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Exploring the Automotive Analogy of Neoplastic Progression: How Do Cancer Cells 'Gear Up' to Evade & Invade?

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Abstract

Cancer is a multi-factorial and multi-step disorder driven by acquired mutations/defects in components that contribute to coordinating replication, behaviour and fate in the individual cells of multi-cellular body organizations. Ten 'hallmark' cellular defects have been broadly-documented in the chronologies of neoplastic progression from cancer cases, two of which have previously been compared to the malfunction of automobile pedals. Weinberg's car-centric analogy is hereby extended to the other hallmark cellular defects and the inherent survival strategies that they employ, towards understanding transformation from the perspective of parallel mechanical defects that may plague the control network in an automobile during its 'lifetime', and how making timely repairs may prevent a catastrophic chain of dysfunctions in both systems, as they age.

Keywords: Cancer; Ageing; Car; Analogy.

Introduction

An automobile is engineered to give the driver complete control over its direction and momentum. As you may know, this control is achieved via a number of mechanistic input mechanisms within the driver's reach. The structural and functional unit of life – the cell – can be envisaged as a biophysical system controlled and coordinated via complex biochemical circuitry which responds to genetically-encoded commands and to a spectrum of environmental stimuli that influence cellular decision-making. In the context of cancer progression, factors that promote cellular growth have previously been compared to a car's accelerator, while anti-growth factors then function as the brakes [2]. Perturbation of such control mechanisms could have catastrophic consequence– for both a mechanical and a cellular system. While cars need fuel to run, dividing cells demand a steady supply of essential biomolecules that get incorporated into their dynamic biophysical structure and drive its biochemical metabolism. In this mechanical analogy, one revolution of a car's tyres is compared to one round of cell division, wherein the cell grows and divides subsequently to yield two identical 'daughter' cells. The tyre revolution rate would then correspond to the mitotic index or cell cycle rate, which depends on the cellular metabolic rate or, correspondingly, the mileage of the car. The latter two quantities (i.e. metabolism and mileage) represent the outputs of the cell (growth) and the car (velocity), respectively, at a given time point.

Cellular Components & Controls

The body frame of an automobile is the enveloping structure within which the driver and passengers are accommodated, and around which the rest of the vehicle is assembled. A contiguous planar lipid bilayer, called the plasma membrane, envelops the cellular contents. This double-layered membrane is fluidic on the whole, and rigidity is conferred to it by an underlying polymeric meshwork– termed 'cytoskeleton' **(see Figure 1)**. The plasma membrane and cytoskeleton represent, respectively, the framework and chassis of a cell. Cell surface chemical receptors and channels are then 'windows' to monitor the external environment. Just as automobiles have guarded fuel and oil caps, cells possess selective entry points for different classes of permitted molecules, except for the freely diffusible ones like water and certain gas molecules, like CO_2 and O_2.

Lacking wheels, motile cells employ cytoskeletal elements to move around, typically in response to external chemical or physical cues. The net structure of a motile cell is polarized in the direction of its intended motion. This polarity is conferred by none other than its dynamic cytoskeletal elements, the

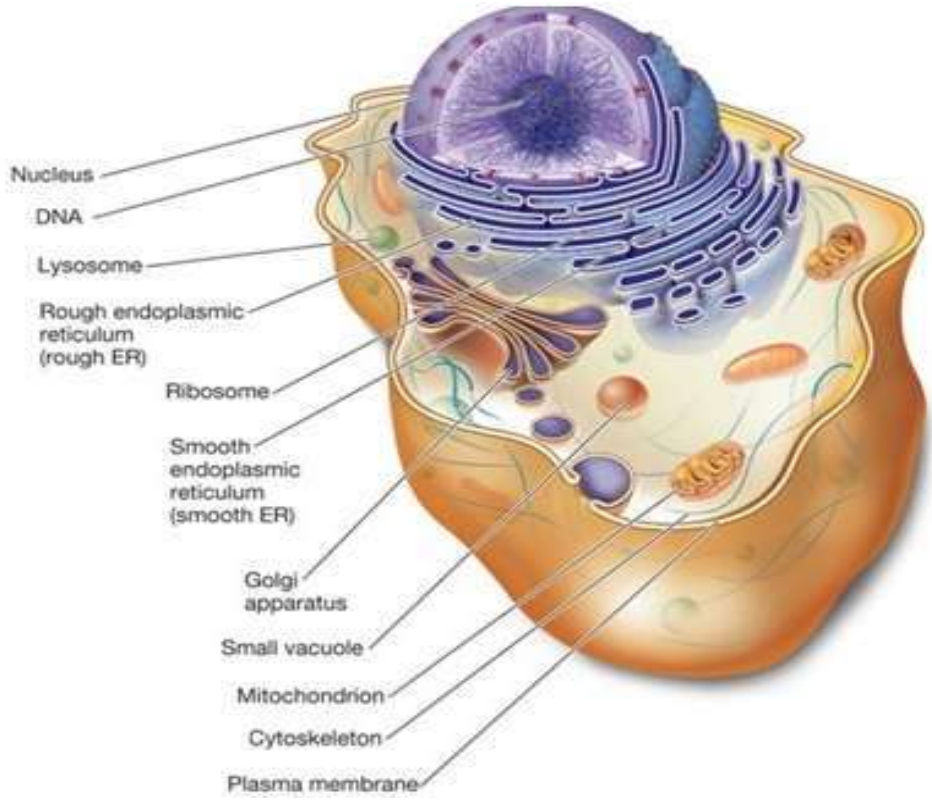

Fig. 1: Diagram of the structural elements in a typical animal cell

Source: Prokaryotic and eukaryotic cells (adapted) [Reprinted with permission from *Biology Now* © 2017 by W.W. Norton & Co., Inc].

assembly of which is energy-dependent, akin to the way a car needs fuel for propulsion. The steering column of a cell is thus connected to and controls elements of its chassis.

Proteins (polyaminoacids) are the workers of the cell, playing both structural and functional/catalytic roles. Ribosomes (see **Figure 1**) are the manufacturing units of proteins, which receive orders in the form of messenger polynucleotide (mRNA) molecules. These biosynthetic 'machines' may collectively represent the cellular engine which, much like an internal combustion engine, 'translate' inputs from the driver into system performance, at the cost of energy consumption. The cell nucleus plays the driver's role, sending mRNA-encoded instructions to the ribosomes in response to environmental and internal stimuli. "The general information flow from the 'driver' nucleus is schematically rendered in **figure 2". Box 1** Cell growth and division require 'enrichment' of the cellular protein pool, to ensure

Box 1: Fine-tuning gene expression

Each human cell harbours ~2 m of DNA within a nucleus ~μm across–a million-fold compaction! Such packaging to accommodate the information of $>10^4$ genes within each cell also facilitates tight regulation over the steps of information flux (see **Figure 2**) from gene to ribosome. The negatively-charged phosphodiester backbone of DNA is wrapped around positively-charged hisone proteins, and these nucleoprotein complexes–termed 'nucleosomes'–are the fundamental unit of chromosomes. In general, the rate of transcription of a gene is inversely proportional to its degree of compaction within the nucleus, based on its accessibility by the transcriptional machinery that generates messenger RNAs from it. Since the described paradigm influences gene expression without making sequence alterations (mutations), they are termed 'epigenetic' factors ('epi' – 'above'). Importantly, this fine-tuning of the genetic information flux is environment-adjustable.

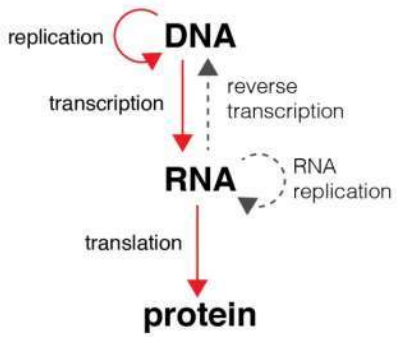

Fig. 2: Flowchart of how genetic information is decoded and regulated.
Sources: B. Farley, *What is the central dogma of molecular biology? Is it true?*, www.quora.com, 2015.

that each daughter cell inherits a full proteomic complement (not just one half). So higher the mitotic index, greater would be the proportionate ribosomal 'information' flux to generate the requisite protein content. Moreover, as the enrichment of essential non-protein cellular components, like DNA and lipids, is achieved by none other than catalytic proteins, called enzymes, the flux through their respective biosynthetic pathways will proportionate with the ribosomal flux! Consequently, the translation rate in a growing cell may proxy the sum total of the biosynthesis towards supporting its mitotic index.

Mitochondria (see **Figure 3**) may well represent the (collective) cellular fuel tank, a 'powerhouse' that maintains steady state levels of the cellular energy currency– the ribonucleotide adenosine triphosphate (ATP) – employing a biosynthetic process called oxidative phosphorylation (OP). OP essentially drives the build-up and channelized dissipation of a proton (H^+) gradient through ATP synthase – a rotating molecular machine – that converts the electrochemical energy stored in the H^+ gradient to catalytic energy for ATP synthesis, from ADP and inorganic phosphate (P_i). The structure of a mitochondrion (see **Figure 3**) and the net equation representing OP is shown in Box 2. In the mitochondrial structure (see Figure 3), ATP synthase particles and OP machinery are embedded in the inner mitochondrial membrane.

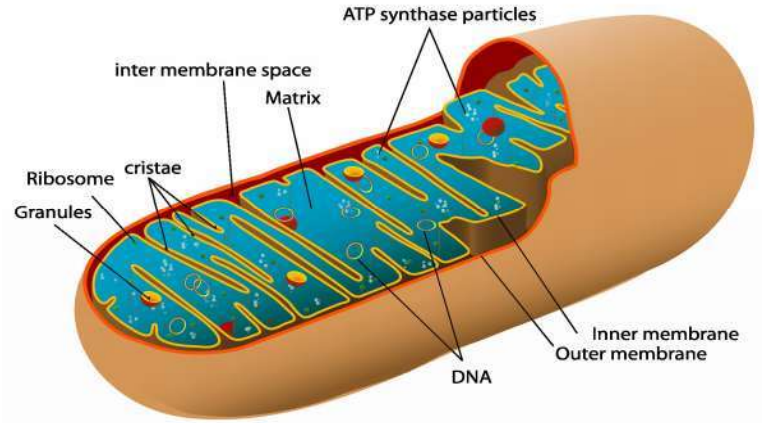

Fig. 3: Cartoon rendering of the mitochondrial ultrastructure

Sources: M. Villarreal, *Animal mitochondrion diagram*, Wikimedia Commons, 2006.

Box 2: Converting fuel to energy

Keeping engine longevity in mind, the cylinders in an automobile engine are configured to optimally balance the torque on the rotating crankshaft, which drives the wheels, and to minimize vibrations. Interestingly enough, mitochondrial architecture provides a scaffold for an electron transport chain, which is the site of OP. Macromolecular redox complexes are embedded in the inner membrane, permitting their physical proximity to allow for the transfer of electrons to the neighbouring complex possessing a higher reduction potential. Electrons pass through a series of four such complexes, which essentially harness the redox energy generated via electron transfer to pump glucose-derived protons (from the citric acid cycle) for generating the proton gradient required to drive ATP biosynthesis. The free electrons are ultimately accepted by dioxygen to reduce the latter to water:

$$C_6H_{12}O_6+6O_2+38ADP+38P_i(glucose) \rightarrow 6CO_2+6H_2O+38ATP(energy)$$

Interestingly, mitochondria seem to have evolved from a chemosynthetic species of bacteria that got internalized by ancestors of the eukaryotic cell [3].

Despite these organelles harbouring their own unique set of DNA and ribosomes of prokaryotic origin, they are incapable of surviving outside the host cell – a cost of the symbiotic relationship with our cells – just as a fuel injection system is pretty much useless outside of an automotive system. Moreover, there is a well-studied bioenergetics feedback system from the mitochondrion to the nucleus, and based on which cellular decisions are taken so as to ensure that the desired ATP level is actively equilibrated. This parallels the dashboard fuel gauge indicating the relative amount of fuel remaining.

Pedals

Pressing down on the accelerator pedal increases the fuel supply to the engine and, proportionately, the vehicular velocity goes up. Pro-growth factors perform a similar function in cells, wherein they support cell growth and division. When genes encoding growth factors acquire mutations that cause them to function constitutively, triggering hyper-proliferation, they are termed 'oncogenes'. Such 'accelerating' factors essentially enhance the net information flux to the ribosome.

Applying the footbrake typically acts on all four wheels of an automobile, bringing them to a synchronous halt when desired, while the hand brake is designed to act on the rear wheels, to prevent the vehicle from rolling passively once applied. Anti-growth factors, as opposed to pro-growth signals, act as cellular brakes on potential hyper-proliferation. They are hence termed 'tumour suppressors'. Such 'braking' factors attenuate the net information flux to the ribosome.

The transmission system allows a driver to decide, using a hand-held gearshift, the range of torque (rotational force) to be supplied by the engine to the flywheel that rotates the car wheels. The gearshift positions analogy the ribosomal flux rates required towards *de novo* syntheses of biomolecules, proportional to the mitotic index. Each gear thereby imposes a range of fuel consumption, and lagging which would bring on a stall or, correspondingly, mitotic arrest in a dividing cell. Application of higher torque by the engine demands higher fuel consumption, similar to how a high ribosomal translation rate levies proportionately higher ribosomal ATP demand, to meet the increased information flux coming from the nucleus (via coding mRNAs). Hence, the mitotic index of a cell must be gear-matched with its ATP-dependent protein biosynthesis, to prevent mitotic arrest. Neutral gear would then represent a quiescent or 'idling' state, in which division is halted, and from which the cell may be put back into gear, when the necessary growth factors are available. When cells are damaged beyond their repair capacity, say due to an ionizing radiation exposure, they are programmed to 'die silently'. This Cell fate choice, when triggered, is executed along a cell- wide biochemical circuit, causing a systematic cellular 'demolition' wave. In essence, the metabolic cellular engine is switched off for good – similar to the effect of a vehicle's ignition control key – before it is dismantled and disposed of. Indeed, both the ignition system and the death circuitry decide the fate of their respective systems, reprising their role as master circuits.

Similar to how a car has windowpanes through which its surroundings are observed, the cell 'feels' its way around, responding to chemical and physical cues from its microenvironment, and based on which it can sense if it's in the right anatomical location. Indeed, cells can feel each other, in a manner analogous to how drivers see and hear other vehicles in the vicinity of their car. The navigation system (eg. GPS) displays a driver's precise geographic coordinates, based on satellite inputs. Modern systems also provide timely updates on traffic patterns, according to which a suitable route can be planned. Similarly, the 'roadmap' that a specific cell follows is dictated by the environmental cues it senses, parallel to how drivers manoeuvre their vehicles in road-space and time, in accordance with traffic signals, road signs, and neighbouring vehicular positions. The 'driver' nucleus thus integrates multiple cues to adjust cell fate and trajectory in space and time, in cooperation with traffic signals and signs from other drivers.

An 'Unfortunate' Series of Events

During a road trip, a man finds the clutch pedal of his car stuck, rendering him unable to switch to higher gear. To avoid heavy clutch replacement charges, he avoids getting his vehicle repaired, thereby opting to continue driving it permanently in 1st gear. From the next drive onwards, the owner starts flooring the accelerator pedal in order to quickly pick up speed in the sluggish automobile. One fine day, the fatigued gas pedal gets stuck down, and the vehicle accelerates uncontrollably. In response, the driver immediately kills the ignition and stops. The owner opts to avoid the accumulating repair charges, and continues to drive around in his faulty automobile, employing just the foot brake to control its speed. After long and heavy usage, the foot brake suddenly fails. There is now a dependence on the hand brake to stop at signals, which also fails one day owning to its heavy usage, and the driver once again kills the ignition in response.

The highly determined owner–true to his 'no repairs' decision–seals his fate by opting to use the ignition key and steering to move around in his 'repair-free' car, timely switching off the ignition to come to a stop! One fateful day, in order to stop at a red light, the driver turns off the ignition key, only to find it unresponsive–thereby rendering him completely incapable of bringing the steadily accelerating car to a halt. The driver employs his GPS to find and detour over to an abandoned ground, where he can drive around in circles till the runaway vehicle runs out of fuel. But instead, the outdated navigation software leads the swerving driver to the

recently repurposed and currently crowded ground. On arrival at the scene, law enforcement takes the matter into their hands and, seeing no other option, employs heavy artillery to take down the unstoppable car. Their destructive action results in some collateral damage, but the rouge vehicle and its ill-fated driver are destroyed.

Accident Report

The driver's choice of mechanical negligence led to the automobile sustaining unrepaired damages over time. Due to getting stuck in the 1st gear, the engine gave the lowest possible mileage with a disproportionately high fuel demand. Once the ignition system was rendered constitutive, the driver was incapable of obeying any traffic signals in the runaway car. The nearby road users were forced to take sudden evasive action to avoid the ensuing police fire, and some vehicles incurred collateral ballistic damage which – if also left unrepaired – may incur similar catastrophic consequence. **Table 1** compares the car components that failed in the hypothetical repair-deficient automobile described above, to the analogous cellular components which generally get mutated during tumour progression.

Table 1: Comparison of the vehicular systems that failed, in chronological order (left to right), with their cellular analogues

Car	Maintenance	Transmission system	Accelerator pedal	Brake pedal & Hand brake	Ignition system	Navigation
Cell	Repair	Nutrient demand	Pro-growth factors	Anti-growth factors	Cell fate choice	Migration

In the scenario elucidated above, it was the sequential failure of multiple vehicular components that rendered the car refractory to its driver's inputs, especially if one considers vehicular maintenance *per se* as being a component of the automobile, under the driver's control. Then, the 'no repairs' decision of the owner represents the first defect to plague our hypothetical automobile.

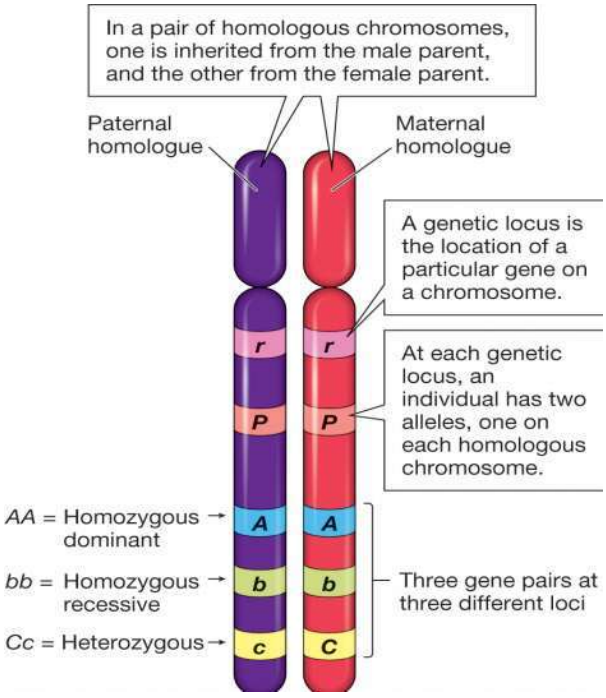

Fig. 4: Schematic depiction of paired DNA loci on homologous chromosomes
Sources: Genetic loci on homologous chromosomes [Reprinted with permission from *Biology Now* © 2017 by W.W. Norton & Co., Inc].

Importantly, cancer hallmark-enabling mutations are generally not acquired in any particular order, and there are multiple pathways of 'malfunction' that may render the disease. Moreover, mutations in multi-functional regulatory elements can render multiple hallmarks simultaneously. For example, *TP53* mutations may render the hallmarks of genomic instability (no repair), cell death resistance and, additionally, blood supply acquisition [4]. Each human cell (barring the gametes) possesses exactly two copies of each of its 20,000 to 25,000 protein-coding genes (refer **Box 3**). When random mutations

Box 3: Two 'copies' per pedal

The genetic information of most human cells is in the form of 23 pairs of homologous chromosomes (see **Figure 4**)-, comprising 44 'autosomes' and 2 sex chromosomes (XX in females and XY in males). There are thus two copies of each gene, including those encoding pro- and anti-growth factors. Mutational inactivation of one tumour suppressor gene can be at least partially compensated for by its allelic partner on the homologous chromosome, similar to how a car with two brake pedals can be brought to halt even if one pedal fails. However, note that this is not the case for a car with two accelerator pedals; when one gets stuck down, the other will only serve to aggravate the defect.

rendering growth control defects are acquired by gamete cells (egg/sperm), they contribute to early-onset cancer risk in subsequent generations. For instance, mutations in the *BRCA* tumour suppressor genes drive familial breast cancer [5]. In fact, acquired heritable mutations are part of the evolutionary process, and so incipient cancer cells evolve faster than the host organism, due to (acquired) deficiency in DNA repair. Cancer cells thus spawn populations of rapidly mutating daughter cells, which undergo diversification and natural selection at evolutionary rates far greater than normal, to ultimately out-compete the host's physiological and immune systems. This causes the high morbidity and mortality rates associated with invasive cancer cell migration– - termed 'metastasis'.

Survival Strategies

Cancer cells are notorious for employing a number of pro-survival strategies, some of which are characteristic of the early embryonic programmes of patterning and development. In light of this, tumours are now regarded as aberrant organs, possessing independent blood supply, tissue architecture, and resident (cancer) stem cells to renew tumours post surgery/therapy.

Human cells typically lose their replication capacity after dividing ~40 to 60 times, a phenomenon termed the 'Hayflick limit'. This loss is associated with the shortening of chromosomal ends, called telomeres, to critical lengths. Cellular immortality, or infinite mitotic potential, is essentially achieved by maintaining full length chromosomal ends, by virtue of the action of an RNA-dependent protein complex called 'telomerase'. Just like chromosomal ends, car tyres tend to undergo wear and tear with distance traversed, but also gradually lose air pressure. When either of these losses occur, a 'pit stop' becomes necessary to timely replace or refill the tyres. Hence, the telomerase strategy may be compared to a car befitted with reinforced, self-inflating tyres! Cells with finite mitotic potential, which do not express telomerase, are then comparable to cars fitted with only one set of tyres during their lifespan; once the structural integrity of the rubber gets compromised, driving on them is discontinued. Some normal body cells, particularly stem cells, are also immortalized owning to telomerase expression.

Counter-intuitively, in a disease driven by non-maintenance of genomic integrity, telomerase-directed chromosomal end maintenance plays a role not only in conferring replicative immortality to damage-accumulating incipient cancer cells, but also in rendering physical/steric hindrance to chromosome rearrangement events that can create oncogenes, like the Philadelphia chromosome abnormality in leukemia [6]. However, the benefit of immortality seems to outweigh this disadvantage.

Cancer cells tend to switch their glucose catabolism pathway from OP to one normally employed during low oxygen (hypoxic) conditions to 'break' glucose, hence termed 'aerobic glycolysis' (AG) when active under normal oxygen levels. AG occurs outside mitochondria in the cytoplasm, generating lactic acid ($C_3H_6O_3$) as a fermentation by-product instead of CO_2. This strategy somewhat parallels the fuel switch in bi-fuel 'hybrid' cars, with more than one fuel reservoir– typically petrol and natural gas. AG may be represented by the following net reaction:

$$C_6H_{12}O_6 + ADP + 2P_i \text{ (glucose)} \rightarrow 2C_3H_6O_3 + 2ATP \text{ (Lactate) (energy)}$$

Note that AG is 18 times less efficient than OP at ATP production per glucose molecule consumed, and so the former energy pathway may be regarded as natural gas combustion, while the latter (OP) may then represent petrol consumption; both fuels power the same engine at different calorific values. Consequently, elevated glucose uptake has been observed in cancer cells, perhaps to compensate for the low efficiency of AG metabolism. Not surprisingly, elevated blood glucose levels are correlated with poor cancer survival! Importantly, unlike the more fuel-efficient mitochondrial OP pathway, AG metabolism provides for metabolic 'shunting' of intermediate products of glycolysis into *de novo* nucleotide biosynthesis– towards maintaining the reactant pool of deoxynucleotides required for replication synthesis of DNA before cell division. Indeed, this cross-benefit may serve to overcome the cost of switching over to low efficiency AG, and is akin to condensing and electrolyzing the water (vapour) liberated from natural gas combustion in a bi-fuel car to generate its alternate energy potential– dihydrohen gas.

Like many others, cancer cells display on their external surface a characteristic myriad of embedded biomolecules – termed antigens – that is typical of its cellular identity, and by virtue of which it can be 'profiled' by the immune surveillance system. Being defective in nature, these mutant cells would be 'interrogated' and eliminated before they can spawn tumours. To maximise their chances of survival, incipient cancer cells may modulate the aforementioned cell surface display, to avoid being perceived as dangerous. Tampering with the license plate/registration number of a vehicle might have an analogous effect, in order to mislead traffic police. Note that ridding a car of its license plates altogether would not be too useful a strategy, as doing so would incur equal, if not more suspicion from the police.

Phone call

Cells communicate with their environment vis-a-vis intercellular exchange of signalling molecules. Secretion of such signals into extracellular space facilitates long-range communication with cells that are 'receptive' for the secreted factors. For example, insulin hormone released from pancreatic â-cells signal liver and skeletal muscle cells to uptake blood glucose. Cellular communication is exploited by mutant cancer cells in all stages of the disease to advantageously manipulate their tumour microenvironment, which typically comprises both normal yet 'servile' cells and other mutant cells. This situation may well resemble drivers of various vehicles talking on their mobile phones while driving. Exploiting this rather dangerous habit, a driver can make arrangements with a fuel trucker to pull up and refuel the car on-the-go, once the fuel (CNG?) runs low. Similarly, incipient cancer cells are notorious for ordering their own blood supply, termed 'angiogenesis', when the oxygen tension in their microenvironment becomes insufficient to meet the metabolic demand of the growing tumour mass by means of diffusion alone. Once established, such illegal blood supply lines also act as conduits for metastatic migration of cancer cells to distant sites, via the bloodstream 'highway'.

Interestingly, extracellular messenger secretion is also employed for self-communication, wherein the cell is receptive for its own secreted messengers; signal amplification via positive feedback is achieved when signal reception triggers an enhanced release of the same messenger molecule(s). This 'self-signalling' strategy, which is known to drive cellular hyper-proliferation within the tumour milieu, is parallel to remote-hacking of traffic signals to keep them on green.

Recall that in the aforementioned example, the destructive police action taken against the runaway automobile also caused damage to nearby vehicles caught in the artillery fire. As mentioned, all would be well and good if these unintentionally damaged cars received servicing immediately after the incident. However, if even one of the (non-target) drivers involved follows a 'no-repairs' policy like our ill-fated owner did, his/her deteriorating vehicle could well become the next threat to road safety! In our body, the interaction of biomolecules from foreign and potentially dangerous cells with their cognate host receptors triggers a pathogen-sensitive response mechanism, enabling cycles of localized inflammation till the perceived threat is destroyed. Inflammation enables the enzymatic/oxidative disincorporation of non-host molecular structures encountered, termed 'immunogens'. The generation of reactive oxygen species (ROS) by immune cells to damage potential pathogens is known to cause collateral oxidative damage to components of healthy (non-target) cells. When ROS adducts formed with DNA bases go unrepaired before replication synthesis, they get fixed in the daughter cell genomes as stably acquired mutations.

Cancer and Ageing

A build-up of cells in the body that have reached their Hayflick limit (post-mitotic), together with their cumulative damages contribute to ageing in a major way. The latter i.e. accumulating cellular damage with age appears as a common denominator with cancer, which otherwise seems to be an opposite process. Indeed, cancer risk increases with ageing, and the disease manifests when the balance between cell death/'idling' and growth/division is tipped in favour of the latter [7], by acquired mutations. In fact, ageing versus cancer appears to be determined, at least partially, by whether a mutation decreases or increases a cell's 'fitness', towards natural selection. Analogously, in an automotive system, a mechanical perturbation may either decrease an automobile's performance and bring it a step closer to retirement, or enhance it instead (eg. accelerator stuck down). In the hypothetical scenario discussed previously, the clutch pedal getting stuck while the transmission is in 1st gear may well represent a loss of fitness, although the vehicle in concern ultimately gained in performance (speed) from the subsequent defects. On the other hand, if a car's hand brake somehow became irreversibly engaged, its pickup could be severely compromised– a loss of fitness. Ignition system failure would then represent a mechanical death scenario for the automobile, in contrast to a catastrophic unstoppable one. Note that epigenetic (non-sequence) alterations in cells (refer Box 1) also contribute to and stratify both cancer risk and expected lifespan.

Prevention over cure

A growing body of compelling yet controversial evidence suggests that the risk of developing cancer in an organ is proportional to the total number of cell divisions that its pool of resident stem cells undergo, towards maintenance of their respective organ systems [8]. This intrinsic risk stems from 'accidental' mutations rendered during DNA replication. More the number of divisions undergone by a cell during its lifetime, greater would be the genetic 'mistakes' accumulated. Indeed, frequently driven vehicles would incur on average greater usage-associated

damage during their lifetime than would lesser driven ones. Moreover, the effect of lifestyle/environmental risk factors, like tobacco usage, appears to be less pronounced in organs with a relatively lower stem cell division rate, like the brain. On the other hand, lung epithelial stem cells, which divide frequently to maintain alveolar integrity for gaseous exchange, exhibit both elevated intrinsic and environmental risk. Nonetheless, increasing cross-protective lifestyle factors against cancer and ageing (senescence) can both reduce cancer risk in general as well as promote longevity, similar to how timely repair and maintenance will extend the lifespan of any automobile.

Conclusion

A single car can hold up traffic on a narrow road, nucleating a vehicular jam, in response to which oncoming vehicular positions may start getting patterned out kilometres away from the spot, for which oncoming drivers will receive traffic alerts in real time. Our complex human anatomy and physiology develop from just a single fertilized egg cell, called the zygote. In essence, the lone zygotic cell, derived from gamete fusion (fertilization) nucleates a chronology of cellular organization that is extrapolated over our entire anatomical map, extending across the ~10^{12} cell-lengths that comprise the human body. In this orderly-derived system, neoplastic progression represents a chronology of malfunctions in cells that not only become refractory to the command signals from their microenvironment, but also activate embryonic development programmes to survive, proliferate and evolve. Lifestyle-associated factors like diet and exercise levy influence on cellular repair, which keeps metabolism in top condition to promote longevity, just as unleaded fuel and timely maintenance can extend an automobile's 'healthspan'. **Table 2** below compares each hallmark of cancer with the parallel scenario in an automobile.

Table 2: Comparison of the ten cancer hallmarks and their mechanical analogies

Cell	Car
Unchecked genomic damage	Negligent ownership
Deregulate nutrient demand	Transmission/gear stuck
Pro-growth signals constitutive	Accelerator stuck on
Anti-growth signals ineffective	Foot/hand brake failure
Death resistance	Unstoppable ignition
Invasive migration	Inaccurate GPS
Immortality	Self-inflating tyres
Immune evasion	Tampered license plates
Manipulate microenvironment	Wireless communication
Inflammation	Collateral damage

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