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The Hallmarks of Cancer are also the Hallmarks of Wound Healing

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Abstract
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 studies. In this Review we highlight how tissue repair and cancer share cellular and molecular processes that are regulated in a wound but mis-regulated in cancer. From sustained proliferative signalling 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 impact on cancer in the clinic.

Introduction and background

For over a century it has been considered that tumours appear to behave like 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, tumours behave more like 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 those that are less clearly true for both (Fig. 2). We also speculate on additional shared parallels to be considered prospective "hallmarks" or "enabling characterists", and discuss what happens when cancers meet wounds in the clinic, such as during biopsy and surgery.

Hallmarks and Enabling Characteristics where there are the clearest parallels:

Hallmark 1: Sustaining proliferative signalling

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

Cell proliferation during wound repair is restricted to a zone behind the leading edge

In a cancer scenario, cell proliferation can appear haphazard and disorganised, but wounding triggers a more coordinated and synchronised proliferative response. Classic studies of repair described proliferative zones behind the migrating epidermal leading edge (*10, 11*) . More recent investigations of mouse wounds have refined this proliferative zone and shown that it arises several hours after wounding and persists for several days; whilst the proliferative zone is indeed behind the immediate leading edge, it can be dynamic and encroach into the zone of migration (*12, 13*) . Once the epidermal wound edges have met and migration ceases, cell proliferation spreads into the just-sealed central zone (*13*). Whilst an inability to proliferate is incompatible with repair of large skin lesions, cell division does not necessarily drive re-epithelialisation; indeed, tissues that do not divide, for example, 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-epithelialisation (*12*).

What are the signals for initiating and stopping wound proliferation?

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 calcium-dependent phosphorylation of extracellular signal–regulated kinases 1 and 2 (ERK1/2), leading to *cyclin B* transcription, which is necessary to drive mitosis. This change in tissue mechanics will be sensed by cells experiencing reduced density as migration begins (*17*). 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, fibroblast growth factor 7 [FGF7, also known as keratinocyte growth factor (KGF)] is strongly stimulated by dermal fibroblasts in a skin wound (*19*), and blocking the epidermal response to this signal by expressing a dominant negative FGF2 receptor largely prevents cell divisions in the advancing wound epidermis and leads to impaired wound re-epithelialisation (*20*). Other important epidermal wound growth factor signals include epidermal growth factor (EGF) and transforming growth factor alpha (TGFα) (*21*), both of which are delivered to the wound largely through the degranulation of platelets and infiltrating macrophages, and hepactocyte growth factor (HGF), 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/c-Jun and Egr1 (*23-25*) within hours of wounding. However, access to the DNA by these immediate early transcription factors will be dependent 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 removed, enabling the previously-silenced genes, including that encoding EGFR, to be transcriptionally activated (*26*). It is tempting to speculate that at least some of these wound-induced genes that are first epigenetically un-silenced before they can be transcribed, are those that drive key cancer associated mechanisms including proliferation and migration, and thus need failsafe regulation.

Many epidermal wound mitogens will naturally disappear as platelets are cleared and the inflammatory response resolves, but very likely there are also additional active mechanisms that shut down epidermal cell proliferation in the wound epidermis as closure is achieved. These will include the very same contact inhibition

cues whose release in part drove the initial proliferative surge, as wound edge cells now re-establish contacts with their opposite partners (*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 metastasise, and so this has become one of the most keenly investigated of the Hallmarks by cancer researchers. During wound closure, the process of re-epithelialisation bears considerable resemblance to those processes that occur in the early migratory stages of carcinoma invasion.

Mechanisms of epithelial migration and partial EMT shared by wounds and invasive cancers

Several hundred genes are switched on in the advancing epidermal wound edge cells and many of these are also part of the gene signature(s) of invasive carcinomas (Reviewed in (*28*)). For a good number of these genes we still don't know their precise function in the repair process but others have characterised roles in transient tethering, or proteolysis, or 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 pared down to only one or two cell layers at the advancing tip. Wound re-epithelialisation requires leading edge basal keratinocytes and all follower cells to leave their usual basement membrane (BM) substratum and migrate onto and across a wound provisional matrix. This transition requires an alteration in the integrin expression profile to accommodate the changing matrix and enable cells to make transient adhesions for forward migration. To migrate from the basement membrane, cells switch off the hemidesmosomal $\alpha 6\beta 4$ integrins and upregulate several others not normally expressed in unwounded skin; these new integrins are essential for migration across the new provisional wound matrix as revealed by wounding of knockout (KO) mice for $\beta 1$ integrin in epidermal cells in which re-epithelialisation is retarded (*29*). Whilst integrin expression is generally confined to the basal layer in unwounded skin, in the advancing wound edge, all epidermal cell layers express them (*30*) , suggesting that all cells are active migrators; indeed, recent 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*). A recent study indicates how one migration specific cell:cell and cell:matrix adhesion molecule, L1CAM, appears to be necessary and sufficient in both tissue repair and

cancer scenarios in the gut, being produced at colitis lesion sites and wherever colorectal cancer cells are metastasising along the basement membrane of nearby blood vessels (*31*).

All adhesion mediated traction-based cell migrations require regulation of a cell's cytoskeleton - largely actin and microtubular – achieved through the Rho GEF and GAP regulation of Rho small GTPase switches which, in turn, control when and where in a cell the actin-rich machineries of filopodia, lamellipodia and contractile stress fibres assemble (reviewed in (*32*)). In this regard several studies have shown how Rho family small GTPases are absolutely required for wound re-epithelialisation (*14*), and in many cancers Rhos and their regulators are mutated or mis-regulated in other ways (*33*).

It is generally believed that carcinoma cell invasion involves reversion via a developmental programme whereby epithelial cells can convert, at least partially, towards a mesenchymal cell phenotype, and then back to epithelial, once migration is complete. This epithelial-to-mesenchymal transition (EMT, and the converse, MET) occurs partially or fully to enable cells to migrate either as a loosely adherent collective or as individual cells (*34*). Frequently E-cadherin, the linchpin component of adherens junctions linking epithelial cells together, is dysregulated in human carcinomas (*35*). Both basal and suprabasal layers of an advancing wound epidermis also exhibit considerable loosening of adhesions between neighbours and these junctional changes extend many tens of cells back from the leading edge. It appears that high levels of the EphrinB1 ligand, and thus activation of several Eph receptor sub-types, may lead to reduced components of both tight and adherens junctions leaving epidermal cells more loosely linked to one another by modified desmosomal junctions; this loosening of junctions between cells then provides space for shuffling forward of cells within the advancing epidermal wound front (*36*). In developmental biology and in cancer it is believed that EMT/MET is regulated by a series of transcription factors including Snail, Slug and Twist (Reviewed in (*34, 37*)) but in wound repair, whilst there is evidence for involvement of at least Slug in some aspects of re-epithelialisation (*38, 39*), this remains a somewhat understudied area of research.

Escaping the basement membrane for both wound-edge and cancer cells

As discussed above, the wound edge epidermis must migrate across a denuded wound surface where BM is missing. This new substratum requires epidermal cells to first re-equip with the appropriate integrin matrix receptors (see above), and, in order for the wound tongue to cut a pathway between scab and healthy wound

granulation tissue, it also needs to upregulate several proteases, in particular, MMP1 which may facilitate integrin:matrix adhesion dynamics by locally cleaving various extracellular matrix (ECM) and ECM-associated proteins (Reviewed (*40*)).

These steps have parallels in all skin cancers during early invasive events where a rate limiting step is breakdown of the BM barrier that separates epidermal from 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 routeways also allow immune cells to traverse the BM in response to damage attractant signals released by pre-neoplastic cancer cells (*41*). 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 (*42*), and subsequently, the BM beneath a growing clone of cancer cells becomes locally eroded by invadopodia delivered MMPs which breach the barrier and enable full blown cancer invasion (*41, 43*).

Association of the invasive front with other cell types

In recent years it has become clear that invasive cancer cells can be supported in their migration by other cell lineages in the cancer microenvironment. CAFs tunnel through matrix, apparently leading the way for invasive cancer cells (*44*). Macrophages, similarly, co-migrate with invading breast cancer cells (*45*), 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-epithelialisation macrophages are attracted to and associate with the advancing epidermal wound margin (*46*).

Hallmark 3: Tumour- and repair-promoting inflammation

It has long been apparent from patient studies that several cancers are a consequence of long term, chronic inflammation (*47*), and that the presence and phenotypic state of inflammatory cells within different cancer types can significantly alter prognostic outcome (*48*). 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.

Intravital imaging studies in mice have shown the involvement of macrophages in tumour metastasis, where they help shuttle cancer cells from the primary tumour to nearby vessels from where they then disperse via the circulation to secondary sites (*48*). These studies have revealed a mutually supportive paracrine loop with cancer

cell synthesized CSF-1 and macrophage-derived EGF together guiding the directional movement of both cell lineages towards local vessels (*49, 50*). There is increasing evidence, that neutrophils too can play a metastasis-enhancing role at the cancer site (*51*). At much earlier stages of cancer initiation, which are difficult to study 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 pre-neoplastic 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 micro-environment resemble a chronic wound (*52-54*).

Some attractants drawing inflammatory cells to wounds are also attractants for cancer

Wounding induces a rapid calcium flash in leading edge epidermal cells that spreads across the wounded epithelium as a wave, as shown in studies of worms, flies and fish (*55-58*). This calcium signal activates the NADPH oxidase (NOX), Duox to generate hydrogen peroxide (H_2O_2) (*58*) which appears to be a key damage attractant drawing inflammatory cells to wounds, at least in flies and fish (*59, 60*). In mammalian tissues, particularly those with a non-mucosal epithelium, we might speculate that other NOXes play similar functions.

Just as hydrogen peroxide acts as an early damage signal responsible for drawing immune cells to wounds, it has a similar function in recruitment of inflammatory cells to pre-neoplastic cells as they first arise in tissues; these “abnormal” cells, and their immediate neighbours, release hydrogen peroxide pulses that appear to draw innate immune cells to them; that this is a necessary attractant is shown by blocking the wet epithelium NOX, called DUOX, in zebrafish larval tissues which “blinds” immune cells to growing clones of pre-cancer cells (*53*). Other damage attractants, including HMGB1, appear also to draw leukocytes to both acute wound and to cancer cells (*61-63*) and studies in zebrafish have shown that various chemokines, including those binding CXCR2, act as attractants for neutrophils to wounds and also to clones of pre-neoplastic cancer cells (*52, 64*).

Inflammatory cells deliver trophic and other signals to both wound and cancer cells

The zebrafish studies described above show innate immune cells have the capacity to kill and engulf pre-neoplastic cells; generally, however they are instead subverted into nurturing them as indicated by genetic knockdown studies where depletion of leukocytes prevents further pre-neoplastic growth (*52, 53, 65*).

Interestingly, 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 (*66*). 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 (*67*), and see later. However, adult tissue repair does seem to depend on macrophages for efficient wound healing. Transient depletion of macrophages with Diphtheria Toxin in mice results in wound healing deficiencies that vary according to which phase of the repair process macrophage killing is targeted: early macrophage depletion results in impaired re-epithelialisation, reduction of wound granulation tissue and eventually decreased scar size, whereas killing of macrophages at later stages results in failure of granulation tissue maturation and contraction and eventually leads to wound haemorrhaging (*68*), suggesting a role in wound angiogenesis (see later).

Genetic depletion of leukocytes in various models at various stages in cancer progression suggests a similar "supportive" role for neutrophils and macrophages towards cancer cells (*69-75*). Indeed, 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.

Transforming growth factor betas, (TGF-ßs) 1 and 2, for example, are delivered to the wound both through degranulation of platelets and through expression by macrophages, and have multiple functions, influencing several cell lineages within the wound granulation tissue including immune cells and wound fibroblasts which may drive aberrant collagen deposition resulting in a wound scar, reviewed in (*76*). TGF-ß1 has more complex roles in cancer, being both positively and negatively associated with tumour progression. Initially TGF-ß1 was discovered as a tumour suppressor, with mutations in TGFβR1 and 2 and the downstream regulators SMAD1 and SMAD4, indicating a suppressive role for TGF-ß signalling. However, overexpression of TGF-ß1 has also been linked to multiple cancers including breast, lung, colon, oesophageal and pancreatic cancer, and correlates with poor prognostic outcome. This may be, in part, because of its capacity to drive tumour immune evasion (*77*). Frequently it seems, in early stage cancers a high level of TGF-ß is prognostically favourable, whereas in late stages, TGF-ß in the microenvironment promotes tumour growth, leading to the TGF-ß paradox (*78-81*).

The TGFβ related growth factor, activin, also has both pro-tumurigenic 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 (*82*).

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 overactivity of PDGF signalling (*83*), and similarly they appear to have multiple and complex activities, both positive and negative, during tissue repair (*21*). Ectopic expression of PDGF-B in murine non-healing "diabetic" wounds leads to faster wound closure (*84*) but PDGF released at the wound site by macrophages has been shown to trigger production of osteopontin in wound fibroblasts which, in turn, leads to scar collagen deposition (*85*).

Hallmark 4: Angiogenesis

It is generally considered that tumours cannot grow beyond 1mm in diameter without recruiting their own vascular supply, largely from pre-existing vessels in the vicinity of the growing tumour, and as a consequence there has been considerable research, led by initial studies from the Folkman lab (*86*), into what are the tumour-derived angiogenic signals and how might they be dampened to block this rate limiting step in cancer progression.

Cancer and wound vessels share the characteristics of being hyper-branched and leaky

Cancer vessels are visibly different from normal tissue vasculature. Perhaps due to overexpression of various angiogenic factors they tend to be tortuous, disorganised and leaky and remain so throughout cancer progression, reviewed in (*87*). Wound angiogenesis also initially consists of a complex intertwining network of leaky capillaries, but this is only a transient condition and they rapidly acquire a pericyte layer and become fully patent after several days (*88*). Angiogenesis at sites of tissue repair appears to be similarly rate limiting as it is for a growing cancer, and its failure is associated with chronic non-healing wounds, whilst an inability to resolve wound vessels has been linked to overgrowing keloid scars (*89-91*) reviewed in (*92*).

Inflammatory cells play pivotal roles in both developmental and wound angiogenesis

For tumour vessel growth it is believed that the "angiogenic switch" is a complex interplay involving reduced levels of a portfolio of poorly characterised angiogenesis inhibitors, complemented by a new local source of pro-angiogenic signals, primarily thrombospondin and vascular endothelial growth factor (VEGF) (*93*). At least some of this pro-angiogenic signalling is believed to be a consequence of inflammation (*94*). 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 subsequent remodelling and anastomosing of developing vessels (*95*). At a site 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 (not present in the early embryo), which 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 via secretion of truncated VEGF receptors); macrophages release this inhibitory signal by dislodging the early recruited neutrophils as well as subsequently being a local source of pro-angiogenic VEGF (*88*).

Resolution of angiogenesis

During embryogenesis there are several transient vascular networks that must eventually resolve. This developmental pruning is partially mediated by Wnt7a signals delivered by macrophages, which likely act by countering VEGF angiogenesis-promoting signals (*96, 97*). As a cancer therapeutic, several anti-VEGF drugs are approved, but while they have had some success, particularly in combination therapies, they are not the magic cancer blockers initially hoped for; rather, they may excessively prune tumour vessels leading to local hypoxia, which can trigger ectopic early metastatic spread (*98, 99*). In a wound scenario, late-stage macrophages switch from a pro-inflammatory phenotype and have a second, contrasting role, this time driving vessel regression, but unlike in development, Wnt7 signalling seems not to mediate this vessel resolving instruction (*88*).

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 they can be considered as a continuum for the purposes of tissue repair since 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 signalling imbalances associated with sustained proliferative signalling, 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 (see earlier), not to mention cancer therapeutics including chemotherapy and radiotherapy. And yet the apoptotic switches appear subdued, or even shut down in cancer cells (*100*). This capacity to ignore pro-apoptotic cues is achieved in numerous ways, including, most commonly, loss of the tumour suppressor p53 which has critical DNA damage sensing functions

(reviewed in (*101*)), or upregulation of anti-apoptotic signals including those of the Bcl-2 family (reviewed in (*102*)). Rather little research has been undertaken to investigate these apoptotic-regulator pathways during tissue repair, but there is some indication that p53 plays a role in wound re-epithelialisation and indeed that its transient shut down can accelerate normal repair (*103, 104*).

Cancer cells must also avoid surveillance and destruction by both innate and adaptive arms of the host immune system. One of the key mechanisms whereby cancer cells "evade immune cell destruction" is by "masking" themselves through upregulation of inhibitory checkpoint molecules, and this strategy has been recently highlighted as a therapeutic Achilles heel with new anti-PD1 and anti-CTLA4 antibody treatments which expose aberrant cells to T-cell killing. (Reviewed in (*105*)). In a wound repair scenario there is now good evidence that some elements of an adaptive immune response are activated alongside the more fully studied wound inflammatory response, namely a local sentinel subpopulation of γδT (*106*) and a transient influx of T-regs (*107*); both of these contribute to healing, and are nurturing to host repairing cells. However, the innate immune response is "clumsy" and non-specific in its killing strategies (see below).

Several tissue resilience pathways are activated soon after tissue damage

As described above, any tissue damage will trigger a rapid inflammatory response in order to counter potential infection. Inflammatory cells, particularly the early recruited neutrophils, release microbiocidal factors including reactive oxygen species (ROS) to eliminate pathogens but of course these will also be 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 signalling pathways that enable host tissues in the wound vicinity to survive in this hostile environment. One of these, Nrf2, is rapidly activated downstream of Ca^{++} signals in a rim of epidermal cells at the margin of the wound and this leads to activation of a number of ROS sequestering enzymes which "shield" cells and permit their survival where they otherwise would die (*108, 109*). In parallel with the ROS sequestering "shield" downstream of Nrf2 signalling, DNA and other repair machineries are also produced, including for example GADD45, which appears to enable more effective access to damaged DNA and is produced as a consequence of inflammation, since in flies and mice devoid of inflammation, GADD45 levels did not increase in the wound epidermis (*108, 110*). Ectopic expression of GADD45 in *Drosophila* epidermis is sufficient to protect it from UV-induced killing even in the absence of a wound (*108*).

Hallmark 7: Deregulating Cellular Energetics

This is one of the newly highlighted Cancer Hallmarks although its underpinning research began almost a century ago when Warburg first described how cancer cells tend to utilise glycolysis rather than oxidative phosphorylation to fuel their activities (*111, 112*). Recent studies in *Drosophila* show how lactate dehydrogenase (LDH), a key enzyme in Warburg effect metabolism, is necessary and sufficient for the switch from hyperplasia to neoplasia in skin cancer models (*113*). Indeed, PET scanning in the clinic takes advantage of this phenomenon since cancer cell glycolysis is hugely more demanding of radioactively tagged glucose than healthy cells and so highlights cancer cell location in tissues (*114*). The altered metabolic cancer "signature" can even be used to guide a surgeon's "iKnife" as they excise the margins of a tumour (*115*).

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, just as in cancer. In the 1960s Thomas Hunt and colleagues revealed high levels of lactate in healing wounds and speculated that several cell lineages switch to a glycolytic pathway and that this might be key to some elements of the repair process (*116*). Gene expression studies in the regenerating *Xenopus* tadpole show that many genes linked to glycolytic metabolism are locally induced here also (*117*) . More recent single cell transcriptomic analysis of mouse skin wounding indicates a dramatic alteration in expression of metabolism-associated genes with those associated with reduced oxidative phosphorylation and complementary active glycolysis-associated genes in sub-populations of wound edge cells (*118*). 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 significantly impairs fish heart repair (*119*).

Inflammation is known to be key in both cancer and wound healing (see above), and it may be that inflammatory cells, in part, have these pivotal roles by being the key sensors of altered microenviromental conditions, for example hypoxia, as well as being the mediators of changes to metabolic signalling in other cells, (*120*).

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/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 those signalling pathways that enable proliferation and migration are transiently epigenetically "unsilenced" as discussed above, but when the wound has 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 become immortal. On the contrary, epidermal and fibroblast cells at the wound margin may become senescent and recent studies suggest that the senescence-associated secreted phenotype (SASP) includes signals that are beneficial to repair (*121*). 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 WT sibs (*122*).

Genomic Instability and Mutation

Here, again, it doesn't 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, potential excessive viral load, and exposure to unprotected UV damage; all of these may result in secondary mutations leading to neoplastic lesions in this vulnerable, exposed tissue, as, for example, occurs in Marjolin's ulcers at the margins of venous leg ulcers (*123*). In the context of cell abnormalities in cancer, and possibly of broader relevance to general tissue repair than currently understood, are observations in larval *Drosophila* where wound edge epithelial cells fuse and become syncytial, although this is not linked to mutation or genomic instability (*124*).

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 tumours and wound healing.

Microbiome alterations

From birth—and possibly earlier—all external-facing human epithelial tissues, including the skin and gut, are colonised by bacteria that eventually establish homeostasis and symbiotically influence the local immune cell repertoire and systemic immunity (*125*). Disturbances of the microbiota, known as dysbiosis, have been implicated directly and indirectly in cancer development with the presumption that such changes will likely impact on local inflammation to drive cancer initiation and progression ((*126*) 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 (*127*). More direct 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 (*128*), and it is now clear that many other cancers have associated microbiome signatures (*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 William Coley in the early 1900s of some patients with inoperable cancers, in which infections leading to fevers occasionally resulted in their tumours "melting" away (*131*). Although the mechanisms underpinning this phenomenon are still not entirely clear, loading the bladder with Bacillus Calmette-Guérin (BCG), an attenuated strain of *Mycobacterium bovis*, has remained a standard treatment for bladder cancer (*132*). Clearly, 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 (*135*).

Advances in high throughput 16*S* bacterial sequencing have provided the first detailed insights into the complexity of the skin microbiome and how it varies between individuals and across anatomical sites, and some of the changes that occur post wounding (*136*). The host wound response has clearly evolved ways to counter these dramatic changes in bacterial flora; in instances of tissue damage where bacteria invade a wound site, some of this protective machinery is now coming to light, including NOD2, which is an intracellular receptor recognising motifs from both gram-positive and gram-negative bacteria. NOD2 null mice have an altered skin microbiome favouring pathogens over commensal species, and this dysbiosis becomes exaggerated following wounding leading to severely delayed healing (*137*). Moreover, the dysbiotic microbiome is dominant because mixing of NOD2 null mice with WT sibs results in the WT mice "catching" impaired healing (*137*).

Aberrant matrix deposition

Extracellular matrix defines the mechanical properties of all tissues, and is a key element of the cancer microenvironment that can directly impact on prognostic outcome of the cancer (*138*). For example, the presence of perpendicular, cross-linked and stiffened collagen bundles has been shown to associate with invasive regions of breast cancers and to link to worse outcome for patients (*139*).

Cancer cells may be, in part, responsible for signalling aberrant collagen deposition themselves, but equally this will also be driven by inflammatory and other cells in the cancer micro-environment. TGFβ, 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 (LOX), which are rate limiting in cross-linking collagen fibres, are also frequently reported as mis-regulated in many tumour types and likely involved in regulation of metastatic spread (*141*). A crosslinked, stiff matrix encourages integrin clustering and sustained PI3K/Akt and ERK signalling which promotes both survival and migration, and provides tracks to facilitate invasion away from the primary tumour site (*142, 143*). Indeed, in a mouse model of pancreatic cancer, LOX inhibition suppresses invasion of cancer cells and prolongs tumour free survival of these mice (*144*).

A fibrotic environment also provides the ideal pre-metastatic niche for cancer cells to home to as revealed by studies of bleomycin-induced lung damage which triggers a fibrotic response and favours the seeding of tail vein injected tumour cells in mice (*145*).

In a wound scenario it is clear that inflammation, whilst pivotal and required for various aspects of adult healing (see above), is also causal of aberrant collagen deposition resulting in a fibrotic wound scar. In embryonic tissues where leukocytes are not yet present, wounds can heal without a scar (*66*), and PU.1 KO neonatal mice lacking all leukocytes also can also repair without fibrosis (*67*). Inflammation drives fibrosis in wounds via several signalling pathways including TGFβs 1 and 2 which are known to trigger collagen and other matrix deposition by wound fibroblasts; blocking TGFβ signalling at the wound site has been shown to dampen the fibrotic response (*146*). IL4 activated macrophages at the wound site also drive fibroblast expression of the collagen cross-linking 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 cancer types (*148*). During weight gain, adipocytes become hypertrophic and eventually many die, which in turn triggers an accumulation of phagocytic macrophages which envelope the dying adipocytes and form characteristic crown-like structures (CLS) which are phenotypically and transcriptionally different from other adipocytes (*149*). Particularly in hormone-driven cancers with close proximity to large fat deposits, for example, breast and prostate, it seems that positive CLS status is associated with a poor prognostic outcome; there is also evidence for systemic endocrine effects on cancers at distant sites (*150*).

Aside from these indirect effects on tumour cells through inflammation and fibrosis, adipocytes can also deliver adipokines and other signals that influence tumour cell growth, and there is clear evidence, also, of them becoming metabolic slaves to the cancer cells. A recent study of human biopsy material and in vitro co-culture indicates how advanced melanomas invade and make direct contact with subcutaneous adipocytes which can directly transfer fatty acids to the tumour cells (*151*) and similar 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 tumour cells adjust their own metabolism and downregulate lipogenesis genes (*151*).

Obesity has close association with 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 pre-disposition to infection because of chronic high levels of blood glucose (*153*). In the wound repair community there is new interest in a more direct role for adipocytes and their pre-adipocyte precursors. For example, in *Drosophila* pupae, fat body cells, which are the fly equivalents of adipocytes, have been shown to utilise a novel adhesion-independent "swimming" motility to home towards and plug a wound, where they also upregulate antimicrobial peptides and collaborate with macrophages to clear cell and matrix debris (*154*). In murine wounding studies there is no evidence yet for adipocyte migration, but myofibroblasts have been shown to transdifferentiate into adipocytes (*155*) , and adipocyte precursors differentiate into mature adipocytes, and while 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 (*156*). Just as in *Drosophila* wound repair, mammalian adipocytes may also play a role in microbe killing since impaired adipogenesis results in increased skin infections (*157*).

Wounding can activate 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 since tissue biopsies are the mainstay of screening for and grading various cancers, and surgery (and radiotherapy) are still two of the most effective means for curing a patient of cancer. In recent decades a trickle of papers address how cancer biopsy and surgery, which by necessity will damage tissues and thus trigger a wound inflammatory response, might impact on residual cancer cells.

There have been several clinical studies over the years describing how tissue damaging cancer treatments, may locally or systemically influence cancer growth or progression to malignancy (*28*). These local influences have been mirrored in basic science studies beginning with the observation that Rous sarcoma injected chicks tended to only develop tumours at the site of injection (*158*), and similarly, wounding was needed to trigger tumorigenesis in v-jun transgenic mice (*159*). Subsequently, studies using a variety of animal models, have all shown that wound-triggered cancer initiation is mediated by inflammation (*160-164*). In the case of melanoma patients there is clear clinical evidence that local tissue damage can

exacerbate cancer progression and worsen patient prognosis (*164*). Similarly, needle biopsies for breast cancer are believed to be a potential activator of cancer progression (*165*). A further support to the concept that "wounding activates cancer" is the fragile skin disease, recessive dystrophic epidermolysis bullosa (RDEB) in which patients with mutations in collagen 7, a linker protein between epidermis and dermis, suffer from persistent cycles of skin blistering and 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 (SCC) as a consequence of the constant wound inflammation and infection (*166*).

Conversely, however, for some other cancers, including basal cell carcinoma (BCC), tissue damage, and local activation of an inflammatory response, is sometimes reported to lead to cancer regression, and is even occasionally used as a therapeutic strategy, particularly in elderly patients where surgery is not possible (*167*). 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 lead to inhibition of tumour growth (*168*).

Aside from local influences, tissue damage can also lead to systemic activation of cancer growth as 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 micrometastasis (*169*). This activation of distant "dormant" T-cell restrained cancers has recently been replicated in mice and shown to be mediated by systemic mobilisation of innate immune inflammatory cells, and moreover can be dampened by transient treatment with anti-inflammatory drugs (*163*) .

Clearly more research is needed to understand better 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 judgements can better be made in the clinic, and appropriate anti-inflammatory treatments considered wherever tissue damaging procedures need to be undertaken on 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 that we all must capitalise on. Good examples include our fuller

understanding of pro-angiogenic mechanisms which are pivotal in both cancer and wound repair, and which will lead towards strategies for improving chronic wound healing, as well as for starving a cancer or enhancing the vascular supply of chemotherapeutic drugs to the cancer. Similarly, figuring out precisely how inflammation is triggered and how it influences downstream targets and how it too can be modulated or re-programmed, will underpin development of important therapeutics for both wound healing and cancer. One clear shared goal here will be novel immunomodulatory strategies developed to dampen fibrosis which should be beneficial both for reducing extensive scarring, for example in burn victims, and also for retarding metastatic spread of several cancers. In that regard, the antifibrotic drug pirfendon, which in part acts to modulate TGFβ signalling, 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 (*170, 171*).

We can 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, while prostaglandins are implicated in driving cancer progression, they are barely 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. And while 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 "switching off" of this same machinery in cancer cells which will undoubtedly harness these same protective pathways for their own better 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, for example, how epidermal cells stop migrating (and proliferating) once wound edges have met, and similar for "shutting down" of all the other aspects of tissue repair, then some of this knowledge might offer particularly useful insights into how we might develop better "brakes" to stop cancers progressing.

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 signalling role to play in wound repair (*172, 173*), and indeed, innervation is critical for regeneration of limbs in salamanders and fins in fish (*174*), but innervation is not well studied in cancer biology. As we described above,

Folkman and others observed how a tumour, like an aberrantly growing organ, draws in a vascular supply, but it is now becoming clear that the growing cancer recruits in a source of innervation too (*175*) and, just as in a wound, this innervation could be a source of growth signals and thus a potential target for anti-cancer therapeutics also. And conversely, whilst there is a considerable literature on the development of cancer lymphatics because of their being a route for cancer cell dissemination (*176*), only recently have they been investigated in repair scenarios with the first studies being in the regenerating heart of zebrafish (*177*). 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 analysis of transcriptomic and epigenetic parallels (and differences) between repairing wounds and the signatures of various cancers at different stages of their progression

These insights together will hopefully guide us towards more shared Hallmarks and further opportunities for repurposing drugs that are trialling for cancer to be test driven 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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Figure Legends

Figure 1. The classic "Hallmarks of Cancer" circle adapted from Hanahan and Weinberg (2011) to illustrate parallels between cancer and wound healing. Hallmarks and Enabling Characteristics are mirrored in a Wound Healing circle as discussed in the text of this Review. A green tick reflects where parallels are very clear, a black cross suggests we see no parallels, and a blue question mark hints that there may be parallels. Three new prospective Enabling characteristics or Hallmarks that may fit for both cancer and wound healing sit centrally in red, and all lead towards or derive from tumour (and wound) promoting inflammation.

Figure 2. How the "Hallmarks" extrapolate to a healing wound. Here the "Hallmarks and Enabling Characteristics" Wound Healing circle with three additional prospective Hallmarks, are all mapped onto a schematic of a healing skin wound to illustrate how cell migration and proliferation drive re-epithelialisation and how this tissue is also dependent on altered cellular energetics, as well as mechanisms to avoid immune destruction and resist cell death. Several "damage" signals, as well as those activated by the microbiome and fat cells, trigger an inflammatory response which in turn regulates both wound angiogenesis and matrix "scar" deposition. In the circle is Galen's 16th Century Wound Man.

Figure 1

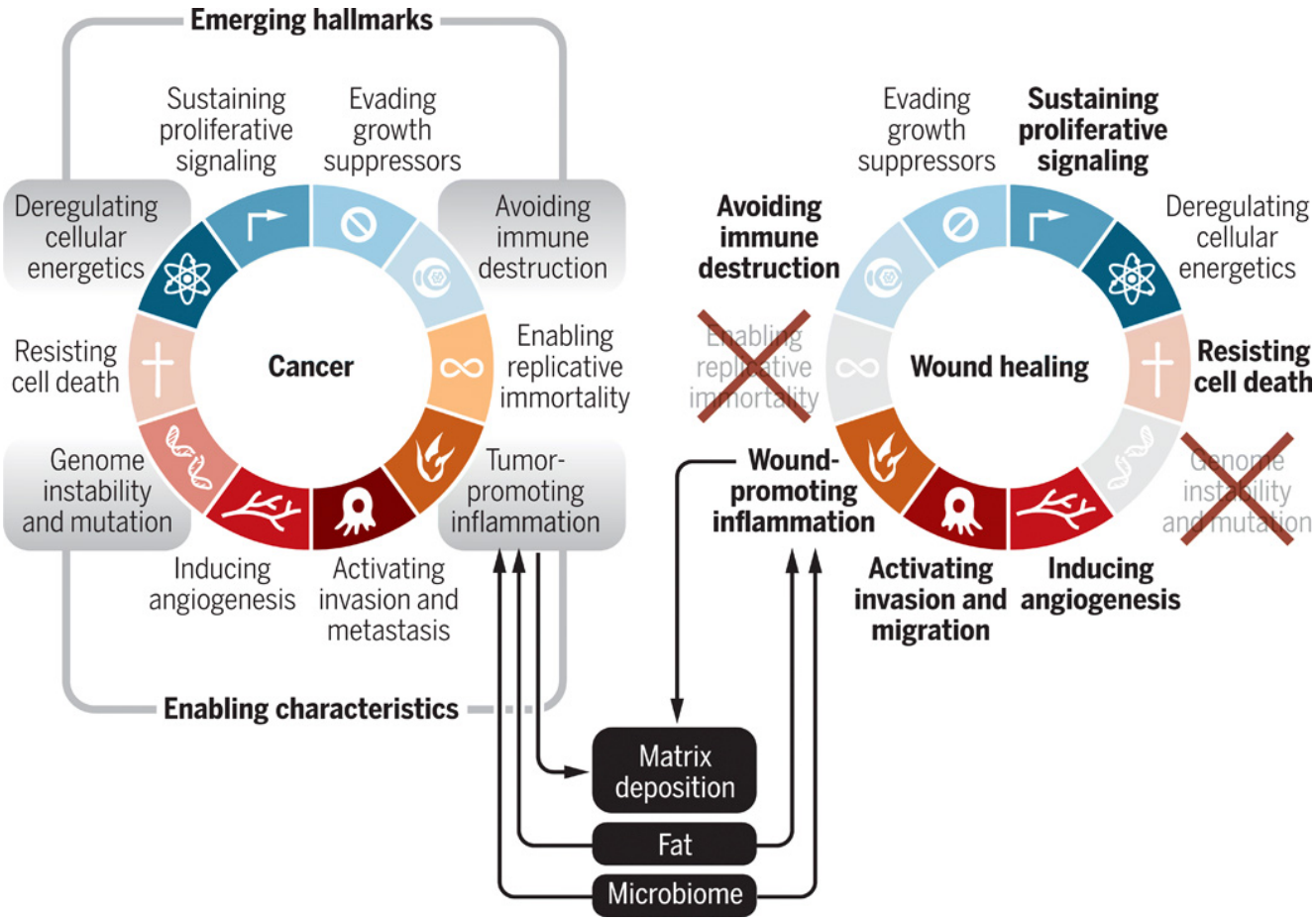
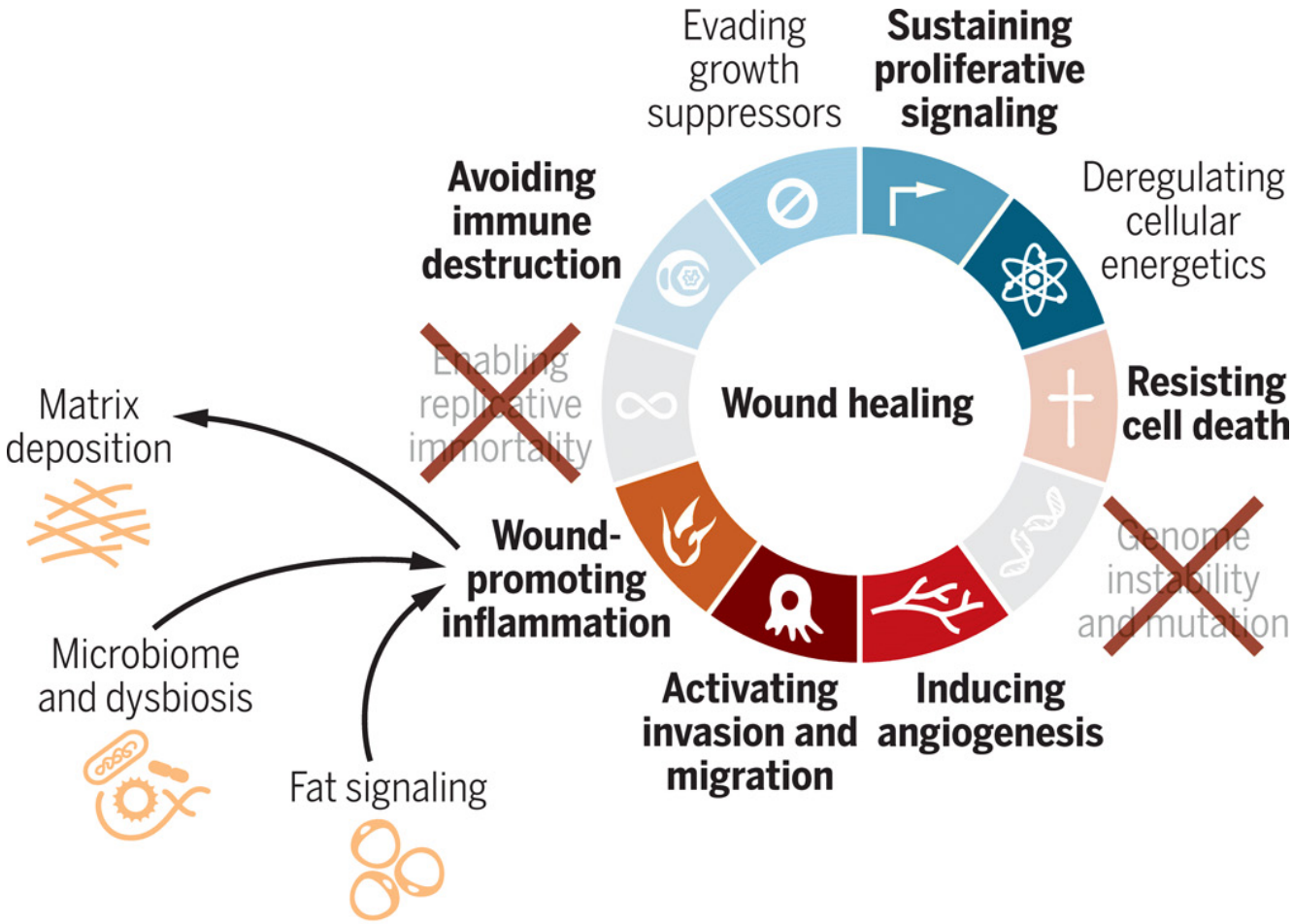
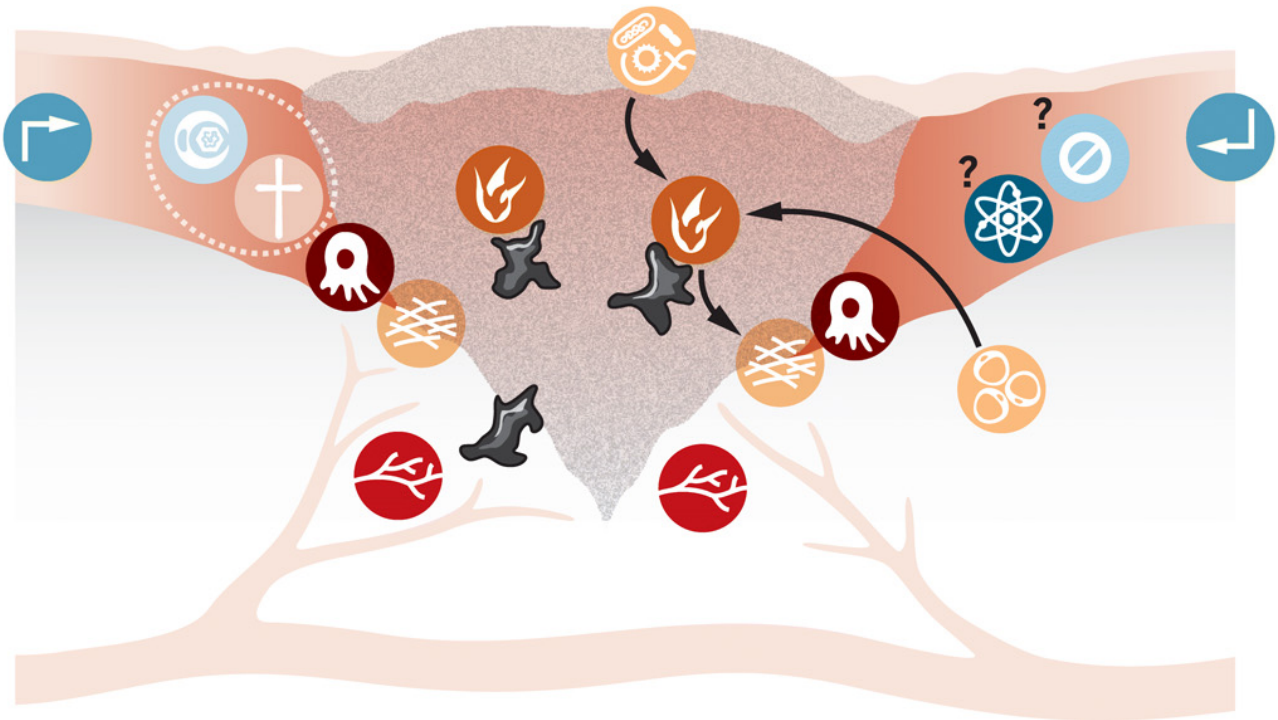

Emerging hallmarks
Sustaining proliferative signaling
Evading growth suppressors
Deregulating cellular energetics
Avoiding immune destruction
Resisting cell death
Cancer
Enabling replicative immortality
Genome instability and mutation
Tumor-promoting inflammation
Inducing angiogenesis
Activating invasion and metastasis
Enabling characteristics
Evading growth suppressors
Sustaining proliferative signaling
Avoiding immune destruction
Deregulating cellular energetics
Wound healing
Resisting cell death
Wound-promoting inflammation
Activating invasion and migration
Inducing angiogenesis
Matrix deposition
Fat
Microbiome

Figure 2


Evading growth suppressors
Sustaining proliferative signaling
Avoiding immune destruction
Deregulating cellular energetics
Enabling replicative immortality
Wound healing
Resisting cell death
Matrix deposition
Wound-promoting inflammation
Genome instability and mutation
Microbiome and dysbiosis
Activating invasion and migration
Inducing angiogenesis
Fat signaling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