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CONCEPT

STEM CELL

What Is a Stem Cell?

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HIGHLIGHT

A Letter-To-The-Editor asking a very basic but important question in stem cell research − What Is a Stem Cell − was rejected by *Cell* and *Stem Cells*. Why would these "top" journals refuse to publish a different view on stem cells?

ABSTRACT

From a different perspective on cell life, stem cell is redefined as a cell born from a fertilized germ cell early in the multicellular life and possess the capacity of producing baby cells with further branching capability in cell lineage formation. This clear and practical definition may eliminate unnecessary confusion on stem cells and set stem cell research back on the right track.

KEY WORDS

Stem cell, Misunderstanding, Differentiation, Deception, Self-Renewal, Self-Cheating, Editorial ethics

Stem cell is the "hottest" cell in cell research. Its popularity can be reflected not only by the ever increasing coverage of stem cell research by the scientific journals as well as the popular press but also by an increasing number of journals dedicated to it such as the quarter century-old *Stem Cells* [1] and the upcoming *Cell Stem Cell*. The emphasis on stem cells or hope for a positive outcome of stem cell research has gone to such an extreme that some researchers even claimed that stem cells may be the fountain of youth that may eventually give immortality to multicellular life [2]. As a matter of fact, even a meeting on Functional Genomics of Aging was actually centered on just the stem cells [3] and a true knowledge on biotic aging [4] was totally ignored by majority of the meeting participants. Believe it or not, the meeting organizer even expressed a pity that Hwang was unable to give his invited talk (because by the time of the meeting his landmark high-profile publications in *Science* had already been retracted as a result of spectacular fraud).

Nevertheless the question remains: what is a stem cell?

At first, many people may think that I am crazy if not totally naïve to even ask this question. This is because not only stem cells were already discovered but also have been intensively studied for over forty years. However, I must say that this question is not only a very legitimate one but also a pressingly urgent question that has to be answered correctly first if any future research on stem cells can be fruitful and meaningful.

Let's first see what the pioneers of the stem cells had just stated recently about stem cells.

In a Commentary written by McCulloch and Till on occasion of their reception of the 2005 Laskar Award they stated that "Much about stem cells is controversial. For example, even the question 'what is a stem cell?' arouses controversy." [5]

An authoritative and also a very popular definition on stem cell is that "Stem cells are primal cells common to all multicellular organisms that retain the ability to renew themselves through cell

division and can differentiate into a wide range of specialized cell types."[6]

However, the so-called "self-renewal" capacity as first proposed by McCulloch and Till [7] is in fact a self-cheating because no life can be self-renewed and the so-called unique self-renewing capacity for stem cells is in fact a universal cell reproduction process common to many types of cells [8]. In addition, stem cells are in fact not the "undifferentiated" cells because they are already somehow differentiated from their ancestral germ cells [9]. Furthermore, the differentiating capacity is not an exclusive feature of stem cells because at least germ cells as well as progenitor cells possess such capacity [10].

I firmly believe that the lack of a correct and truly differentiating definition for stem cell has been a rooting cause for all the problems associated with stem cell research. As more and more researchers step into this highly profit and also dangerous research field and each with their own agenda in mind, this field may become more and more confusing. As a recent publication states, "stem-cell nomenclature is in a muddle!" [11]

If "self-renewal" is a self-cheating and differentiating capacity is not a unique feature of stem cells what kind of cell should be called as a stem cell?

Before giving my answer to the above question a fundamental redefinition is necessary. Otherwise, my ideas will make no sense, just as they were already treated in the past as the "nonsense". But if people have a little patience and can be somehow objective, I welcome everyone to compare what I published years ago with what others are now "discovering" to see if what were considered as unbelievable are actually very truthful.

Firstly, we must realize that the so-called "one mother cell divides into two daughter cells" is a pseudo-scientific emperor without any cloth [12]. As an highly ordered and organically coordinated hierarchical system cell can be reproduced but not divided [13]. Cell reproduction means generation of a new baby (daughter) cell from an existing old parent (mother) cell which means that no cell is actually "cycled" or "renewed" [14].

Secondly, we must realize that cell differentiation is a process by which a parent cell generates a baby cell with a different phenotypes even though both generations share the identical or at least very similar genetic information. How could this happen? This is because heredity is not just passing down only the genetic information but also the epigenetic information [15]. It is in the difference of this epigenetic state that cell differentiation happens. However, this epigenetic differentiation occurs at the very beginning of life so that even the very first stem cells are already epigenetically differentiated [9]. This epigenetic modification will continue over the entire lifespan so that, for multicellular organisms, cell differentiation is a very common process for many types of cells including cells formed very later in the developmental hierarchy downstream of the stem cells [9].

Now I have discarded both of the defining features for conventional understanding of stem cells. Then how could we identify a stem cell?

I believe a simple way to identify stem cell is to somehow mark a stem cell in the very early stage of the multicellular life and then track the life history of this cell while it lives inside a multicellular organism. From this kind of tracking experiment people will find that a stem cell should be that kind of cell which is not only born early in chronological time but also possesses the capacity to give birth of baby cell(s) which in turn can reproduce baby cells with different roles.

So the term "stem cell" is really a developmental one, not any anatomical or functional one. To be a stem cell, a cell has to be in the stem position of the development as early as possible and has to be able to produce cells capable of forming as many branching lineages as possible.

If we realize that stem cells are not only formed early in the multicellular life but also stay alive for more than just one "cell cycle" then the so-called distinction between embryonic stem cell and adult stem cell may just be some artificial division that actually reflect the same stem cells in their different cell ages. More importantly, we can see that stem cells are not immortal cells but will also age and die [16]. The so-called "immortal DNA strand" hypothesis is a total misunderstanding because the template strand of DNA contained and retained by a stem cell is in fact one of the oldest DNA molecules inside a multicellular organism that might contain more damages and thus is likely more liable to breakdown than any other later formed DNA molecules [17].

From that aging perspective we should realize that stem cells are not the fountain of youth because they will dry out naturally as stem cells have to obey the natural order of aging and death. As stem cell age their epigenetic state also changes and thus the same stem cell may have altered capability of yielding more and/or different baby cells. As a matter of fact, this alteration may happen even in the very early life of a stem cell as baby cells with different developmental potentials have to be formed in the early part of the multicellular life so that different cell lineages can be formed and formed early.

Unlike genetic alterations (mutations) which are generally irreversible, epigenetic alterations are often reversible and thus some so-called "de-differentiation" or "reprogramming" can happen to already differentiated or programmed cells. However, these re-programmed cells are not stem cells because they were not born early and thus were not in the "stem" positions of the developmental hierarchy. If we do not enforce this timing criterion for identifying stem cells then any cell can be named as a stem cell.

So a simple and practical definition for a stem cell is: a cell born from a fertilized germ cell early in the multicellular life and possess the capacity of producing baby cells with further branching capability in cell lineage formation.

I hope this still unconventional insight on stem cells from an "outsider" of the professional stem cell research will contribute to furthering the understanding of stem cells by the stem cell research insiders so a better outlook for stem cell research can be realized.

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*This manuscript was first submitted to *Cell* on 2007-01-29 but was rejected on 2007-01-30. It was then submitted to *Stem Cells* on 2007-01-31 and was rejected on 2007-02-18. An appeal was filed on 2007-02-18 which was further rejected on 2007-02-26. A complaint was filed on 2007-02-27 to *Stem Cells* which issued a final statement on 2007-03-02 insisting on its rejection. The publication here contains the original content as submitted to *Stem Cells* with the added highlight, abstract and keywords.

Appendixes

1. Rejection Statement from *Cell* (Excerpt)

2007-01-30

"The Cell editors have discussed your presubmission inquiry on redefining the current views on stem cells. Unfortunately, we are unable to publish your article".

2. Initial Rejection Statement from *Stem Cells* (Excerpt)

2007-02-18

"Your manuscript, entitled "What Is a Stem Cell? SC-07-0090," has been carefully read by our Editors, and we have decided not to pursue an outside review and further consideration for publication in STEM CELLS. We hope that by making this decision, we save you the considerable time that can be required for the external review process, and thereby allow you to pursue another publishing venue in a timely fashion."

3. Initial Appeal Submitted to *Stem Cells* (Excerpt)

2007-02-18

I am very disappointed with Stem Cells' decision to not publish a Letter-To-Editor that asks a very fundamental question about stem cell. What is the ground for this rejection? Can you elaborate a little bit more your about scientific reasons for rejecting this legitimate question on the stem cell definition?
I appreciate your quick decision for saving me time. But I must say that , while you saved my time to publish my view in another way, you will cause a lot of waste in time from many other stem cell researchers by suppressing the issuing of my justifiable warning against some confusions and misleading in stem cell research.
Thus, I consider your decision as a typical irresponsibility in scientific publishing.

Sincerely,

Shi V. Liu

4. Further Rejection Statement from *Stem Cells* (Excerpt)

2007-02-26

"The editorial board takes letters such as the one you sent very seriously and we considered all the points you raised. Having done so however, we have decided to stand by our original decision not to publish your manuscript in Stem Cells."

"The Editor who reviewed your manuscript concluded that it was not sufficiently focused to merit publication at this time. Also, the Editor indicated that the manuscript does not represent an updated, unbiased review of the current literature and is unsubstantiated by published experimental or conceptual data."

"We hope you can understand that space is limited in the journal and we have made a conscious decision to publish only those works which receive the highest priority scores and which all reviewers unanimously feel will advance the field."

"We regret that your manuscript did not fall into this category."

5. Further Complaint against *Stem Cells*'s rejection (Excerpt)

2007-02-27

I have read your reply and understood every point that you raised.

However, I must to say that none of the points that you cited for rejecting my manuscript can stand on the test of existing knowledge, not to say the test of future time.

Firstly, it is **ridiculous** to say that a short letter asking a single question of "What Is a Stem Cell" is "not sufficiently focused". Obviously, to answer this question fully and correctly, I must examine the two so-called "defining" features of stem cells. However, my unique insight on the true nature of "self-renewal" and "cell differentiation" is the very reason that your journal should publish my letter.

Secondly, it is **incorrect** to say that my letter "does not represent an updated" review of the current literature. To fully capture the essential status of the stem cell research, I have included (within the tight space limitation for this type of communication) not only a conclusion on stem cell research made by the pioneers of the stem cell research – McCulloch and Till but also the most recent definition on stem cell which is widely circulated among not just professional stem cell researchers but also layman public – the wikipedia definition. Furthermore, some key experimental findings that have challenged the legitimacy of the dogmatic definition on stem cell were cited so was a very recent conceptual paper expressing a different view on stem cell (different from the mainstream view and also my view).

Thirdly, it is **unreasonable** to ask my letter to present a so-called "unbiased" review of the current literature. Why should my letter (intended to express my own view) be a composite of others' views, especially when I have no intention to agree with their views? I guess whoever made this conclusion even does not know the distinction between a Letter-To-The-Editor and a review. Then how could s/he qualify as an editor for a scholar journal?

Fourthly, it is **unknowledgeable** to say that my manuscript is "unsubstantiated by published experimental data". I guess the editor who read my manuscript even does not read *Science* or *Nature*. If s/he does, then s/he should immediately recognize that all the statements that I made in this manuscript have been largely validated by the existing experimental data. For example, in a research article published in *Nature* (445: 214-218, 2007) it has been shown that cell differentiation occurs very early in embryogenesis. In another research article published in *Science* (315: 518-521, 2007) it has been shown that mother centrosome and daughter centrosome are asymmetrically inherited. All these "new" findings actually accommodate my "old" theory but they still lack a key insight that I have had for decades – the two cells formed by the asymmetrical cell "*division*" are not two different "daughter" cells but are one mother cell and one true *daughter* cell *reproduced* from that *mother* cell. There are many more such accommodating wet-lab evidences to support the every aspect of my global cell life theory. However, I will not re-iterate what I have published before unless you sincerely invite me to write such a review (and pay me for my contribution).

Finally, it is **unethical** to deny the existence of a large body of "conceptual data" especially when they are already present in various published formats such as world-wide accessible electronic journals and authoritative patent archive. The editor may have his/her right to look down on my publications (including some published in the mainstream journals), but s/he has no right to deny the existence of a knowledge that is critical to the journal s/he serves. Such deny is not only a form of arrogance but also a true act of scientific irresponsibility.

As the oldest dedicated journal on stem cells, it should not lightly discard a letter asking the key questions on stem cells. If you feel that my above criticisms against you decision of rejecting my manuscript are unreasonable and you have more ground to insist on your decision, I wish you can show me the full content of your reviews. Remember, I have paid the full submission fee for this Letter-To-The-Editor thus I have

all the right to request a full copy of the review (I do not ask you to reveal the name of the editor since his/her name is unimportant for this debate).

I wish that you will at least give me a reply to let me know your final position after reading my above arguments because I will make my decision on how to handle this rejection by your journal very soon.

Sincerely,

Shi V. Liu

6. Final Rejection by Stem Cells (Excerpt)

2007-03-02

"I have considered your first appeal, followed by your complaint. However, I have decided to stand by the review team's decision."

Editor-in-Chief
STEM CELLS