, LOX inhibition suppresses cancer cell invasion and prolongs tumor-free survival (*144*). A fibrotic environment, characterized by inflammation and increased ECM deposition, also provides an ideal premetastatic niche for cancer cell homing. This is illustrated by the finding that bleomycin-induced lung damage, which triggers a fibrotic response, favors the seeding of tail vein–injected tumor cells into the lungs in mice (*145*).

In a wound scenario, it is clear that inflammation, although pivotal and required for various aspects of adult healing, is also causal of aberrant collagen deposition, resulting in a fibrotic wound scar. In embryonic tissues in which leukocytes are not yet present, wounds can heal without a scar (*65*), and PU.1 knockout neonatal mice lacking all leukocytes also can repair without scarring (*66*). Inflammation drives fibrosis in wounds through several signaling pathways, including TGF-β1 and TGF-β2, both of which trigger the deposition of collagen and other matrix components by wound fibroblasts; blocking TGF-β signaling at the wound site dampens the fibrotic response (*146*). Interleukin-4–activated macrophages at the wound site also drive fibroblast production of the collagen crosslinking enzyme lysyl hydroxylase 2, which, as in the vicinity of a cancer, leads to the stiffened unresolvable collagen of a dermal scar (*147*).

Adipocytes: Not silent bystanders

There is now considerable epidemiological evidence indicating a link between obesity and several types of cancer (*148*). During weight gain, adipocytes become hypertrophic, and many eventually die. This, in turn, triggers an accumulation of phagocytic macrophages that envelop dying adipocytes and form characteristic crown-like structures (CLSs), which are phenotypically and transcriptionally different from other adipocytes (*149*). Particularly, in hormone-driven cancers with close proximity to large fat deposits, such as breast and prostate cancers, it seems that positive CLS status is associated with a poor prognostic outcome, and there is also evidence for these structures having systemic endocrine effects on cancers at distant sites (*150*).

Aside from these indirect effects on tumor cells through inflammation and fibrosis, adipocytes can also deliver adipokines and other signals that directly influence tumor cell growth, and there is clear evidence of adipocytes also becoming metabolic slaves to the cancer cells. A study of human biopsy material and in vitro coculture indicates how advanced melanomas invade and make direct contact with subcutaneous adipocytes, which can then directly transfer fatty acids to the tumor cells (*151*), and a similar phenomenon has been shown for omental adipocytes "feeding" ovarian cancer cells (*152*). In vivo zebrafish studies show how engrafted melanoma cells tend to home to subcutaneous sites adjacent to endogenous adipocytes and, as a consequence of taking up extrinsic lipids from these cells, the tumor cells adjust their own metabolism and reduce their expression of lipogenesis genes (*151*).

Obesity has close association with the onset of type 2 diabetes, and diabetic individuals are known to be much more prone to impaired wound healing as a consequence of neuropathy, poor vascularity, and predisposition to infection because of chronic high blood glucose (*153*). In the wound repair community, there is new interest in a direct role for adipocytes and their preadipocyte precursors. For example, in *Drosophila* pupae, fat body cells, which are the fly equivalents of adipocytes, use a novel adhesion-independent "swimming" motility to home toward and plug a wound, where they also increase their production of antimicrobial peptides and collaborate with macrophages to clear cell and matrix debris (*154*). In murine wounding studies, there is evidence for adipocyte lipolysis being partly responsible for inflammatory cell recruitment and for dermal adipocytes transdifferentiating into myofibroblasts (*155*) and vice versa (*156*). Adipocyte precursors can differentiate into mature adipocytes in the wound vicinity, and, although little is known about the mediating signals, these cells appear to contribute

to repair because blocking their differentiation leads to defects in migration of fibroblasts into the wound and to impaired matrix deposition (*157*). Just as in *Drosophila* wound repair, mammalian adipocytes may also play a role in microbe killing because impaired adipogenesis results in increased skin infections (*158*).

WOUNDING CAN STIMULATE CANCER INITIATION OR REAWAKEN DORMANT CANCERS

Besides sharing many cell and molecular mechanisms, as discussed in the hallmarks comparisons above, tissue damage and cancer are frequently juxtaposed in the clinic because tissue biopsies are the mainstay of screening for and grading various cancers, and surgery is still one of the most effective means for curing a patient with cancer. In recent decades, a trickle of papers have addressed how cancer biopsy and surgery, which by necessity will damage tissues and, thus, trigger a wound inflammatory response, might affect residual cancer cells.

There have been several clinical studies describing how tissue-damaging cancer treatments may locally or systemically influence cancer growth or progression to malignancy (*5*). These local influences have been mirrored in basic science studies beginning with the observation that chicks injected with Rous sarcoma virus tended to only develop tumors at the site of injection (*159*), and similarly, wounding was needed to trigger tumorigenesis in v-jun transgenic mice (*160*). Subsequently, studies using various animal models have all shown that wound-triggered cancer initiation is mediated by inflammation (*161*–*165*). There is clear clinical evidence that local tissue damage in patients with melanoma can exacerbate cancer progression and worsen patient prognosis (*165*). Similarly, needle biopsies for breast cancer are believed to be a potential activator of cancer progression (*166*). A further support to the concept that wounding activates cancer is the fragile skin disease, recessive dystrophic epidermolysis bullosa, in which patients with mutations in the gene encoding collagen VII, a linker between epidermis and dermis, suffer from persistent cycles of skin blistering, repair, and scarring. Because of better infection control, these children are now surviving into young adulthood, but all succumb to multiple, aggressive cutaneous squamous cell carcinomas as a consequence of the constant wound inflammation and infection (*167*). Conversely, however, for some other cancers, including basal cell carcinoma, tissue damage and local activation of an inflammatory response are sometimes reported to lead to cancer regression and even occasionally used as a therapeutic strategy, particularly in elderly patients when surgery is not possible (*168*). That local wounding might sometimes be inhibitory to cancer progression is supported by a study in mice showing that for some xenografted human cancers, the presence of a nearby ulcer or ischaemic wound can inhibit tumor growth (*169*).

Aside from local influences, tissue damage can also lead to systemic activation of cancer growth. This has been mostly clearly described for breast cancer where reconstructive plastic surgeries are believed to occasionally trigger subsequent inflammation-associated "reawakening" of otherwise dormant lung micrometastases (*170*). This activation of distant "dormant," T cell–restrained cancers has been replicated in mice and shown to be mediated by systemic mobilization of innate immune inflammatory cells and moreover can be dampened by transient treatment with anti-inflammatory drugs (*164*). More research is needed to better understand which cancers are most likely to be exacerbated by wound-triggered inflammation—locally or at a distance—and for which the converse might be true so that cost-benefit judgments can better be made in the clinic and appropriate anti-inflammatory treatments can be considered wherever tissue-damaging procedures need to be undertaken in patients.

LESSONS FROM CANCER FOR WOUND HEALING AND VICE VERSA, NOW AND IN THE FUTURE

For all of the hallmarks and enabling characteristics discussed above, there are obvious overlaps in research insights from the cancer and wound healing communities on which we all must capitalize. Good examples include fuller understanding of proangiogenic mechanisms that are pivotal in both cancer and wound repair and that will lead toward strategies for improving chronic wound healing and for starving a cancer or enhancing the vascular delivery of chemotherapeutic drugs to the cancer. Similarly, figuring out precisely how inflammation is triggered, how it influences downstream targets, and how it, too, can be modulated or reprogrammed will underpin the development of important therapeutics for both wound healing and cancer. One clear shared goal is the development of novel immunomodulatory strategies to dampen fibrosis, which should be beneficial both for reducing extensive scarring, for example, in burn victims, and also for retarding the metastatic spread of some cancers. In that regard, the antifibrotic drug pirfenidone, which, in part, acts to modulate TGF-β signaling and is already used to treat idiopathic pulmonary fibrosis, is proving effective as a blocker of cancer-associated fibrosis in several mouse models and also appears to make cancers more prone to chemotherapy killing (*171*, *172*).

We can also see several, as yet untapped, opportunities where one of our fields could learn more from the other. For each hallmark, there are examples of known wound-activated pathways that are not yet fully investigated in cancer and vice versa. For example, although prostaglandins are implicated in driving cancer progression, they are not sufficiently studied in wound healing, and a converse imbalance of research effort is true for studies of platelet function in wound clotting and repair versus in cancer biology. In addition, whereas we are beginning to know about how tissues in the vicinity of wounds make themselves "resilient" to a harsh environment, we have yet to extrapolate all of this knowledge to develop tools for inhibiting this same machinery in cancer cells, which likely harness these same protective pathways for their own survival.

One general area of tissue repair that is relatively under-researched and yet would clearly offer considerable insight to cancer studies across several hallmarks, involves those mechanisms that lead to shutting down of the repair process. If we had a fuller understanding of the molecular cues underpinning the attenuation of repair processes—for example, how epidermal cells stop migrating and proliferating once the wound edges have met or the inflammatory response at a wound site is attenuated—then some of this knowledge might offer particularly useful insights into how we might develop better brakes on cancer progression.

Outside of the classic hallmark territories, there are other potentially fruitful areas for crossover. For example, there has long been an understanding that cutaneous innervation may have some signaling role to play in wound repair (*173*, *174*), and indeed, innervation is critical for the regeneration of limbs in salamanders and fins in fish (*175*), but innervation is not well studied in cancer biology. As described above, Folkman and others observed how a tumor, similar to an aberrantly growing organ, draws in a vascular supply, but it is now becoming clear that growing cancers can also become innervated

(*176*) and, just as in a wound, this innervation could be a source of growth signals and, thus, a potential target for anticancer therapeutics. And conversely, although there is a considerable body of literature on the development of cancer lymphatics because of their being a route for cancer cell dissemination (*177*), only recently have they been investigated in repair scenarios, with the first studies being in the regenerating heart of zebrafish (*178*). Nerves and lymphatics could both prove to be much more important than currently presumed for wound healing and for cancer biology.

Ever-growing human genomic datasets will provide the means for further exchange of concepts between the cancer and wound healing fields. Harnessing population health approaches in patient datasets will enable the analysis of transcriptomic and epigenetic parallels (and differences) between repairing wounds and the signatures of various cancers at different stages of their progression. All of these insights together will hopefully guide us toward more shared hallmarks and further opportunities for repurposing drugs designed to treat cancer as wound healing therapeutics and vice versa. The flip side of such a reciprocal approach, of course, is a consideration that because of the multitude of shared mechanisms, any drug that might improve one might also have unexpected consequences on the other.

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Acknowledgments: We thank current and former members of our laboratory (in particular Y. Feng and M. van den Berg) for feedback and discussions related to this manuscript. **Funding:** Work in our laboratory has been supported by grants from Cancer Research UK (C20590/A15936) and the Wellcome Trust (217169/Z/19/Z). **Author contributions:** L.M.-M. and P.M. conceptualized and wrote this review and prepared the figures together. **Competing interests:** The authors declare that they have no competing financial interests.

Submitted 14 May 2020
Accepted 14 August 2020
Published 8 September 2020
10.1126/scisignal.aay8690

Citation: L. MacCarthy-Morrogh, P. Martin, The hallmarks of cancer are also the hallmarks of wound healing. *Sci. Signal.* **13**, eaay8690 (2020).

Science Signaling

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Sci. Signal. **13** (648), eaay8690.
DOI: 10.1126/scisignal.aay8690