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MINI REVIEW

Persistent use of “false” cell lines

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From HeLa and its multiple identities, to MDA-MB-435, erroneously and widely used as breast cancer cells, the history of cancer cell lines is rich in misidentification and cross-contamination events. Despite the fact that these problems were regularly signaled during the last decades, many actors of research still seem to ignore them. A never-ending story? Solutions exist, notably based on recent technical advances in cell line authentication (short tandem repeat analysis). However, a collaborative action involving users of cell lines, cell banks, journals and funding agencies is needed to achieve success.

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Key words: cell lines; misidentification; cross-contamination; authentication; short tandem repeat; HeLa; MDA-MB-435; misuse

Review

Examination of the current scientific literature indicates that a large percentage of papers reporting on experimental cancer research use human cell lines. Indeed, cell lines are expected to provide an unlimited source of specific self-replicating material, free of contaminating cells and often easily cultured in simple standard media. Alas, since the establishment of the first cancer cell lines, problems with misidentification and cross-contamination have occurred and seriously compromised research. These problems were regularly brought to light during the past decades,^{1–14} but have received few audience until cell banks (American Tissue Culture Collection, ATCC; Deutsche Sammlung von Mikroorganismen und Zellkulturen, DSMZ; European Collection of Cell cultures, ECACC; Japanese Collection of Research Bioresources, JCRB) decided to act by informing their clients or even by withdrawing the false cell lines from their catalogue. It must be noted that the DSMZ has been a pioneer and is still a major actor in that process.

Various recent studies have shown that between 18 and 36% of cell lines were incorrectly designated.^{5,6,14} It is likely that new false cell lines continue to be established without the knowledge of their originators. At the same time, detection of false cell lines is rendered increasingly difficult as numbers and varieties of circulating cell lines increase. Even more worrisome is the fact that many cell lines that have been proven false, sometimes since years, are still used by researchers who seem to ignore their true identity or who act as if they were ignoring it.

T1 This is notably illustrated by Table I, which presents a nonexhaustive list of misidentified or cross-contaminated cell lines that have been cited during the first semester of 2007 by scientists apparently not aware of their exact identity. The search was performed using the HighWire database (<http://highwire.stanford.edu>) including PubMed journals.

A significant part of these cell lines have been contaminated with HeLa cells,³¹ which, indeed, are frequently used in the laboratories, are robust, and multiply rapidly.³² In a recent (2004) survey of 483 mammalian cell culturists, it was shown that 32% of respondents used HeLa cells and 9% well-known HeLa contaminants (including Hep-2, KB, WISH, Chang Liver, INT407). Only about a third of respondents were testing their lines for cell identity.³³ Thus, it is not surprising that many researchers are still using HeLa contaminants without apparent awareness of their true identity.

Some of the cell lines mentioned in the Table I are intensively used under their false identity. This is notably observed for Chang Liver, ECV304, KB, SK-N-MC, MCF-7/ADR, MDA-MB-435 cells. . . In some cases, the incriminated articles are from researchers not always familiar with the world of tumor cell lines, for instance toxicologists or chemists who wanted to test natural or modified compounds on a well-known cell line, which they therefore considered as highly representative.

For 6 of the cell lines listed in Table I, a more detailed HighWire database search was performed to identify the number of articles mentioning them under their false identity during the last years (Table II). From the Table, it appears that: (i) WISH and Hep-2/Hep2 cell lines are still used under their false identity by several researchers, despite the fact that their misidentification was shown in 1976¹⁵ or 1988,¹⁶ respectively; (ii) the misuse of DAMI (identified as HEL erythroleukemia cells in 1997²⁷) and ECV-304/ECV304 (identified as T24 bladder carcinoma in 1999²²) cell lines does not appear to rapidly decrease over years, and the incertitude on the exact origin of HBL-100 cells (presence of Y chromosome mentioned before 2003) is apparently not a problem for dozens of research teams.

The misuse of several cell lines appears to be relatively more frequent in works originating from various emerging countries (South Korea, India, . . .), and particularly from China. For instance, 45 on 102 (44%) papers published in 2006 and presented ECV-304/ECV304 cells under their false identity were from China, as there were 21 on 66 (32%) articles describing Hep-2/Hep2 cells as laryngeal cells and 5 on 22 (23%) articles in which WISH cells were used as amnion-derived cells. China was culturally isolated a long time, what could explain why so many chinese researchers seem not be as aware of cell line cross-contamination.

Paradoxically, it can arrive that false cell lines are exactly appreciated because they have a characteristic that distinguish them from other cell lines of the same supposed (and actually erroneous) origin. For instance, one of the most recently unmasked cell lines, the putative “breast cancer” cell line MDA-MB-435 had gained a great popularity due to its unrivaled metastatic efficiency in nude mice.^{34,35} Contrasting with most breast cancer cell lines, which have an epithelial-like aspect, MDA-MB-435 cells express a mesenchymal-like portrait.³⁵ This feature has favoured the use of MDA-MB-435 cells, since it was previously widely believed that most breast cancer cells should undergo an epithelial-to-mesenchymal phenotype transition (EMT) to be able to metastasize.³⁶ MDA-MB-435 cells were for that reason considered as very advanced in the process of metastasization. It is now established that EMT is in fact rarely seen in breast cancer progression.³⁷ The melanocytic nature of MDA-MB-435 cells was first suspected following micro-array studies, where these cells were found to cluster with melanoma cells, rather than with other breast cancer cell lines.³⁸ Afterward, MDA-MB-435 cells were found to express several genes commonly transcribed in melanocytes, such as RXRG, TYR, ACP5 and DCP, but which are not found in vari-

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Received 25 July 2007; Accepted after revision 19 September 2007

DOI 10.1002/ijc.23233

Published online 00 Month 2007 in Wiley InterScience (www.interscience.wiley.com).

TABLE I – NONEXHAUSTIVE LIST OF MISIDENTIFIED OR CROSS-CONTAMINATED CELL LINES THAT HAVE BEEN CITED DURING THE FIRST SEMESTER OF 2007 BY SCIENTISTS APPARENTLY NOT AWARE OF THEIR EXACT IDENTITY

Cell line	Putative origin	True identity	Reference(s) identifying cross-contamination or misidentification
Chang liver	Liver cells	HeLa cells (glandular cancer of the cervix)	15
Girardi heart	Atrial myoblast cells	HeLa cells	15
Hep-2 (or Hep2)	Larynx carcinoma cells	HeLa cells	16
INT407 (or INT-407, or Intestine 407)	Embryonic intestine cells	HeLa cells	15
J111	Monocytic leukemia cells	HeLa cells	15
KB	Oral epidermoid carcinoma cells	HeLa cells	2,3,17,18
L132	Embryonic lung epithelium cells	HeLa cells	15
MT-1 (or MT1)	Breast cancer cells	HeLa cells	6
NCTC2544	Skin epithelium cells (keratinocytes)	HeLa cells	15
WISH	Amnion cells	HeLa cells	15
Wong-Kilbourne	Conjunctiva-derived cells	HeLa cells	15
RPMI-8402 (or RPMI8402)	T cell leukemia	Unknown	19
IM-9 (or IM9)	Multiple myeloma cells	Epstein-Barr virus-transfected B cell lymphoblastoid line	20
HBL-100 (or HBL100)	Breast transformed but non-tumorigenic cells	Unknown, and not female (found to contain Y chromosome)	ATCC website (www.atcc.org/SearchCatalogs/probline.cfm)
TSU-Pr1 (or TSUPr1)	Prostate cancer cells	T24 cells (bladder cancer)	21
ECV-304 (or ECV304)	“Spontaneously transformed” umbilical cord endothelial cells	T24 cells	22–24
EJ138	Bladder cancer cells	T24 cells	14 and ECACC website
EJ-1 (or EJ1)	Bladder cancer cells	T24 cells	14 and ECACC website
PPC-1 (or PPC1)	Prostate cancer cells	PC-3 cells (prostate cancer)	25
ALVA-31 (or ALVA31)	Prostate cancer cells	PC-3 cells	25
ALVA-41 (or ALVA41)	Prostate cancer cells	PC-3 cells	25
SK-N-MC	Neuroblastoma cells	Ewing family tumor cells	26
DAMI	Megakaryocyte	HEL cells (erythroleukemia)	27
HS-Sultan	Plasma cell line (multiple myeloma)	Jijoye cells (Burkitt’s lymphoma)	20
ARH-77 (or ARH77)	Plasma cells from a multiple myeloma patient	Epstein-Barr virus-transfected B cell lymphoblastoid line	19
WiDr	Colon cancer cells	HT-29 cells (colon carcinoma)	28
SNB-19 (or SNB19)	Glioblastoma cells	U-373MG cells (glioblastoma)	14 and ATCC website
U251	Glioblastoma cells	U-373MG cells	14 and ATCC website
MCF-7 _{ADR} (re-designated NCI/ADR-RES)	Breast cancer cells	OVCAR-8 cells (ovarian cancer)	29
MDA-MB-435 (or MDA-MB-435S, or MDA-MB435, or MDA-435)	Breast cancer cells	M14 cells (melanoma)	30

ATCC, American tissue culture collection; ECACC, European collection of cell cultures.

TABLE II – NUMBER OF ARTICLES CITING SEVERAL CELL LINES UNDER THEIR FALSE IDENTITY

Cell line	Year									
	1990	1995	2000	2001	2002	2003	2004	2005	2006	2007 ¹
ECV-304 or ECV304	1	15	101	124	132	111	120	109	102	>53
DAMI	2	28	19	16	20	15	15	9	7	>7
HBL-100 or HBL100	22	19	57	59	51	48	47	31	40	>16
Hep-2 or Hep2	18	25	52	58	48	65	58	87	66	>53
MDA-MB-435 or MDA-MB-435S or MDA-MB435 or MDA-435	5	33	101	141	164	173	276	276	272	>140
WISH	6	7	22	19	31	30	23	23	22	>11

¹Search performed in August 2007.

ous commonly used breast cancer cell lines.³⁹ Expression of melanocyte proteins tyrosinase and melan-A by MDA-MB-435 cells was also shown.⁴⁰ However, these published observations were not followed by a decrease in the use of MDA-MB-435 as breast cancer cells (see Table II). MDA-MB-435 cells are in fact derived from the melanoma cell line M14. The misidentification is likely to have occurred prior to 1982 and therefore, nearly all of the existing literature using the MDA-MB-435 cell line describes the M14 melanoma cell line, which has been far less studied under its true name.³⁰

Of note, another cell line, LCC15-MB, which has not been mentioned in 2007, was recently identified as being MDA-MB-435,⁴¹ thus in reality M14 melanoma cells. LCC15-MB had drawn attention due to its invasive and metastatic phenotype. Moreover, as these cells were believed to originate from a bone metastase in a breast cancer patient, they seemed to constitute a useful model for studying molecular mechanisms important for breast cancer metastasis to bone.⁴²

In a recent white paper,⁴³ Dr. Roland Nardone proposed cell line authentication as a condition for the award of research grants

and for the publication of research findings. Clearly, resolution of the problem of misidentification and cross-contamination requires the conscientization and the collaboration of all involved actors: users (including originators) of cell lines, cell banks, journals and funding agencies.

Users normally do not wish to use false cell lines that are the basis of misleading publications, which can potentially have a very high cost in terms of invalid hypotheses and paradigms, mis-spent effort and protracted development of patient treatments. Indeed, only in a very few investigations is the exact origin of a cell line devoid of any importance. However, most (new) cell lines are freely exchanged between laboratories, rarely having their identities checked. To avoid cross-contamination of these lines, periodic reauthentication of cell lines is advisable. In addition, working from validated freeze-downs, where cells are maintained in culture, and ideally separated from other cell lines, should minimize the risk of cross-contamination.^{12,44}

All reputable cell banks now employ methods to confirm the identity and origin of the cell lines they distribute. This is notably because distribution of misidentified or cross-contaminated cell lines, even when supplied in good faith, may later be the subject of costly and embarrassing recall actions. Moreover, cell banks may facilitate de novo detection of cross-contamination by identifying untoward matches between new and existing cell lines. Most cell banks may also test, to a low cost, cell lines provided by their users or originators. While various techniques, not described here, have been used in the past, recent technical advances have led to the development of short tandem repeat (STR) analysis. STRs are repetitive sequences characterized by a variable number of repeated short sequence elements of 2–7 bp in length as a unit

(e.g., di-, tri-, tetra-nucleotide sequences), also known as microsatellites or simple sequence repeats. They are highly polymorphic, the repeat sizes are small and can be easily amplified by the polymerase chain reaction method. Furthermore, when the sizes of the products (accurate to 1 base pair) are determined, a series of numbers are generated, which can be used as a bar code for that DNA source. A registry of bar codes would make it easy to compare DNA samples and thus allow efficient cell line authentication, as notably shown by an international consortium.⁴⁵ The STR method, although not perfect,⁴⁶ is easy, reliable, inexpensive and can be done "in house" or analyzed by a commercial laboratory.^{14,45,47–50}

The peer review process carried out by many (but not all) journals and funding agencies still fails to consider the authenticity of the cell lines used. Editors of journals and heads of agencies should be encouraged to examine such issues and, *in fine*, to reject papers from authors unable to substantiate the authenticity of the cell lines they have used. Along the same line, publication of new cell lines by originators, or the funding of their production should be conditional upon these lines being made freely available to other investigators, for instance by reposition in cell banks.

It is now time for a concerted action. Otherwise, days and costly resources will continue to be wasted, as a result of spurious experimental results, and some scientific reputations will continue to face the risk of being compromised.

Acknowledgements

Many thanks to "Fondation Fornarina" and SciMedWeb. This article is dedicated to the memory of my father, Mr. Albert Lacroix (1935–2006).

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