



Research article

Appropriate citation of placenta cell lines 3A(tPA-30-1) and 3A-sub E [post crisis of 3A(tPA-30-1)] in medical literature

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ABSTRACT

Introduction: To determine how often placenta cell lines 3A (tPA-30-1) and 3A-sub E [post crisis of 3A (tPA-30-1)] are appropriately cited, or identified, as “term”-gestation placental cell lines in medical literature.

Methods: We performed a literature search on two databases, PubMed and One Search, using the terms “3A (tPA-30-1),” “3Asub-E,” “3AsubE,” “tPA-30-1,” “tPA30-1,” and “3A AND (placenta OR placental OR trophoblast OR trophoblastic) AND (cell OR line OR cell line).” Of the 218 citations retrieved, 181 were excluded due to duplication, article content irrelevance or lack of access to a full manuscript. The remaining 37 citations were thoroughly reviewed for 1) the presence of a full citation as designated by the supplier, and 2) the identification of the placental lines as “term.”

Results: Of the 37 eligible citations included in the study, five demonstrated complete identifications of the placental cell lines of interest, while 32 demonstrated partial identifications that failed to match the designations provided by the manufacturer. Furthermore, of the 37 citations, eight accurately identified the cell lines as “term,” while 27 lacked any description of gestational age, and two incorrectly identified them as “first trimester” cell lines. Overall, only three citations contained both a full citation and correct identification as a “term” placenta cell line.

Discussion: Only 5 of the 37 (13.5%) publications demonstrated a complete citation and only 8 publications accurately identified the gestational age of the placenta cell line as “term”. Such findings confirm the need for a representative set of standards for the documentation of cell lines to improve the quality of publications in the scientific community.

1. Introduction

While there are no official scientific guidelines for using cell line use in biomedical research in the United States, most authors do describe the cell line(s) that they utilize in their experiments and report whether the cells were purchased from a commercial cell bank or acquired as a “gift” from a collaborator's laboratory. However, citations of “gifted” cell stocks often do not cite the passage number or the unique manufacturer's identification numbers to allow for study reproducibility and become subject to some ambiguity when comparisons are being made with other similar cell lines during literature reviews [1, 2].

Well-established placenta cell lines are commonly used in cellular and molecular biology research because primary placenta trophoblast cells

are relatively unstable and spontaneously fuse under *in vitro* culture conditions. However, there is a lack of standardization regarding the level of detail required in the “Materials and Methods” sections of scientific literature when reporting on cell lines [2]. Placenta trophoblast cells, for example, exhibit cellular behaviors that vary significantly with gestational age, such as in its invasive capacity in the first trimester [3] compared to its pattern of secretion of placental hormones in the mature third trimester placenta [4]. In addition, placenta cell lines may become genetically unstable with serial passages which may change their behavior in subsequent experiments [46]. Given these concerns, it is critical for investigators to not only accurately report the source and derivation of their placental lines, but also more accurately describe why

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Table 1. Definitions used on title and abstract review.

Definitions: Title & Abstract Review

- “Relevant”
 - Title and/or abstract explicitly cites a cell line with any of the following: "3A-sub E," "post crisis of 3A (tPA-30-1)," "tPA-30-1," "CRL-1584," "CRL-1583," or any term pertaining to the placental cell line of interest.
- “Irrelevant” (ANY of the following)
 - Title and abstract makes no reference of any *human* placental cell line.
 - Title and abstract does not imply the use of any human placental cell line in study (e.g. may reference the use of cell line by *another* author, but not in own study).
 - Title and/or abstract explicitly cites one or more cell lines; however, name(s) of cell line does not contain "3A-sub E," "post crisis of 3A (tPA-30-1)," "tPA-30-1," "CRL-1584," "CRL-1583," or any term potentially pertaining to the placental cell line of interest (e.g. "3A").
- “NFI”
 - Title and abstract implies use of one or more human placental cell lines in study; however, no explicit citation is present. Explicit citation may be present in full manuscript.

Table 2. Definitions used on full text manuscript review.

Definitions: Full Text Manuscript Review

- “Relevant”
 - Manuscript explicitly cites a cell line with any of the following: e.g. "3A-sub E," "post crisis of 3A (tPA-30-1)," "tPA-30-1," "CRL-1584," "CRL-1583," or any term pertaining to the placental cell line of interest.
- “Irrelevant” (ANY of the following)
 - Manuscript makes no reference of any *human* placental cell line.
 - Manuscript does not imply the use of any human placental cell line in study (e.g. may reference the use of cell line by *another* author, but not in own study).
 - Manuscript explicitly cites one or more cell lines; however, name(s) of cell line does not contain "3A-sub E," "post crisis of 3A (tPA-30-1)," "tPA-30-1," "CRL-1584," "CRL-1583," or any term potentially pertaining to the placental cell line of interest (e.g. "3A").

Table 3. Identification as “Term” vs no gestational age stated vs “First trimester”.

	3A (tPA-30-1)	3A-sub E [post crisis of 3A (tPA-30-1)]
Descriptors of placental cell lines quoted from each full text manuscript:	"3A (tPA-30-1) cells, derived from human term placenta and transformed by SV40" ¹ [8]	"trophoblast cell line 3A-Sub-E (ATCC CRL-1584)" ² [23]
	"3A(tPA-30-1), a temperature-sensitive SV40 tsA30 virus-transformed human placenta cell line" ² [9]	"human placental cell line, 3ASubE" ² [24]
	"transformed trophoblastic cell line TPA-30-1" ² [10]	"3ASubE cells derived from trophoblasts of terminal placenta by temperature-sensitive SV40 immortalization" ¹ [25]
	"SV40 (temperature-sensitive mutant)-transformed TPA 30-1 human trophoblast cell line" ² [11]	"human placental cell line, 3ASubE" ² [26]
	"a term placental cell line (tPA30-1)" ¹ [12]	"human placental cell line 3ASubE" ² [27]
	"SV40-transformed placental cell line tPA30-1" ² [13]	"human placental cell line, 3A-SubE (tPA30-1)" ² [28]
	"tPA30-1 cells...established by transformation of the human term placenta using a temperature-sensitive simian virus 40 mutant of the A class" ¹ [14]	"human 3A trophoblast cells (CRL-1584, ATCC, Manassas, VA)" ² [29]
	"SV40 tsA30 mutant-transformed term placental cell line (TPA30-1)" ¹ [15]	"term villous trophoblast 3A-subE cell line" ¹ [30]
	"3A human trophoblastic cells" ² [16]	"villous 3A cytotrophoblast first trimester placental cell line (CRL-1584) was purchased from American Type Culture Collection (ATCC) (Manassas, VA)" ³ [31]
	"Human 3A trophoblasts (ATCC CRL1583)" ² [17]	"3A cells, derived from first-trimester human trophoblast by SV40 ts30 transformation, were purchased from ATCC (CRL-1584; Rockville, MD, USA)" ³ [32]
	"Human 3A trophoblasts (ATCC CRL1583)" ² [18]	"Human placental trophoblast, SV40 transformed cell line 3A- sub-E (3A) from American Type Culture Collection (ATCC # CRL-1584)" ² [33]
	"3A trophoblasts (ATCC CR-1583)" ² [19]	"term trophoblasts (3A-Sub-E and primary culture trophoblasts)" ¹ [34]
	"3A trophoblasts (ATCC CRL1583)" ² [20]	"human SV40 transformed 3A-Sub-E trophoblast cell line (ATCC, Manassas, VA, USA)" ² [35]
	"3A(tPA-30-1) cells (ATCC CRL 1583), derived from human term placenta and transformed by SV40" ¹ [21]	"a post-crisis SV40-transformed human placental trophoblast cell line 3A-Sub-E (CRL-1584) used in this study were obtained from American Type Culture Collection (Rockville, MD)" ² [36]
	"trophoblastic cell line (tPA30-1)...obtained from the American Type Culture Collection (Rockville, MD, USA)" ² [22]	"Human normal placental trophoblast, SV40 transformed cell line (3A-sub-E) from American Type Culture Collection (ATCC # CRL-1584)" ² [37]

(continued on next page)

Table 3 (continued)

3A (tPA-30-1)	3A-sub E [post crisis of 3A (tPA-30-1)]
	"Postcrisis clone of SV-40 tsA-transformed placental cells (tPA30-1), CRL 1584" ² [38]
	"human non-cancer trophoblast cell line (3A-Sub-E)" ² [39]
	"trophoblast cell line 3A-Sub-E (ATCC CRL-1584)" ² [40]
	"Trophoblast cell line 3A-sub E post crisis of the 3A (tissue plasminogen activator-30-1) (American Type Culture Collection [ATCC] CRL 1584)" ² [41]
	"trophoblast cell line, 3A-Sub-E (ATCC CRL-1584)" ² [42]
	"human non-choriocarcinomic trophoblastic cell line BeWo and 3asubE cells were obtained from the American Tissue Culture Collection (ATCC)" ² [43]
	"Human placental cell line, TPA30-1 (Chou 1978), was obtained from Dainihon Seiyaku (Osaka, Japan)" ² [44]

Legend.

Placental cell line identified as:

- ¹ "Term".
- ² No gestational age stated
- ³ "First trimester".

the respective cell line is an appropriate model for the focus of their research.

In this study, we investigated the citations of two placental cell lines: 3A (tPA-30-1) (American Type Culture Collection [ATCC] CRL-1583), a term villous trophoblastic cell line [5]; and 3A-sub E [post crisis of 3A (tPA-30-1)] (ATCC CRL-1584), a term villous trophoblastic cell line derived from 3A (tPA-30-1) cells that were rescued from senescence [6]. We hypothesized that most scientific publications in a literature search of

articles using these two cell lines would appropriately 1) identify the full name of the cell lines or its accession numbers as explicitly demonstrated by their respective ATCC product sheets, and 2) denote that these cell lines represented a "term" or third trimester placenta cells, rather than attribution to a first- or second-trimester placenta. The results of this study would shed light on the current scientific rigor and precision of placenta cell line reporting in publications, which could potentially

Table 4.. Full vs partial citations.

	3A(tPA-30-1)	3A-sub E [post crisis of 3A(tPA-30-1)]
Screenshots acquired from individual ATCC product sheets [5, 6]:	Citation of Strain If use of this culture results in a scientific publication, it should be cited in that manuscript in the following manner: 3A(tPA-30-1) (ATCC® CRL-1583™)	Citation of Strain If use of this culture results in a scientific publication, it should be cited in that manuscript in the following manner: 3A-subE[post crisis of 3A(tPA-30-1)] (ATCC® CRL-1584™)
Most complete citations quoted from each full text manuscript:	"3A (tPA-30-1) cells, derived from human term placenta and transformed by SV40" [8] "3A(tPA-30-1), a temperature-sensitive SV40 tsA30 virus-transformed human placenta cell line" [9] "transformed trophoblastic cell line TPA-30-1" [10] "SV40 (temperature-sensitive mutant)-transformed TPA 30-1 human trophoblast cell line" [11] "a term placental cell line (tPA30-1)" [12] "SV40-transformed placental cell line tPA30-1" [13] "tPA30-1 cells...established by transformation of the human term placenta using a temperature-sensitive simian virus 40 mutant of the A class" [14] "SV40 tsA30 mutant-transformed term placental cell line (TPA30-1)" [15] "3A human trophoblastic cells" [16] "Human 3A trophoblasts (ATCC CRL1583)" [17] "Human 3A trophoblasts (ATCC CRL1583)" [18] "3A trophoblasts (ATCC CR-1583)" [19] "3A trophoblasts (ATCC CRL1583)" [20] "3A(tPA-30-1) cells (ATCC CRL 1583), derived from human term placenta and transformed by SV40" [21]	"trophoblast cell line 3A-Sub-E (ATCC CRL-1584)" [23] "human placental cell line, 3ASubE" [24] "3ASubE SV40-transformed trophoblast cells (ATCC)" [25] "human placental cell line, 3ASubE" [26] "human placental cell line 3ASubE" [27] "human placental cell line, 3A-SubE (tPA30-1)" [28] "human 3A trophoblast cells (CRL-1584, ATCC, Manassas, VA)" [29] "3A-subE [post-crisis of 3A(tPA-30-1)] (ATCC CRL-1584) cell line was obtained from the American Type Culture Collection, Manassas, VA" [30] "villous 3A cytotrophoblast first trimester placental cell line (CRL-1584) was purchased from American Type Culture Collection (ATCC) (Manassas, VA)" [31] "3A cells, derived from first-trimester human trophoblast by SV40 ts30 transformation, were purchased from ATCC (CRL-1584; Rockville, MD, USA)" [32] "Human placental trophoblast, SV40 transformed cell line 3A- sub-E (3A) from American Type Culture Collection (ATCC # CRL-1584)" [33] "3A-Sub-E (CRL-1584, ATCC) cells" [34] "human SV40 transformed 3A-Sub-E trophoblast cell line (ATCC, Manassas, VA, USA)" [35] "a post-crisis SV40-transformed human placental trophoblast cell line 3A-Sub-E (CRL-1584) used in this study were obtained from American Type Culture Collection (Rockville, MD)" [36]

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Table 4 (continued)

3A(tPA-30-1)	3A-sub E [post crisis of 3A(tPA-30-1)]
"trophoblastic cell line (tPA30-1)...obtained from the American Type Culture Collection (Rockville, MD, USA)" [22]	"Human normal placental trophoblast, SV40 transformed cell line (3A-sub-E) from American Type Culture Collection (ATCC # CRL-1584)" [37]
	"Postcrisis clone of SV-40 tsA-transformed placental cells (tPA30-1), CRL 1584" [38]
	"human non-cancer trophoblast cell line (3A-Sub-E)" [39]
	"trophoblast cell line 3A-Sub-E (ATCC CRL-1584)" [40]
	"Trophoblast cell line 3A-sub E post crisis of the 3A (tissue plasminogen activator-30-I) (American Type Culture Collection [ATCC] CRL 1584)" [41]
	"trophoblast cell line, 3A-Sub-E (ATCC CRL-1584)" [42]
	"human non-choriocarcinomic trophoblastic cell line BeWo and 3asubE cells were obtained from the American Tissue Culture Collection (ATCC)" [43]
	"Human placental cell line, TPA30-1 (Chou 1978), was obtained from Dainihon Seiyaku (Osaka, Japan)" [44]

Legend:

Complete citation.

Partial citation.

impact on the quality of information transferred to the scientific community in general.

2. Methods

2.1. Search strategy

The databases Pubmed and One Search were used as the primary literature search engines with access as permitted by the University of

Hawaii John A. Burns School of Medicine Health Sciences Library with the assistance of the reference librarian during the timeframe between August 2018 to March 2019. No filters were applied to the Pubmed search (Medline database). One Search was applied with filters for language (English) and material type (articles). Search terms were: "3A (tPA-30-1)," "3Asub-E," "3AsubE," "tPA-30-1," "tPA30-1," and "3A AND (placenta OR placental OR trophoblast OR trophoblastic) AND (cell OR line OR cell line)." Hits for the last keyword (cell OR line OR cell line) on

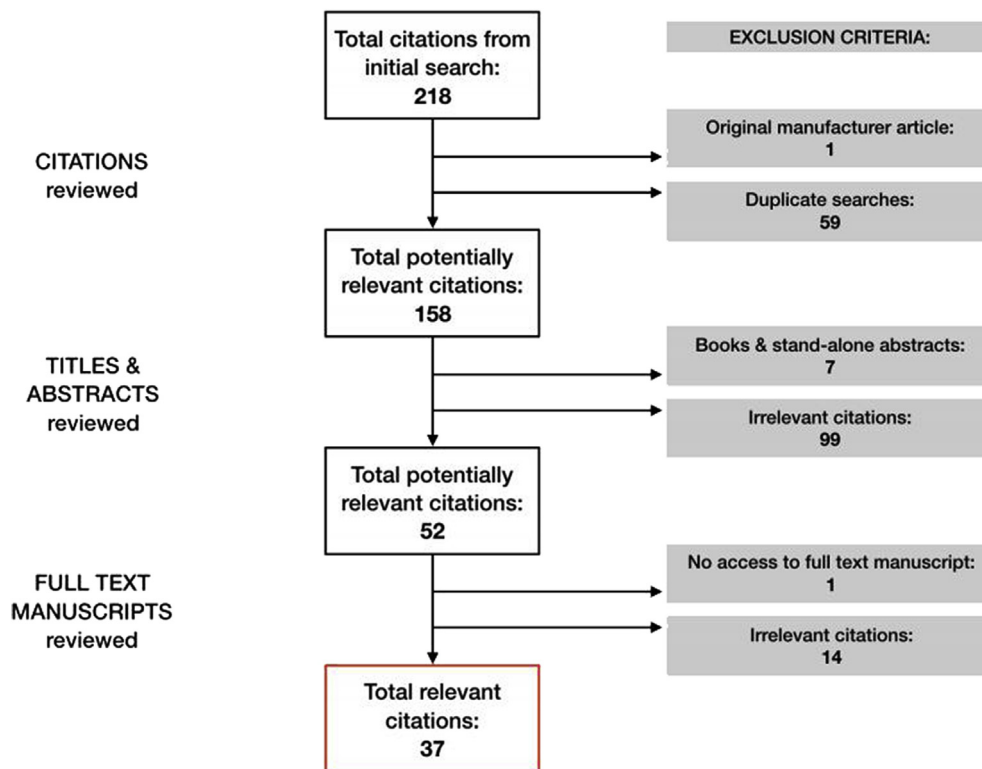


Fig. 1. Flowchart summarizing inclusion and exclusion criteria in literature search.

Definitions: Title & Abstract Review

- “Relevant”
 - Title and/or abstract explicitly cites a cell line with any of the following: "3A-sub E," "post crisis of 3A(tPA-30-1)," "tPA-30-1," "CRL-1584," "CRL-1583," or any term pertaining to the placental cell line of interest.
- “Irrelevant” (ANY of the following)
 - Title and abstract makes no reference of any *human* placental cell line.
 - Title and abstract does not imply the use of any human placental cell line in study (e.g. may reference the use of cell line by *another* author, but not in own study).
 - Title and/or abstract explicitly cites one or more cell lines; however, name(s) of cell line does not contain "3A-sub E," "post crisis of 3A(tPA-30-1)," "tPA-30-1," "CRL-1584," "CRL-1583," or any term potentially pertaining to the placental cell line of interest (e.g. "3A").
- “NFI”
 - Title and abstract implies use of one or more human placental cell lines in study; however, no explicit citation is present. Explicit citation may be present in full manuscript.

Fig. 2. Definitions used on Title & Abstract Review.

Definitions: Full Text Manuscript Review

- “Relevant”
 - Manuscript explicitly cites a cell line with any of the following: e.g. "3A-sub E," "post crisis of 3A(tPA-30-1)," "tPA-30-1," "CRL-1584," "CRL-1583," or any term pertaining to the placental cell line of interest.
- “Irrelevant” (ANY of the following)
 - Manuscript makes no reference of any *human* placental cell line.
 - Manuscript does not imply the use of any human placental cell line in study (e.g. may reference the use of cell line by *another* author, but not in own study).
 - Manuscript explicitly cites one or more cell lines; however, name(s) of cell line does not contain "3A-sub E," "post crisis of 3A(tPA-30-1)," "tPA-30-1," "CRL-1584," "CRL-1583," or any term potentially pertaining to the placental cell line of interest (e.g. "3A").

Fig. 3. Definitions used on Full Text Manuscript Review.

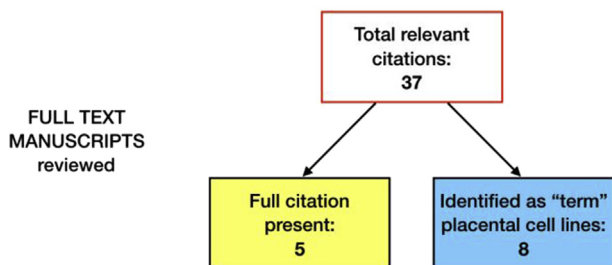


Fig. 4. Analyses performed on Relevant Citations.

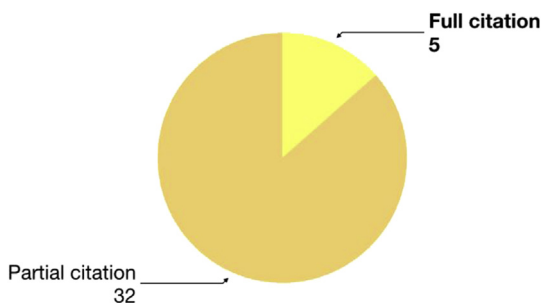


Fig. 5. Full vs Partial Citations.

One Search were entirely excluded as it yielded over 40,900 results (see Tables 1, 2, 3 and 4).

2.2. Search refinement

A total of 218 citations were identified from the initial search. From this list, the original manufacturer article [7] and 59 duplicate searches were excluded, leaving 158 potentially relevant citations. All 158 titles and abstracts were then reviewed and grouped into one of three categories: (a) Citations from books and stand-alone abstracts (7), all of which were excluded; (b) irrelevant citations (99), all of which were also

excluded; and (c) either relevant citations (22) and those “in need for further investigation” (NFI, 30), all 52 of which were included for full text manuscript review. A flow-chart summarizing this information is illustrated in Figure 1. The Definitions of “irrelevant,” “relevant,” and “NFI” for titles and abstracts are listed in Figure 2.

Of the 52 potentially relevant citations, one was excluded due to the lack of access to a full text manuscript. The remaining 51 full text manuscripts were examined individually, including a thorough review of the sections for materials and methods, article abbreviations, and references. Each citation was placed into one of two categories, 14 of which were “irrelevant” and excluded, and 37 of which were “relevant” and included in our study. Definitions of “irrelevant” and “relevant” for full text manuscripts are as described in Figure 3.

3. Results

Of the total 37 relevant citations, 15 cited use of the 3A (tPA-30-1) cell line and 22 cited use of the 3A-sub E [post crisis of 3A (tPA-30-1)] cell line.

3.1. Presence of a full citation or identification

Manuscripts were considered to have a complete, or “full” citation if their citations were as designated by ATCC [5, 6]. Minor discrepancies in the positioning of hyphens, parentheses, or brackets, as well as differences in capitalizations and character-spacing were disregarded. All other citations with discrepancies beyond the typographical errors specified above were considered to have incomplete, or “partial” citations. As displayed in Figures 4 and 5, only five (13.5%) demonstrated full citations out of the 37 identified full text manuscripts. Figure 6 lists the most complete citations that could be found in each manuscript.

3.2. Identification of the placental cell lines as “term”

As displayed on Figures 4, 7, and 8, of the 37 full text manuscripts examined, only eight (21.6%) identified the 3A (tPA-30-1) or 3A-sub E [post crisis of 3A (tPA-30-1)] cell line as correctly derived from “term”

	3A(tPA-30-1)	3A-sub E [post crisis of 3A(tPA-30-1)]
Screenshots acquired from individual ATCC product sheets [5,6]:	<p>Citation of Strain</p> <p>If use of this culture results in a scientific publication, it should be cited in that manuscript in the following manner: 3A(tPA-30-1) (ATCC® CRL-1583™)</p>	<p>Citation of Strain</p> <p>If use of this culture results in a scientific publication, it should be cited in that manuscript in the following manner: 3A-sub E [post crisis of 3A(tPA-30-1)] (ATCC® CRL-1584™)</p>
Most complete citations quoted from each full text manuscript:	<p>*3A (tPA-30-1) cells, derived from human term placenta and transformed by SV40* [8]</p> <p>*3A(tPA-30-1), a temperature-sensitive SV40 tsA30 virus-transformed human placenta cell line* [9]</p> <p>"transformed trophoblastic cell line TPA-30-1" [10]</p> <p>"SV40 (temperature-sensitive mutant)-transformed TPA 30-1 human trophoblast cell line" [11]</p> <p>"a term placental cell line (tPA30-1)" [12]</p> <p>"SV40-transformed placental cell line tPA30-1" [13]</p> <p>"tPA30-1 cells... established by transformation of the human term placenta using a temperature-sensitive simian virus 40 mutant of the A class" [14]</p> <p>"SV40 tsA30 mutant-transformed term placental cell line (TPA30-1)" [15]</p> <p>"3A human trophoblastic cells" [16]</p> <p>"Human 3A trophoblasts (ATCC CRL1583)" [17]</p> <p>"Human 3A trophoblasts (ATCC CRL1583)" [18]</p> <p>"3A trophoblasts (ATCC CR-1583)" [19]</p> <p>"3A trophoblasts (ATCC CRL1583)" [20]</p> <p>*3A(tPA-30-1) cells (ATCC CRL 1583), derived from human term placenta and transformed by SV40* [21]</p> <p>"trophoblastic cell line (tPA30-1)... obtained from the American Type Culture Collection (Rockville, MD, USA)" [22]</p>	<p>"trophoblast cell line 3A-Sub-E (ATCC CRL-1584)" [23]</p> <p>"human placental cell line, 3ASubE" [24]</p> <p>"3ASubE SV40-transformed trophoblast cells (ATCC)" [25]</p> <p>"human placental cell line, 3ASubE" [26]</p> <p>"human placental cell line 3ASubE" [27]</p> <p>"human placental cell line, 3A-SubE (tPA30-1)" [28]</p> <p>"human 3A trophoblast cells (CRL-1584, ATCC, Manassas, VA)" [29]</p> <p>*3A-subE [post-crisis of 3A(tPA-30-1)] (ATCC CRL-1584) cell line was obtained from the American Type Culture Collection, Manassas, VA* [30]</p> <p>"villous 3A cytotrophoblast first trimester placental cell line (CRL-1584) was purchased from American Type Culture Collection (ATCC) (Manassas, VA)" [31]</p> <p>"3A cells, derived from first-trimester human trophoblast by SV40 ts30 transformation, were purchased from ATCC (CRL-1584; Rockville, MD, USA)" [32]</p> <p>"Human placental trophoblast, SV40 transformed cell line 3A- sub-E (3A) from American Type Culture Collection (ATCC # CRL-1584)" [33]</p> <p>"3A-Sub-E (CRL-1584, ATCC) cells" [34]</p> <p>"human SV40 transformed 3A-Sub-E trophoblast cell line (ATCC, Manassas, VA, USA)" [35]</p> <p>"a post-crisis SV40-transformed human placental trophoblast cell line 3A-Sub-E (CRL-1584) used in this study were obtained from American Type Culture Collection (Rockville, MD)" [36]</p> <p>"Human normal placental trophoblast, SV40 transformed cell line (3A-sub-E) from American Type Culture Collection (ATCC # CRL-1584)" [37]</p> <p>"Postcrisis clone of SV-40 tsA-transformed placental cells (tPA30-1), CRL 1584" [38]</p> <p>"human non-cancer trophoblast cell line (3A-Sub-E)" [39]</p> <p>"trophoblast cell line 3A-Sub-E (ATCC CRL-1584)" [40]</p> <p>*Trophoblast cell line 3A-sub E post crisis of the 3A (tissue plasminogen activator-30-I) (American Type Culture Collection [ATCC] CRL 1584)* [41]</p> <p>"trophoblast cell line, 3A-Sub-E (ATCC CRL-1584)" [42]</p> <p>"human non-choriocarcinomic trophoblastic cell line BeWo and 3asubE cells were obtained from the American Tissue Culture Collection (ATCC)" [43]</p> <p>"Human placental cell line, TPA30-1 (Chou 1978), was obtained from Daihichon Seiyaku (Osaka, Japan)" [44]</p>
	<p>Legend:</p> <ul style="list-style-type: none"> - Complete citation - Partial citation 	

Fig. 6. Full vs Partial Citations.

placenta. The majority (n = 27; 73.0%) did not use any descriptors to characterize the gestational age of the placental cell lines, and two manuscripts (5.4%) erroneously identified 3A-sub E [post crisis of 3A (tPA-30-1)] as a "first trimester" placenta cell line instead of "term".

Moreover, these two manuscripts were unrelated in content and neither cited one or the other [31, 32]. Overall, only three citations contained both a full citation and a correct identification as "term" [8, 21, 30].

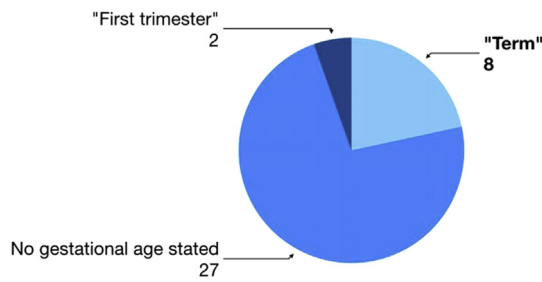


Fig. 7. Identification as “Term” vs no gestational age stated vs “First trimester”.

4. Discussion

Contrary to our hypothesis, only a minority 13.5% of the 37 full text manuscripts demonstrated full citations of our placental cell lines of interest. This is surprising given that each ATCC product sheet provides unequivocal directions on how to cite the strain in a publication (Figure 6) [5, 6]. Arguably, per ATCC Technical Services, the 3A (tPA-30-1) cell line was contributed by its original scientist in December 1980; therefore, the authors from one publication in October 1980 [15] may have reasonably been uninformed of its later-designated citation format. Nevertheless, this would not apply to the remaining 31 manuscripts whose publication dates did not pre-date the acquisition of 3A (tPA-30-1) cell line in 1980.

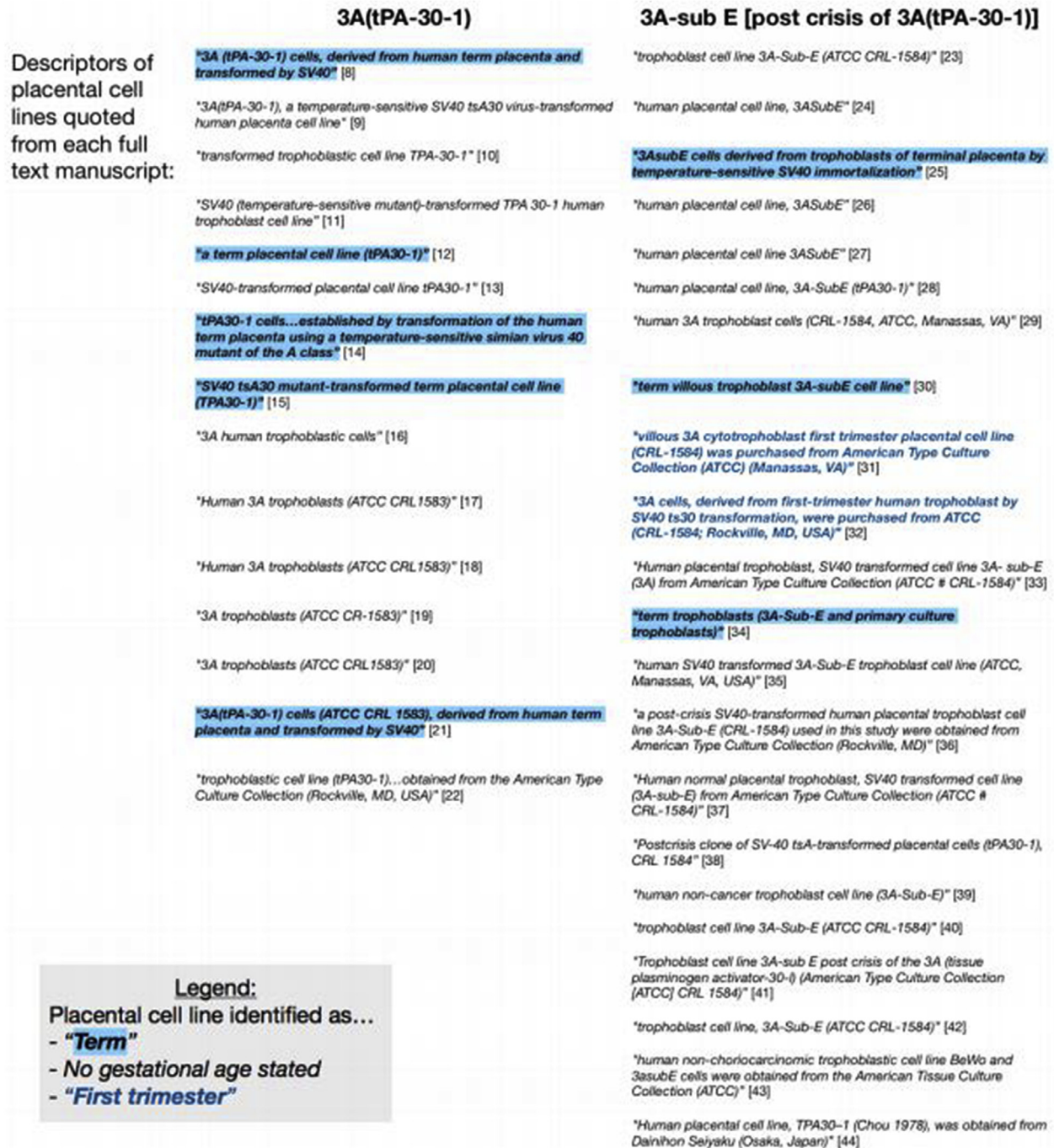


Fig. 8. Identification as “Term” vs no gestational age stated vs “First trimester”.

One possible explanation for this observation may be that researchers have unknowingly cited an incomplete citation from a previous related publication to their own manuscript or received an aliquot of the cell line as a gift from another investigator that did not come with a complete citation. Ideally, the first publication should have included the full cell line designation with an accession number from its donor cell bank such that all subsequent publications citing this work, at minimum, will “copy-forward” a correct and complete citation [1]. In reality, however, prior to the establishment of a national cell line repository, an initial misidentification of the cell line may have propagated through a series of publications without background verification.

Contrary to our hypothesis, only 21.6% of the 37 full text manuscripts demonstrated awareness that 3A (tPA-30-1) and 3A-sub E [post crisis of 3A (tPA-30-1)] were derived from a “term” placenta. A reasonable explanation for this may be that gestational age was deemed irrelevant by investigators for whom a placental cell line was a convenient basis to study colony-stimulating factor expression [11, 28], alkaline phosphatase gene regulation [15], or human papilloma virus replication [17, 18, 19, 20] to compare with other tissue cell lines. Nevertheless, given the well-recognized molecular and functional differences between the first and third trimester placenta [4], it would be appropriate to acknowledge the appropriate gestational age from which the cell line is derived to take advantage of its invasive versus hormonal production properties that might otherwise affect cell proliferation, rather than dismiss its unique effects altogether.

Interestingly, two manuscripts identified 3A (tPA-30-1) and 3A-sub E [post crisis of 3A (tPA-30-1)] as “first trimester” placental cell lines which were missed during the review process. As a consequence, this misconception pervaded the interpretation and discussion of the experimental results, and will likely continue to misinform future readers [31, 32]. The issue of cell line misidentification has also been described by other groups [47], notably, in the misrepresentation of a cancer cell line KB (HeLa) in certain studies [48]. Therefore, it is crucial to maintain scientific rigor in accurately reporting on placental cell lines in publications to avert potential misrepresentations which propagate through a succession of publications. A renewed attention to detail would optimistically improve general awareness of this and associated issues and transcend the area of precision scientific writing to an overall refinement in scientific and clinical practices.

5. Conclusion

In summary, this study involved a literature search of publications utilizing two popular placental cell lines and demonstrated significant discrepancies in their citations and characterization. We identified several articles that did not have complete or “full” citations for the 3A placenta cell lines as designated by its manufacturer product sheet, and two publications that incorrectly identified the 3A cell line as derived from a “first trimester” instead of a “term” or third trimester placenta. However minor these errors might be, both sources of ambiguity could have been easily preventable in the editorial review process. This raises some recommendations for future publications using established placental or other cell lines or chemical compounds in scientific and clinical studies. We suggest first that, whether a cell line is purchased directly from a cell bank or is transferred from another laboratory, the authors have a responsibility to cross-examine the manufacturer’s product sheet to verify for themselves its citation and origin and to report these details in resulting publications. Secondly, just as certain scientific journals now require proof of cell line authentication and absence of contamination as prerequisites for publication [2, 45], peer reviewers should place greater attention to the accuracy and level of detail in cell line identification. Finally, we hope that our findings call for a representative set of standards and guidelines for the documentation of established cell lines in biomedical research in order to strengthen the quality of publications in our scientific community. Future work includes reviewing all other publication sources and databases to fully capture the

misrepresentation of placental cell line citations in the scientific and medical literature.

Declarations

Author contribution statement

M. Lee: Conceived and designed the experiments; Wrote the paper.
 A. Ono and M. Griffith: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.
 P. Benny: Analyzed and interpreted the data; Wrote the paper.
 C. Litton: Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Additional information

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