Is Type 2 Diabetes One of Such Aging Phenomena That Lack an Irreversible Structural Change?

Qingwen Jia*, Xiaohan Chen*, Yuping Jia1, Xixi Dou1, Lewis Ezeogu3, Ningzhi Xu4* and D Joshua Liao3*

1 Shandong Academy of pharmaceutical Sciences, Jinan, Shandong, 250101, P.R. China
2 Guangxi Academy of Fishery Sciences, Nanning, Guangxi 530021, P.R. China
3 Hormel Institute, University of Minnesota, Austin, MN 55912, USA
4 Laboratory of Cell and Molecular Biology, Cancer Institute, Chinese Academy of Medical Science, Beijing 100021, P.R. China

Abstract

All biological functions should have a structural basis. Any functional change should be due to an alteration in the related structure. If a functional change is irreversible, it should be due to the irreversibility of the structural alteration. For instance, cancer is irreversible because cancer cells have irreversible genetic mutations. However, Type 2 Diabetes (T2D) with Insulin-Resistance (IR) as a central mechanism is irreversible but seems to lack a corresponding irreversible structural change. IR and T2D exhibit many abnormalities that are attributable to altered mitochondria or altered cellular RNAs, proteins, lipids, etc. without genetic mutations involved. These alterations are reversible, because mitochondrial biogenesis can be induced by such as exercise whereas RNAs, proteins and lipids will degrade after some time. Aging is irreversible but many aging manifestations also lack corresponding permanent structural changes, and IR may be one such manifestation. IR affects mainly striated muscles, adipose tissue, brain and liver that are collectively defined herein as the “catabolic cell type” for their low proliferation rates but high metabolism of glucose via oxidation-phosphorylation in mitochondria. In contrast, fast-proliferating cells are defined as the “anabolic cell type” because they are the main cancer origins and often metabolize glucose via glycolysis. Dichotomizing T2D- and cancer-targeted cells and pointing out that the irreversible IR as an aging phenomenon lacks a corresponding irreversible structural change may help understand the differences between, and the mechanisms of, T2D and cancer, although these concepts challenge the “structural-functional relationship” dogma in not only biology but also philosophy.

Keywords: Type 2 diabetes; Insulin resistance; Cancer; Mutation; Aging

We have been Taught that a Function is Based on a Structure

We as biologists or medical researchers are well educated on structures of various organisms, including the human one. Here, a structure can be something fairly large, such as the anatomy at the macroscopic and microscopic levels, but can also be something very small at the molecular level, such as the sequences and conformations of the DNAs, RNAs, proteins, lipids, starches, etc. Out of this educational background, a concept of structural-functional relationship has been firmly entrenched in our mind. This concept says that a function is based on one sort of architecture or makeup, and any change in a function ultimately can be causally linked to an alteration in the related structure. If the structural alteration is reversed, the function will return to normal as well. For example, based on this rationale, cardiac surgery is performed to fix congenital heart malformation of children. Conversely, irreversible change in a function should be due to an irreversible alteration of a structure.

At the molecular level, for a long time it had been thought that proteins were the only executors of cellular functions and all genes had to be expressed ultimately as proteins to be functional, but we now know that many RNAs can also elicit cellular functions, coined collectively as regulatory RNAs. Nevertheless, in all organisms except retroviruses, RNA is transcribed from DNA and protein is translated from RNA. All RNAs, proteins and lipids as well as most, if not all, other cellular components are relatively short-lived and will degrade sometime after they were produced, and their productions via biochemical reactions are controlled by a group of proteins dubbed as enzymes. Therefore, changes in cellular functions are reversible unless irreversible mutation(s) occur in the nuclear DNA, which is the ultimate governor of all cellular functions. Expression of mitochondrial RNAs and proteins from mitochondrial DNA (mtDNA) in eukaryotic cells involves proteins encoded on the nuclear genome, making mitochondrial functions reversible and controlled indirectly by the nuclear DNA. Although mutations of nuclear DNA sometimes can be spontaneously reversed to the normal, as clearly seen in some genetic diseases [1], such “reverse mutation” or “mutation of mutation” occurs as rare events. Epigenetic alterations may also alter cellular functions, but they are impermanent, although probably abiding, such as the mutual reversion between DNA methylation and demethylation.

Cancer is a good example of irreversible cellular abnormalities: A patient gets a cancer because one of his cells initially developed a
Cachexia usually incepts with the loss of adipose tissue. These features with normal fasting glucose and decreased body fatty tissue. Actually, lower or normal. However, IR in these cancer patients is associated elevated gluconeogenesis while the serum insulin level may be higher, IR in association with elevated hepatic glucose production and with cancer is basically irreversible. Some cancers may spontaneously regress, but more due to other reasons such as the clearance by the innate immunity, and not because of reverse mutations. Very often the above described chain of genetic changes during carcinogenesis is accompanied by epigenetic modifications, especially methylations and demethylations, as mentioned above, they are not perpetual and thus not liable for the irreversibility of cancer.

Type 2 Diabetes (T2D) is Irreversible, but Sans an Irreversible Structural Change

T2D occurs mainly in adults, with insulin resistance (IR) as a central mechanism, unlike the type 1 that occurs mainly in children and is due to the lack of sufficient insulin to control the blood glucose level. Most pertinent publications describe that IR appears in "peripheral tissues" but do not clearly tell us whether or not IR attacks all cells of the patient. We surmise that probably all cells of the body are affected but those major glucose-consuming organs or tissues, such as striated (cardiac and skeletal) muscles, may be more severely affected than the others.

It is clear that IR can be controllable, and we are now able to slow down or even stop the progression of T2D with the blood glucose level controlled in the normal range in many cases. However, our overarching assumption is that overt IR and T2D, with pre-diabetes culled away, are irreversible and thus cannot be cured completely. This means that those well-controlled T2D cases will still require management or medication. For instance, a bariatric surgery can be performed to alter the gastrointestinal anatomy to provide a permanent management that is irreversible and thus accountable for the irreversibility of overt IR and T2D?

Decreases in the number of mitochondria and mutations in mtDNAs have been reported frequently in T2D patients. One cell has hundreds to thousands of mitochondria. Determining the existence of an mtDNA mutation is easy with today's sequencing technique, but determining how many mitochondria in one cell, one tissue, and one person bear this mutation is difficult, if not impossible. Of many unanswered questions are whether and how the decreased number of mitochondria can be manipulated to return to normal and to what extent those normal mitochondria can override the abnormal function of those with mtDNA mutations in individual cells. Moreover, it has rarely been addressed and thus is still obscure whether in some situations one mitochondrion may have additional copies of mtDNA but only one of them is mutated. Since one cancer cell can be polyploid, one mitochondrion may be polyploidy as well when it goes abnormal, which in turn makes it even more uncertain how an mtDNA mutation contributes to IR in individual patients (but no in individual cell lines). Regardless what answers for these questions may be, mitochondrial alterations are irreversible despite exercise and oxidative fluids can induce mitochondrial biogenesis, and since the number of mitochondria may be increased in some cancer cells. Besides mitochondria, many abnormalities seen in T2D are also ascribed to abnormal mitochondrial RNAs, proteins, lipids, etc., such as decreased phosphorylation or conformation of proteins. These abnormalities are also permanent and will last long after the RNAs, proteins and lipids have degraded, since no genetic mutations are involved. Hence, an overarching question occurs to our mind: what is the alteration in a biological structure in so many cells of the body that is irreversible and thus accountable for the irreversibility of overt IR and T2D?

IR is One of Those Manifestations of Aging Sans a Permanent Structural Change

Aging is inevitable and irreversible, although it may be manageable; otherwise the slang “as reliable as death and taxes” becomes unreliable. Aging of some cell types or tissues has a structural base. For instance, aging of those cell types with a regeneration ability, such as bone marrow cells or epidermal keratinocytes, may be causally related to telomere shortening as its structural basis. Persistent activation
of telomerase can maintain the length of the telomere and thus can sustain an unlimited cell proliferation, which is a state called cellular immortalization and is a hallmark of tumor cells [30,31]. However, some other cell types such as neurons and cardiac muscle cells have lost their replication ability during adulthood, but they still age. Therefore, not all types of cells or tissues age via telomere shortening. Aging is a gradual change of cellular biochemical reactions and ensuing cellular functions that lead to incremental increase in the possibility of death, but what is the irreversible structural change(s) that are accountable for these aging-related biochemical and functional changes in these cell types that can no longer replicate remains a conundrum to us. In our meditation, many aging phenomena do not require an irreversible structural change, and IR is one such phenomenon.

If we agree on that T2D is irreversible once it is well established, and is dissociated with an irreversible alteration in a biological structure, just like many aging phenomena as inferred above, we automatically arrive at an astonishing conclusion that the structural-functional relationship is not always right, which is astounding in a way that shakes our philosophy. This is partly because it is against Darwin’s “natural selection” theory, which says that an environmental change gradually, i.e. evolutionarily, leads to the development of a new structure with a new function in an organism, or even the development of a whole new species of organism. Whether “a function should base on a structure” can be extended to “an irreversible change in the function should also base on an irreversible change in the structure” is a philosophic question that bewilders us. Its answer should contribute significantly not only to our understanding of T2D but also to theoretical biology and even to philosophy.

**Cancer and T2D Mainly Affect “Anabolic” and “Catabolic” Cell types, Respectively**

Cancers and T2D are similar in their life-threatening and irreversible natures and both manifest abnormal control of cell death: cells mistakenly become immortal in cancer but, on the contrary, senesce earlier in T2D, as expounded later. However, cancer and T2D often impinge on different types of cell and tissue. Since the most striking yardstick of cancers is a constant cell proliferation and since sporadic cancers are derived only from those cell types that retain a regeneration ability, we define cancer origins collectively as the “catabolic cell type”, which includes those fast-proliferating cells in such organs or tissues as hair follicles, bone marrow, epidermal skin, and the gastrointestinal mucosa. Embryonic cells are typical of the anabolic type. Of course, cancer cells as the malignant version of embryonic cells care only for replication and thus are typical of the anabolic type as well. Actually, for this reason, most classic chemotherapeutic drugs target fast-proliferating cells, and therefore many, but not all, anabolic cells are also those responsible for the common side effects of chemotherapy, including hair loss, low blood cell counts, skin itch, nausea, vomiting, diarrhea, etc. [1,2]. In many cells of the anabolic type, especially in cancer and embryotic cells, glucose is usually metabolized via a so-called glycolysis, in which one glucose molecule is converted to not only two molecules of adenosine-5'-triphosphate (ATP) to provide energy but also two molecules of pyruvate and two molecules of reduced Nicotinamide Adenine Dinucleotide (NADH) that can be used as construction materials for building new cells [32,33]. Moreover, a constant cell proliferation also requires a large amount of nitrogen (N) as a constituent of amino acids for protein synthesis. For this reason, the anabolic cell type highly consumes, and thus is addicted to, usually glutamine but sometimes also alanine, to supply N [34-36], N, together with C (carbon), H (hydrogen) and O (oxygen) in the pyruvate and NADH produced from glycolysis of glucose, ensures the high anabolism.

In contrast, although IR likely involves all cells of a diabetes patient, it mainly attacks those cell types that rarely regenerate or are incapable of regeneration, such as the brain neurons, striated (cardiac and skeleton) muscles and adipose tissue, or those retaining a strong regeneration capacity but normally only having a low proliferation rate, such as the liver and brain stroma. Because these cell types normally only have a low proliferation rate or do not proliferate at all but are highly differentiated with a high metabolic rate, we define them collectively as the “catabolic cell type” to contrast them with the “anabolic type”, although this dichotomy may agitate into a semantic Babel. In normal individuals, cells of the catabolic type metabolize glucose, mainly for energy, via the more common aerobic oxidation-phosphorylation in mitochondria, in which a glucose molecule is broken down completely to produce 18-fold more ATPs than in the anaerobic glycolysis, and produce CO₂ and H₂O as wastes without leaving the cell with anything as constituents for building new cells [32]. However, a potential pitfall needs to be noted that a high level of blood glucose will cause a lot of damage to retina, blood capillaries and many other organs or tissues, but these are secondary targets of IR and thus differ from the catabolic cell type that is the primary. In other words, IR causes blood glucose increase (although glucose in turn potentiates IR as well) and the increased glucose causes the cellular and tissue damage.

Anabolic cells can easily develop mutations because they keep replicating to compensate for the routine cell loss, collectively exhibited as a high cell turnover. In contrast, because most catabolic cells replicate only occasionally, the malignancies derived from them are rare, such as rhabdomyosarcoma and liposarcoma. Liver cancer is also rare unless there exists hepatitis, alcoholism or a chemical carcinogen as a constant exogenous inducer or enhancer for the liver injury and carcinogenesis [37,38]. Brain neurons and heart muscle cells hardly develop tumors during adulthood [1,3]. On the other hand, catabolic cells may more easily develop IR than anabolic ones, although this is still purely hypothetical and awaits experimental verification, because they, especially the striated muscle cells and neurons, are much longer-lived and consume much more glucose. Indeed, it would be interesting to know whether anabolic cells are less resistant to insulin than their catabolic counterparts. A caveat needs to be given that when nutrient supplies are sufficient, anabolic cells may take various basic construction materials such as lipids directly from their environment without any need to convert glucose to such constituents via glycolysis. In this situation, anabolic cells may resemble their catabolic counterparts by metabolizing glucose just via oxidation-phosphorylation for energy. This may be a reason why many cancer cells actually do not manifest an obvious glycolysis [39]. On the other hand, in some situations the brain and skeletal muscles may also metabolize a huge amount of glucose via glycolytic processes that differ partly from the one described above for anabolic cells and with resulted lactates accumulated or utilized [40]. Muscle ache after extensive exercise, an experience we all once had, is due to the accumulation of lactic acids resulting from such glycolysis in the muscles. Unfortunately, most diabetes studies are focused on the catabolic cell type but rarely on the anabolic one, whereas cancer researches rarely involve the catabolic cell type and mainly involve the anabolic one from which most cancers derive, albeit liver cancer is often studied because of the epidemic of the aforementioned exogenous etiological factors.
The “Catabolic” vs. “Anabolic” Concept may help Understand IR-related aging

Aging is a natural process of all organisms, although it is still debatable whether prokaryotic (like bacterial) and unicellular eukaryotic organisms that maintain the species by constant cell divisions really age [41]. If IR is one of the aging phenomena, logically IR-caused diabetes should not be considered a disease. Indeed, if a 100-year-old man starts to show IR, we can hardly regard him as a patient. However, IR occurring at an early age is an abnormal aging and thus is a disease (because disease means abnormal), and so is diabetes a disease at a relatively early age. Therefore, categorizing IR into aging muddles things up, in part because how early in age is early cannot be well-defined.

The man in the street knows what aging is and considers it a natural process. In the slang “as reliable as death and taxes”, “death” is the outcome of aging, and, “we start to die as soon as we are born” is a poetic format of definition of aging, as pointed out by Thomas [42]. However, what constitutes aging is actually a very challenging question for biologists and so far is still ill-defined with many fundamental questions unanswered. This is largely because, as pointed out by Leonard Hayflick and cited by Azvolinsky, “for more than 50 years aging research has meant research on age-associated diseases and this will tell us nothing about the cause of aging. It is remarkable to observe that a major medical concept that ‘the greatest risk factor for all aging-associated diseases is aging’ has resulted in so little research on aging… I’ve been vocal about this for 40 years” [43]. For instance, whether aging is a programmed, quasi-programmed, or non-programmed event is among the most hotly debated questions [42,44-48]. A program means a predetermined way, which in our cogitation opposes the plasticity that many animal cells encompass and use to adapt to environmental changes. In other words, the fact that many cells are very plastic and can shift from one form to another, such as the epithelial-mesenchymal transition [41,49-51], seem to disagree with a programmed nature of aging. Aging is programmed in the genome of the fertilized egg, and thus one day we will all die, but in our rumination an aging procedure itself may not be a programmed event, although the difference between the two is difficult to catch, even after it has been repeatedly explained in the literature [42,52,53]. The confusion occurs in part because we often mix up aging or death at the three different levels, i.e., individual cells, the organ or tissue, and the whole organism [41]: Cells may die from telomere shortening, damage by Reactive Oxygen Species (ROS), or one of many other mechanisms, but the host organ or tissue may die for a different reason and the organism die for a third one. Today, we have learned a great detail about how cells age (senesce) and some details about how tissues or organs age but relatively little about how different organisms age. For this reason, we propose the concept of the “catabolic” and “anabolic” cell types as an intermediate level between tissue/organ and organism to roughly distinguish IR-targets from non-targets, which hopefully will help explore IR-related aging. The shorter-lived anabolic cells may age by telomere shortening but in the meantime may be protected by tissue- or organ-specific stem cells that produce younger healthy cells to sustain the life of the tissue or organ [3]. In contrast, catabolic cells, typically neurons and striated muscle cells, have much better survival mechanisms and thus are longer-lived without much need to replicate, which makes them relatively more resistant to telomere-shortening-caused aging, but in the meantime the whole organ or tissue is probably more fragile to ROS-caused aging because of lack of protection from organ- or tissue-specific stem cells to produce new healthy cells as the replacements of the damaged ones [3].

In our deliberation, whether aging has a structural basis or not is an even larger and more important question, although it has so far hardly been raised and addressed. Indeed, Pacific salmon die soon after having returned from sea to their birth places in fresh water and having spawned, and many other semelparous species of animals and annual plants die soon after procreation as well [45-47,54]. What are the irreversible changes in what biological structures in Pacific salmon and these annual animals and plants that cause their sudden deaths? Many aging-regulatory genes have been identified, and genetic manipulations to extend the lifespan of animals have been successful, but immunization has so far been succeeded only at the cellular level, but not yet at the animal level.

Fortunately, IR Attacks Mainly the Catabolic Cell type and thus lacks Irreversible Mutations

We are actually fortunate that it is the catabolic cell type that is the main target of IR, because its low cell turnover rate disassociates IR from fixation of irreversible mutations in the genome [55,56], in strong contrast to the anabolic type that is highly proliferating and mutating. Most, but not all, benign tumors do not progress to malignancy because of two genetic features, i.e. 1) they have only a few nuclear mutations and 2) these mutations usually do not trigger development of more mutations. Only when the nuclear genome has a mutation as seen in benign tumors, does a change in function become irreversible, and only when DNA mutations occur in those genes that can trigger more mutations, such as in those that compromise DNA repair, can more and more mutations emerge as unstoppable events with ensuing irreversible progression, as seen in the evolution of some benign tumors to malignancy and then to metastases or therapy-resistance. Fortunately, none of these two genetic features occurs in T2D, and all pathological phenomena caused by abnormal RNAs or proteins should disappear along with their degradations. These properties disassociate IR from an irreversible structural abnormality and in turn make T2D much more easily controllable than the anabolic-cell-derived cancers that keep mutating.

Although how people get T2D is still hazy, how to prevent and control it is already well known to many of us: it can be effectively prevented in most people by eating less and burning more calories through more exercise or more laborious work. In other words, simply returning back to the life style of over 10,000 years ago, i.e. living just like a species of uncivilized animals with the paleo diet, will do. For those people who are not strongly motivated to restrict calorie intake, a bariatric surgery can help by altering the gastrointestinal anatomy to make a permanent food malabsorption. Before civilization, humans did not have cars, not even carts and horses, and did not carry out agriculture to produce foods. Their daily life was to look for foods and hunt with simple tools for meat. At that time, a low blood glucose level might be a more-real problem than T2D, not only because of starvation but also due to lack of warm clothes to prevent thermal loss in cold weather, and thus our ancestors might have less use of their insulin than we have today. Now, humans use cars to replace their feet and machines to replace labor, and have too much delicious food handily available, which together make their striated muscles having much less usage, giving insulin much more usage. On the other hand, cells constantly convert glucose to lipids, which is actually an anabolism but requires suppression of insulin. Having been working restlessly in this way for long, cells eventually are tired and develop IR. Wild animals that still maintain a natural life style as thousands of years ago may not have much IR. Similarly, plants in the remote areas that have not yet been destroyed by human civilization may still remain the same way of...
aging as thousands of years ago. Therefore, studying aging with animals and plants in the wild as models may help understand aging and thus T2D. On the other hand, various species of livestock today, including hogs, cattle and chickens in large farms, may have much higher IR rates than their wild counterparts if they are allowed to live longer, but unfortunately they are usually slaughtered for meat within the dynamic growing age for cost-effective reasons. Those animals that cease growing at a certain age, such as humans, start to show a decrease in skeletal muscle mass soon after they stop growing [46], suggesting that risk for IR appears at an early age. Of course, we need to be aware that those animals that never stop growing may differ in the mechanisms of aging [46], and it deserves research whether IR may start later, relative to the lifespan, in the skeletal muscles of these animals.

Concluding Remarks

Structural-functional relationship is a central dogma in biology, meaning that all functions have their corresponding biological structures as bases. Any change in a function should be due to a change in the related structure. Accordingly, if a functional change is irreversible, it should be due to a permanent structural alteration. IR as a central mechanism of T2D is irreversible, and therefore T2D is irreversible as well, but, peculiarly enough, IR does not appear perpetually structural. Aging is irreversible, as evidenced by the fact that we are all going to die, but many aging manifestations lack a corresponding irreversible change in a biological structure. Likely, IR is one such aging manifestation. IR attacks mainly those cell types that in a normal situation have a low proliferation rate or do not proliferate at all but have a high metabolic rate, in contrast to the fast-proliferating cells that are the main origins of cancers. We define, for the first time, those main IR-attacked cells collectively as the "catabolic cell type" for their metabolism of glucose mainly via aerobic oxidation-phosphorylation in the mitochondria, and those fast-proliferating cells as the "anabolic cell type" because they are main cancer origins and often metabolize glucose via glycolysis. Because normally cells in the catabolic type proliferate only occasionally or do not even proliferate, there is no IR-causing genetic mutation as an irreversible structural change. This dichotomy of all cells in the body with regard to IR preference will hopefully facilitate T2D research. IR and T2D exhibit many abnormalities that are ascribed to abnormal mitochondria or abnormal cellular RNAs, proteins, lipids, etc. However, all these changes are reversible because mitochondrial biogenesis is inducible (such as by exercise) whereas RNAs, proteins and lipids are relatively short-lived and will degrade. Therefore, consideration of IR as one of those aging manifestations sans any irreversible alteration in a biological structure challenges the "structural-functional relationship" dogma and may provide us with a new understanding of not only T2D but also theoretical biology and even philosophy.

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