前期日程

科目 外国語(英語)

医学部医学科

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1 **Read the following article and answer the questions that follow. All questions must be answered in English. Words marked with an asterisk * are defined at the end of this article in the note section.**

A pioneering British biologist proposed a mechanism for how organisms could adapt to their environment, transforming the early field of evolutionary biology. For this, Conrad Hal Waddington became recognized as the last Renaissance biologist. This largely had to do with his idea of an "**epigenetic*** landscape" — a metaphor he created in 1940 to illustrate a theory for how organisms might regulate which of their genes get expressed in response to environmental cues or pressures, leading them down different developmental pathways. It turned out (A) he was onto something: Just a few years after creating the term, it was found that methyl groups — a small molecule made of carbon and hydrogen — could attach to DNA, or to the proteins that house it, and alter gene expression. Changing (B) [expressed / can / have / is / how / a gene / drastic consequences]: Every cell in our body has the same genes but looks and functions differently only due to the **epigenetics*** that (C) [on / controls / genes / turned / and how / get / when]. In 2002, one development biologist wondered whether Waddington's provocative "ideas are relevant tools for understanding the biological problems of today."

In fact, they are. Fifteen years on, a team of **Johns Hopkins*** researchers, inspired by Waddington's "epigenetic landscape," recently came up with a powerful new way of seeing epigenetics. Andrew Feinberg, a member of the research team and the director of the Center for Epigenetics at John Hopkins School of Medicine, said that the team's results "could (D) [aging-related diseases / have / how / for / we / cancer / and other / major implications / treat]." Their approach, detailed in a ***Nature**** study, enlisted **information theory***, a study of the storage and communication of information. By calculating the tendency of DNA **methylation*** to change across regions of the human **genome***, they could, in effect, understand cells' methylation landscape as a communication system.

DNA methylation changes throughout a cell's lifespan. Consider that stem cells are plastic, highly adaptive to changing their signaling patterns (which genes are expressed) but soon turn into differentiated adult cells that have faithful signaling patterns and convey information in reliable ways. Even adult cells have some degree of variation or fluctuation. But this variation is not just noise, but a cell showing it is still young and adaptable — it allows **immune*** cells to rapidly change to respond to environmental stress, brain cells to form new connections, or cells to turn off genes so that they can repair them. Aging cells begin to fall into states of uncertainty in which they can no longer reliably maintain DNA methylation

information. Since "quantifying uncertainty forms the basis for information theory, we thought that applying information theory to epigenetic data was a natural thing to do," said Feinberg, who with Hopkins colleague John Goutsias, was a senior author of the paper.

They analyzed DNA methylation across the entire genome of 35 types of cells. This created a big picture of how changes occur in DNA methylation across the genomes of cell types as those cells develop from stem cells into more defined **lineages***. The researchers weren't surprised to see that the methylation patterns of cancer cells were computationally distant from healthy adult cells. They were surprised to see, however, that cancer cells were even farther computationally from stem cells, a finding that challenges the conventional thinking that cancer cells return to a molecular state that is similar to stem cells.

"That was indeed a shocking finding for us," Garret Jenkinson, the paper's lead author, and today an instructor of biomedical informatics at the Mayo Clinic, said. Cancer cells are less like stem cells than we thought, and "that just does not fit with the current state of understanding. It indicates that nature is more complex than we previously thought."

In a 1948 paper, "A Mathematical Theory of Communication," Claude Shannon, the founder of information theory, described information as a set of messages sent over a noisy channel that could be measured in "bits," a series of 1s and 0s. A signal could be sharpened, such as shouting down a pipe, or washed out with noise, an effect of other signals that can disturb the clarity of a signal being communicated.

"What we realized," Jenkinson said, "is that DNA methylation" can be conceived as a bit, a 1 or 0, because when it comes to methylation, there are only two options: unmethylated or methylated. Specifically, methyl groups often bind to a particular part of DNA — what's called a "CpG **dinucleotide***," a **cytosine*** [C] paired with a **guanine*** [G] on the **phosphate*** backbone of the **double-helix***. These dinucleotides often occur in clusters, called "CpG islands," which are frequently surrounded by less dense regions, called "CpG shores." Thus, DNA methylation is binary information that is either conserved, or not conserved, through time and cell division.

"At a single CpG site you have a binary signal (methylated or not) that is heritable (transmitted from parent cell to its descendant cell)," Jenkinson said. "This transmission is imperfect, and mathematically can be described as a binary asymmetric channel," meaning the CpG dinucleotide tends to gravitate to a DNA methylation state. The Hopkins team defines this gravitation as an "energy potential," [for / or change / a methylation pattern / to remain / a tendency]. A genetic region analyzed over hundreds of bases could be either unmethylated or fully methylated or any pattern in between. A low potential is a methylation state that is easy to change, while a high potential is a state that is hard to overcome. This

methylation status is determined by the density of CpG nucleotides in the neighborhood and the activity of **enzymes*** which add or strip methyl groups — for adult cells this information is tightly regulated.

(G) The cellular machinery that regulates this epigenetic code is a rapidly developing area of research for scientists who want to learn to modify the code as a possible therapeutic mechanism. For instance, it has long been known that enzymes add methylation to DNA, but it was also long believed that methyl groups eventually fall off of DNA, like tiles breaking off a roof. Only in the last couple of years has it been discovered that proteins exist that actively strip methyl groups from genetic regions.

How responsive and sensitive a gene is to the machinery regulating its DNA methylation — so called (H) "entropic sensitivity" — is critical for a cell's function. Stem cells may be highly responsive to this machinery, and hence very (I) "plastic," while the loss of sensitivity to this machinery, and thus the gene's increasing rigidity, seem to be **hallmarks*** of aging and cancer. Adult cells such as intestinal cells, or liver cells, need to maintain their responsiveness to this machinery and maintain their epigenetic memory of which genes to turn on, a task that depends on its ability to (J) and respond to machinery that maintains it. But aging cells are less responsive to machinery that regulates their methylation status, and are more rigid, often having long blocks of methylated or un-methylated genetic regions. These long stretches of the genome can have a lot of **entropy***, meaning they can change at any time, quite independently from the machinery that normally regulates their methylation. As a result, genes may be far less adaptive to turn on or off as needed in response to various environmental stimuli (as genes are needed to do, as immune cells spring into action, neurons rewire, or as cells repair and fix themselves) but these long stretches of the poorly regulated genes may also be more susceptible to **double-strand breaks*** and other forms of catastrophic damage that can lead to cancer.

As a motivating example, the authors looked at methylation over a short region in the ***WNT1* gene***, which builds a signaling protein key to cell fate decisions, meaning (K) [a specific / differentiated form / a cell / to become / the commitment / makes], such as an intestinal cell. **Colorectal*** cancers occur in the **intestine*** and are among the top three most common cancers in both men and women. In a healthy colon, this gene has little methylation and exhibits (L), meaning it tends to gravitate to an unmethylated state — it is highly regulated. This implies "that significant energy is required to leave the fully unmethylated state," Jenkinson said. "Any (M) from this state, meaning (N) of methyl groups, will rapidly return back," which results in the maintenance of this gene's (O) methylation state in a healthy colon. However, in a cancerous colon, *WNT1*'s methylation states exhibit

low potential, meaning deviations from the unmethylated state in *WNT1* will be "frequent and long-lasting, leading to uncertainty in methylation status." It is (P) entropic, and the information transmitted by this gene is no longer regulated — it is information lost. (Q)

(Jim Kozubek, 2019, *Nautilus Magazine*, extracted and slightly modified.)

*Notes:

epigenetic: the adjective form of epigenetics

epigenetics: the study of the way in which the expression of heritable traits is modified by environmental influences or other mechanisms without a change to the DNA sequence

Johns Hopkins: Johns Hopkins University, a private research university in Baltimore, Maryland, USA

Nature: one of the leading science magazines in the world

information theory: the mathematical theory concerned with the content, transmission, storage, and retrieval of information

methylation: the process of replacing a hydrogen atom with a methyl group

genome: a full set of chromosomes (染色体); all the inheritable traits of an organism ゲノム in Japanese

immune: relating to the production of antibodies (抗体) or lymphocytes (リンパ球) that can react with a specific antigen (抗原)

lineage: the line of descendants of a particular ancestor

dinucleotide: a molecule composed of two nucleotide subunits

cytosine: a base, $C_4H_5N_3O$, that is one of the fundamental components of DNA

guanine: a base, $C_5H_5N_5O$, that is a fundamental component of DNA

phosphate: リン酸 in Japanese

double-helix: the spiral arrangement of the two complementary strands of DNA

enzyme: 酵素 in Japanese

hallmark: a typical feature or quality

entropy: a measure of uncertainty or randomness

double-strand break: a serious DNA damage of breaking a double-strand due to internal and external factors

WNT1 gene: a gene that is considered to be responsible for making a protein, WNT1, which controls cell fates during development

Colorectal: concerning colon (大腸) and rectum (直腸)

intestine: 腸 in Japanese

(1) Why can the author say that (A)he was onto something? Answer the question based on the article.

(2) Put the words in the square brackets of (B), (C) and (D) into correct orders.

(3) The following questions are about "(E)energy potential."

(a) Put the words in the square brackets of (F) into the correct order.

(b) List all the factors that determine the methylation status.

(c) How do energy potential and methylation status correspond to each other?

(4) The following questions are about (G)The cellular machinery that regulates this epigenetic code. Answer them based on the article.

(a) Why has the cellular machinery become a rapidly developing research area?

(b) What biological processes have been involved in the cellular machinery? Itemize your answers in a full sentence form.

(5) The following questions are about "(H)entropic sensitivity." Answer them based on the article.

(a) What does "(I)plastic" mean? Choose the closest phrase in meaning from the list below and write the corresponding number on the answer sheet.

① easy to break	② easy to shape	③ hard to bend
④ hard to rebound	⑤ easy to be formal	⑥ hard to be formed

(b) How are the aging cells described in this article with regard to entropic sensitivity? Complete the sentence on the answer sheet with all the features that are described in the article.

(c) Fill in the blank of (J) with the most appropriate word from the list below.

think	judge	sing	draw	listen	construct

(d) How can aging cells be described in contrast with cancer cells in view of entropic sensitivity? To answer the question, complete the following sentences by filling in each blank with an appropriate word or phrase.

Aging cells often have (①). They can be (②) the machinery normally regulating their methylation and thus, unable to be (③) enough to respond to various environmental stimuli. And then, they also tend to be (④) to very serious damages and this can cause to change aging cells to cancerous ones.

(6) Put the words in the square brackets of (K) into the correct order.

(7) Fill in the parentheses (L) through (P) with the most appropriate word or phrase from the list below.

deviation	high energy potential	low
more	high	low energy potential
less	deletion	addition

(8) What does (Q)information lost mean in terms of aging of cells and DNA methylation? Write your answer in between 30 and 50 English words, starting with 'It means that'.

2 **The following article describes a former professional American football star: Carson Palmer's new life in Ketchum, Idaho. Read the article and answer the questions. Words marked with an asterisk * are defined at the end of this article in the note section.**

KETCHUM*, Idaho —

Just as he did as a **Heisman Trophy***-winning **quarterback*** at **USC***, as a No. 1 overall pick in the **NFL*** draft, and in 15 years as a pro, Carson Palmer still keeps his throwing arm in shape. [(A)] Snowball season. "If I miss you, I'm trying to miss," said Palmer, 40, who threw 299 touchdown passes in his career with **the Cincinnati Bengals, Oakland Raiders and Arizona Cardinals***. "I'm deadly with a snowball."

After Palmer retired at the end of the 2017 season, he and his wife, Shaelyn, moved their four children to this picturesque resort town of 2,800 people, where being a fan of the three major sports means you like to hunt, fish and ski. To the bewilderment of many of his old teammates, Mr. Throw'em is now Mr. Ketchum. "I have buddies who say, 'Where are you living? Wyoming or something? Don't you still have a house in California?'" said Palmer, sitting on the kitchen counter of the family's **sprawling*** home on four snow-covered acres. "I tell them we live in Idaho, and you can see it on their face and sense it in their voice: 'Um ... O ... K.'"

Palmer turned down a job to be a **color analyst*** on **Fox*** and has decided not to pursue coaching opportunities, even though football is in his DNA. He is intensely private, especially when it comes to his family, so when he walked off the **gridiron***, he was determined to step away from professional life. That means fly fishing for rainbow trout in the morning and skiing Sun Valley in the afternoon. It means helping get his kids ready for school — twins Fletch and Elle, 10; daughter Bries, 8; and son Carter, 3 — then tag-teaming with Shaelyn to shuttle them to ski team, ice skating and guitar lessons. Palmer happily has gone from one of the most celebrated and glamorous jobs around, one of 32 starting quarterbacks in a league watched by tens of millions, to the routine of a quieter life.

"This is who Carson is and has always been," Shaelyn said. "He never wanted to be famous. He always turned away from anything having to do with that. [(B)] Being outside. Just being a normal guy. Being a dad."

* * *

The Palmers have yet to decide how long they might stay in Ketchum. They love the town and the one school all their children attend. Both parents grew up playing ball sports — Shaelyn was a soccer player at USC — but those are an afterthought when it comes to youth sports here.

Fletch, a fifth-grader, wants to play quarterback, but his parents won't let him start playing football until eighth grade and the community doesn't offer a **flag-football*** alternative. The family still owns a farm in Ohio and a home in Del Mar. "We wanted to raise our kids away from the hustle," Shaelyn said. "We also didn't want them having pressures because of Carson's career. Especially Fletch. He was getting that really hard-core in Arizona. [(C)] You just want them to be who they are. This took the pressure off him."

Carson and Shaelyn point to their own parents as role models who spent as much time with them as they could. But Palmer said he missed "a ton of stuff, almost everything" when he was traveling and consumed by game preparation as an NFL quarterback. [(D)] "It's an all-consuming job," he said.

To the Palmers now, that feels like a lifetime ago. "He's had a million opportunities since he retired," Shaelyn said. "Job offers, travel. There's a lot of guys who would say, 'Awesome. I'm going to go and travel three days a week and make X amount of money.' But he chose our family."

Some things haven't changed: For several years, Palmer has agonized watching USC's football team struggle on the field. "It's hard to engage when you're very prideful about something," he said. "It's frustrating, like anybody with their **alma mater***, when you just disagree with some of the things that are going on. You know how good it can be, and how easy — not that it's easy — but, man, we should be a top-five recruiting class every year. How are we not?"

* * *

"Playing quarterback is a glamorous job. It's awesome. It's everything I dreamed it would be," Palmer said. "But after a while, it loses its glamour. [(E)] Especially at the end, it became work. Game day was awesome, but all the rest of it was work." So would he trade the life he has now for more NFL glory? Snowball's chance.

(Sam Farmer, 2019, *Los Angeles Times*, truncated and slightly modified)

*Notes:

KETCHUM: a town in the state of Idaho

Heisman Trophy: the award for the most outstanding college football player of the year

quarterback: the player who leads the team's offense, and usually throws the ball

USC: University of Southern California

NFL: National Football League, professional sports league for American football

the Cincinnati Bengals, Oakland Raiders and Arizona Cardinals: NFL teams

sprawling: spreading in an untidy way

a color analyst: a sports commentator

Fox: a television network in the U.S.A.

gridiron: another name for American football field

flag football: a version of American football where the defensive team must remove a flag or flag belt from the ball carrier, instead of tackling players to the ground

alma mater: the school/college/university one went to

(1) Select the most appropriate sentence for each blank (from [(A)] to [(E)]) from the list below. Write the letter corresponding to the sentence on the answer sheet.

(a) He keeps up on what's happening in the NFL because he still does a handful of weekly interviews for radio and podcasts.

(b) Somewhere along those 15 years, it becomes a job.

(c) He does light lifting to strengthen his shoulder joint and maintain his flexibility, all to prepare for the season.

(d) For those who know Carson, this is his most natural environment.

(e) That wasn't just when he was traveling but also while he was studying video, meeting with teammates and getting physical therapy.

(f) Everyone thought he was going to be the best quarterback.

(2) Write an essay of about 200 to 250 words in English, responding in your own words to both the following questions (a) and (b):

(a) What did Carson value when he decided to retire from his professional career? And why did he do so?

(b) If you have had a successful career, do you think you would like to continue working in the same field or to take a very different path of life like Carson? Discuss your ideas. You can refer to your experiences and/or future plans, if it is necessary for your discussion.