Logical Biology 5(4): 308-310, 2005 **CELL AGING**
http://logibio.com
 PERSPECTIVES

"Cellular Senescence": What Does It Really Mean?

Shi V. Liu

Eagle Institute of Molecular Medicine
Research Triangle Park, North Carolina, USA

E-mail: SVL@logibio.com

(Received 2005-10-04; accepted 2005-10-16*)
(Published online 2005-12-15)

HIGHLIGHT

"Cellular senescence" has being believed as an intrinsic cause for the finite replicative lifespan and the appearance of the "Hayflick limit". However, equating cell reproduction capacity with cell aging has both conceptual problems and practical limitations. This perspective tries to explain why this equation is wrong and how a new cell life theory will better explain cell aging and cell aging-related phenomena.

KEY WORDS

"Cellular senescence", Cell aging, Life span, Hayflick limit, Liu's cell life theory

"Cellular senescence" has become a buzzing biological term since Hayflick first observed the phenomenon that normal tissue cells have limited number of *in vitro* passage (*Exp. Cell Res.* 25: 585-621, 1961). That seminar observation led to a realization that normal tissue cells may have limited proliferation potential and thus finite replicative "lifespan". This conclusion ended an era in biology in which cells were essentially treated as immortal reproductive machines that just keep repeating the same "cell cycle" when provided with required nutrients.

Hayflick first proposed that the finite replicative lifespan may be due to the intrinsic process called "cellular senescence" (*Exp. Cell Res.* 37:614-636, 1965). However, as to what actually is and what actually causes this "senescence", even Hayflick himself may still have not find a correct answer. Hayflick, as well as many other biogerontologists, believes that cell *culture* "senescence" is *caused* by the losing of population doubling potential (*Nat. Rev. Mol. Cell Biol.* 1:72-76, 2000; *Cell* 120:437-447, 2005) which theoretically should imply the loss of reproduction capacity in *each* individual cell

composing the population. Thus, a standard way to find and define senescent cells is to see whether or not a cell culture (*population*) can expanded the existing population or can seed and start a new population.

However, it turns out that the limited passage of normal tissue cell culture/population in the *in vitro* conditions is just an experimental artifact (*Logical Biology* 5: 58-65, 2005). Cell cultures/populations at various passages including the so-called "terminal phase" cultures are actually heterogeneous in terms of their population doubling potential (PDL) (*Exp. Cell Res*. 42: 673-684, 1966; *J. Gerontol.* 34: 323-327 and 328-334, 1979), a fact that even Hayflick himself fully agreed early on (*J. Cell Biol*. 62: 48-53, 1974). Thus, if this factual reality was known by Hayflick when he wrote his original papers, I doubt that he might even come up with all the above conclusions or hypotheses. Or if these facts were known a little bit earlier, the absolute claims made by Hayflick might be easily rejected, considering the situation that they were really up against the long-established dogma.

Now we know the existence of this artifact, what about the artifact-initiated research and error-advanced conclusions on cell life?

In order to get a clear answer to the above question, we must first understand the limits of the so-called "Hayflick Limit" (*Logical Biology* 5: 58-65, 2005). I believe that much of the confusions related with the misunderstandings of cell life have been caused by the use of an incorrect approach to study cell life (*Logical Biology* 1: 5-16 and 25-31, 2000). So far, almost all reports on cell "lifespan" have been based on the population approach. I have not seen a single report which actually tracked the complete lifespan of individual cells from their birth to their death. However, equating *population* culture "life" with *individual* cell life is a logical mistake, if not a scientific error. This methodological mistake and logical fallacy has generated many erroneous but important biological "conclusions". These so-called accepted "facts" include the widespread convention of equating cell *life* cycle with cell (division/*reproduction*) cycle and thus *cell age* with cell cycle/*reproduction stage*.

Conceived within the above incorrect framework, it might be the only "correct" or "acceptable" way for Hayflick to make a conclusion that cellular "senescence" is nothing but the cells' incapability to reproduce new cells. However, I must point out that this conclusion is totally wrong.

Equating *cell reproduction* with *cell aging* is wrong because it mixes two distinct biological terms and processes. Although reproduction normally happens only at a specific period of the lifespan and usually occurs at a more mature age, it itself does not equal with aging and certainly not the *senescent* age (here I define senescence as the life cycle stage where an individual is really too old to reproduce). In fact, in some situations, these two processes can be separated. For example, many (healthy) individuals do not reproduce (even if they can) but nevertheless they age and die. On the other hand, many other causes can result in the "sterilization" of cells. These events can happen to reproductive cells at any ages or even to juvenile cells not yet reaching the reproductive age.

The above fundamental error in equating "senescence" in cell *aging* with "sterilization" in cell *reproduction* has resulted in many confusions and misunderstandings in the applied fields of biology and medicine. For example, a hot trend in cancer therapy is to boost cellular "senescence" to treat or even to prevent

cancers (e.g. *Cell* 88:593-602, 1997; *Nature* 436: 636-637, 642-643, 660-665, 720-724, and 725-730, 2005; *Science* 309: 886-887, 2005). However, this approach presents not only a conceptually paradox but also many practical problems. How could a pro-aging process be used for against aging-related cancer? How could the promotion of "cellular senescence" (i.e., the inhibition of cell division/reproduction) be confined within just the cancer or pre-cancer cells without repressing the normal proliferation of other cells?

Even more problematic than this, some people have even promoted the use of *oncogenic* substances or oncogenes to treat or prevent cancers (e.g. *Nature Medicine* 11: 595-596 and 623-629, 2005) because these substances or genes have been found to induce or strengthen the so-called "cellular senescence" (*in pre-malignant but not malignant cells*). It was hoped or hyped that such "cellular senescence" may cause the withdrawal of pre-malignant cells from the "cell cycle" or the prevention of such cells from entering the "cell cycle". However, any patient who still has some normal sense may find that these oncogenic "pills" are hard to swallow.

I must declare that my criticism to the mistaken view of "cellular senescence" does not mean that I accept the even wrong view of cell immortality. In fact, I do believe and have promoted a view for years that every cell (not just normal cells) should and does have limited lifespan (*Science in China* 42:644-654, 1999; *Logical Biology* 1: 5-16 and 25-31, 2000; 4: 1-6, 7-15 and 16-27, 2004; 5:51-55, 58-65, 89-91 and 109-116, 2005). I also believe that cell senescence exists but it is only a *consequence* of cell aging. In my view, cell aging actually starts from the beginning of the life (since the fertilization), not just occurring in the late life stage as commonly believed. Cells still live well after they pass their "menopause" i.e., loss the reproductive capacity, as more vividly shown in unicellular microorganisms as in their "viable-but-non-culturable (VBNC) state (*Logical Biology* 1:17-20, 2000). Thus, for logical and practical reasons, we should under no circumstance confuse *cell aging* with *cell reproduction* and cell age *senescence* with cell reproduction *sterilization*.

So let's give cellular senescence its correct meaning and then to see how this conceptual change could alter our views on many normal and abnormal cellular processes.

* This manuscript was accepted on the condition that it becomes eligible for *Logical Biology* to publish when author finally agrees to publish it after failure in seeking publication in "traditional" journals. The current publication is the same as it was submitted to *Cell* on October 4, 2005. This paper was rejected by *Cell*.