Cell Cycle 12:17, 2709–2710; September 1, 2013; © 2013 Landes Bioscience

Damage-induced aging and perpetual motion

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The United States Patent Office has made an official policy of refusing to grant patents for perpetual motion machines (perpetuum mobile) without a working model. Should we adopt a similar policy for manuscripts claiming that aging is caused by molecular damage by any means such as free radicals, radiation, and errors during normal molecular processes? Is the time ripe? Although thousands of publications suggest that aging is caused by damage, mostly by free radicals, an increasing body of evidence rules out accumulation of random molecular damage as a cause of aging.[1-7] And it does not matter how many publications are (seemingly) in agreement with the prevailing dogma: it is the evidence against it that counts. And where are studies showing that prevention of damage extends lifespan (an equivalent of "a working model")? Most studies represent just wishful interpretations of ambivalent data. Consider a prototypical example. Radiation of rats (or their brains) caused damage, overwhelmed repair, increased free radicals, activated signal transduction pathways, and so on. Furthermore, such rats live a shorter life. Is that the evidence for damage-induced aging? Certainly not! Sure enough, if investigators would shoot rats with rifles or guns, rats would have a shorter lifespan. But we all agree that rifles are not a cause of our aging. There are a billion ways to shorten lifespan and impair health, which have nothing to do with aging: from mutations of blood-clotting factors and lamin to vitamin deficiency and famine. Examples with radiation and rifles are obvious. But they can be more subtle. Calorie restriction and inhibition of the insulin pathway increase lifespan. Yet, these interventions may not extend lifespan in the absence of a particular transcription factor. Does this mean that this transcription factor is involved in aging? Not always. Imagine if an investigator would shoot a rifle at a calorie-restricted animal… Yes, then calorie restriction will not extend lifespan. Still, we all agree that rifles are not involved in aging. In contrast, an intervention that increases lifespan is important in its own right, albeit even in this case it might be unrelated to aging. For example, medical interventions such as coronary stents and defibrillation can greatly extend human lifespan without affecting aging. These interventions increase aging tolerance, namely the ability to survive despite the aging process, such as atherosclerosis.[7] In contrast, calorie restriction and rapamycin can extend lifespan by slowing down aging, preventing atherosclerosis. Inhibition of components of the MTOR (mechanistic target of rapamycin) pathway prevents cellular conversion from quiescence to senescence (geroconversion) and extends lifespan in yeast, worm, flies, and mice. In worm, knockout of PI3K (an activator of MTOR) extends lifespan 10-fold.[8] So partial, or complete, inactivation of aging-promoting genes (gerogenes) increases lifespan. There is a second sign indicating that life-extending intervention is in fact due to slowing down aging. Genuine anti-aging interventions must be harmful early in life during the growth phase of the organism.[7] Gerogenes are beneficial in young animals, at the cost of aging later in life. For example, MTOR is essential, and its knockout is lethal in mouse embryos. Definitely, treatment with rapamycin and calorie restriction is unfavorable during organismal growth. And knockout of PI3K in worm slows development, so that such a worm would not survive in the wild. Only laboratory conditions allowed us to detect the tremendous life extension later in life. On the other hand, everything that is harmful from day 1 (radiation or mutated lamin) cannot be a cause of aging.[7]

The view that aging is caused by accumulated damage is very intuitive, because everything around us accumulates damage. Still, many aspects do not fit precisely this intuition, and, oddly enough, the damage theory suggests that these cases are programmed for a purpose. One famous misconception is that death is programmed in Pacific salmon (in reality, it is quasi-programmed). Menopause is thought to be programmed to benefit grandchildren. In reality, menopause is a clear cut aging-related disease, which has no adaptive value.[7] Aging and its obligatory manifestations, namely age-related diseases, are not programmed but quasi-programmed. A quasi-program is a harmful, useless, aimless, unintended continuation of organismal growth programs, driven in part by MTOR.[7] Similarly, cellular aging is a continuation of cellular growth driven by MTOR (and other gerogenic pathways) and manifested by increased cellular functions (hyperfunctions), leading to alterations of homeostasis and age-related diseases, which, in turn, lead to damage: not molecular damage but instead non-random organ damage.[7] Importantly, pharmacological inhibitors of gerogenic pathways are available. Most importantly, some of them, like rapamycin and metformin, are clinically approved, well-tolerated drugs. Thus, the notion that aging is driven by growth-promoting (gerogenic) signaling pathways has already yielded anti-aging drugs. Today is not the day to discuss competing theories. This is the past. The real arena now is clinical applications of rapalogs (e.g., rapamycin) and other gerosuppressants

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Submitted: 06/20/13; Accepted: 07/01/13
http://dx.doi.org/10.4161/cc.26015

to prevent age-related diseases and extend healthy lifespan.[9] And on this arena a fierce competition is just started.

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