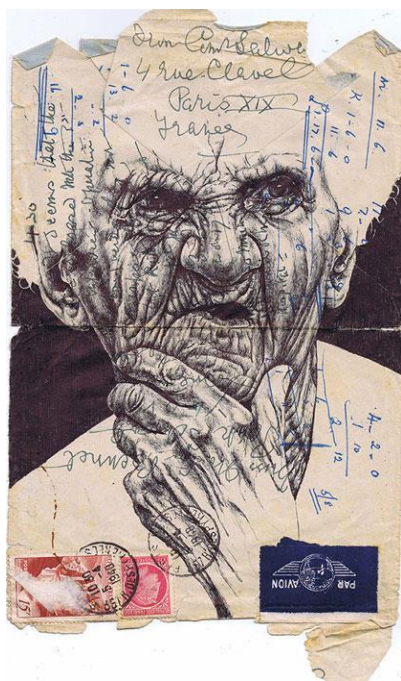


giving in to time

Vivienne Baillie Gerritsen

Time runs its treacherous fingers along everything. The smoothed edges of a pebble. The polished wood of a staircase. The worn joints in our bones. Sometimes, even, the erosion of our memory. Every day, every hour, every minute, we get a little older. Until we reach that invisible threshold when we actually begin to feel the years, and what getting older means. Our pace becomes slower and our muscles, stiff. Our bodies gradually bend forward and parts cave in. One hand begins to shake. Our thoughts are not so nimble. And perhaps for the first time we overhear someone say that we are old. Yet it is less a question of us getting old, than our bodies giving in to time. Cells inside us are losing touch. Information is being lost. Metabolic pathways become hesitant. Cells become weary, stifle and die. Many factors are involved in the very complex process of ageing. One of them is Plasminogen activator inhibitor 1 – or PAI-1. Scientists, however, discovered that a particular mutation in PAI-1 may actually be partly responsible for lengthening a person's life as opposed to shortening it.



Biro pen sketch on envelope, by Mark Powell

Courtesy of the artist

Why do organisms get old in the first place? Why does an organism begin to decline with the passing of time? Why do the cells inside us become weathered? Why are they unable to renew themselves as they did during the first years of our life? Because we are not robots, may well be the

answer. Nature has its flaws. Life has its limits. Just like us, across the years, cells gather their scars. Not everyone, however, gets old in the same way. It is all a question of our genes but also the environment we live in and the lifestyle we lead. It would be impossible to trim longevity down to one factor alone. To date, the oldest human being, a woman whose age has been verified by modern documentation, reached the ripe age of 122. But this hardly compares to the quahog clam (*Arctica islandica*) that can live up to the age of 500, or the bristlecone pine that can last thousands of years.

What does PAI-1 do, to slow our pace down? PAI-1 belongs to a family of protease inhibitors known as serpins. Protease inhibitory activities were, surprisingly, first described in the 1800s, but it took another one hundred and fifty years to isolate a few serpins – so named, because the first to be characterized were **serine protease inhibitors**. In the 1980s, however, researchers began to realise that serpins form a huge family of related proteins – the majority of which are indeed serine protease inhibitors but there are also serpins that target other types of proteases, like cysteine proteases for example. In the past four decades, over 1,000 serpins have been identified, across every known species – from animals, plants and fungi, to bacteria, archaea and even a few viruses.

Proteases are usually part of important metabolic pathways such as coagulation or immune responses for example. So it may sound counterproductive for serpins to stop them from doing their job. However,

it is in fact one clever way of regulating metabolic pathways. If a protease is left to go about its business unceasingly, it will end up causing havoc by unnecessarily keeping a pathway going, and causing some sort of downstream imbalance. As an illustration, serpin deficiency in humans is involved in diseases such as emphysema, cirrhosis, Alzheimer's disease, chronic fatigue, hypertension, diabetes and bleeding disorders. But such disorders cannot always be pinned down to a metabolic pathway gone haywire, as the concomitant accumulation of deficient serpin in the cell also has an effect, by gradually clogging the cell up, and damaging the tissues and organs it is located in.

PAI-1 is involved in several vital pathways, including: coagulation, cell adhesion, cell migration and dentin formation. It is also actively involved in cellular senescence – a very intriguing aspect of biology and the life of a cell. Cellular senescence is the gradual degeneration of a cell and, in the long run, of the organ and the organism it belongs to. It has been known for some time now that telomeres, the protective caps located on the tips of our chromosomes, become shorter and shorter as the years go by. This is explained by the wear and tear caused by years and years of cellular replication, during which little parts of the telomeres are lost. What exactly is lost in terms of information for the preservation of life is still not understood, but telomere attrition seems to be directly linked to old age, and associated with numerous related chronic diseases.

Serpins have been extensively studied because of their conformational structures and the singular way they have of functioning. Most protease inhibitors stop proteases from reaching their targets by blocking the passage to the active site. Serpins, however, delude proteases by making them believe that they are the target. They do this via a loop – known as the reactive centre loop – that protrudes from the core of their body. The protease recognises the loop as its target, binds to it, and before the enzyme has time to hydrolyse its target, the loop

snaps back like the devil's tongue, with the protease still attached to it. This causes the protease to twist into a conformation that paralyzes it, and it remains bound to the serpin for days, sometimes weeks. Trapped in a suicidal embrace, both the protease and the serpin are condemned, and gradually degraded by the cell.

If PAI-1 is involved in cell senescence, then perhaps less of it in an organism would stall the ageing process. A certain PAI-1 variant recently discovered in an Amish community from Berne (Indiana) seems to suggest just this. Members of the community who carried only one copy of the mutation (heterozygous) were healthier than those who carried 2 mutated copies (homozygous) and who can be subject to severe bleeding for example. Carriers of only one copy of the PAI-1 variant, however, had significantly longer telomere lengths, and suffered less from conditions such as hypertension, obesity and diabetes. They also had a longer lifespan, hinting that PAI-1 may well be directly linked to human longevity.

So could we all live a little longer if PAI-1 were partially switched off? No. Not only was the number of Amish participants too small for the study to be statistically relevant – a total of 177 and only 44 carriers of the PAI-1 variant – but the process of getting old depends on multiple genetic and extra-genetic factors ranging from genomic instability and epigenetic alterations, to mitochondrial dysfunction, stem-cell exhaustion and altered cellular communication. Getting to know PAI-1 more intimately will certainly shed more light on cell senescence and the gradual degradation of our bodies. Designing drugs that could selectively target PAI-1 may help to lessen conditions that are age-related, such as hypertension or arteriosclerosis for instance. This said, the very nature of ageing remains a mystery and is a controversial subject among scientists. Perhaps we should learn to give in to time, the way our cells do. Though if it can be done in the absence of physical pain, why not.

Cross-references to UniProt

Plasminogen activator inhibitor 1, *Homo sapiens* (Human): P05121

References

1. Khan S.S., Shah S.J., Klyachko E., Baldrige A.S., Eren M., Place A.T., Aviv A., Puterman E., Lloyd-Jones D.M., Heiman M., Miyata T., Gupta S., Shapiro A.D., Vaughan D.E.
A null mutation in SERPINE1 protects against biological aging in humans
Science Advances, November 2017, doi: 10.1126/sciadv.aao1617
PMID: 29152572

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