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Review Article

Replicative Senescence Markers in Serially Passaged Human Mesenchymal Stromal Cells

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Abstract

Background: Every therapeutic mesenchymal stromal cell lot is expanded for weeks, but the identity criteria used to release it say nothing about how many divisions it has already spent.

Objective: To examine what serial-passage studies have measured, and which readouts could serve as release specifications or potency inputs.

Methods: Narrative review of serial-passage cohorts, telomere and methylation studies, and functional assays.

Findings: Expansion capacity spans roughly 8 to 86 cumulative population doublings across published cohorts. Senescence-associated beta-galactosidase-positive cells rose from 4.23 +/- 1.6% at passage 2 to 90.48 +/- 3.29% at passage 20 in five adipose preparations, and telomere length fell from 9.19 to 8.7 kbp between passages 1 and 9.

Conclusions: The evidence supports a continuous measure of expansion history paired with a mechanism-matched potency assay, but not passage number as a release criterion, nor claims that expansion causes transformation.

Keywords: Mesenchymal stromal cells; Replicative senescence; Serial passage; Methylation drift; Cell therapy manufacturing

Introduction

Human mesenchymal stromal cells (MSC) are defined operationally: plastic adherence, a surface immunophenotype, and trilineage differentiation in vitro [1]. No criterion reports how many divisions a preparation has spent, and all are satisfied by cultures close to growth arrest. Because a clinical dose of 100-200 million cells requires weeks of expansion, every therapeutic lot sits on a replicative trajectory ending in senescence, at a position invisible to the identity assay that releases it.

Replicative senescence is graded: Wagner and colleagues framed it as continuous and organized, with transcriptional and functional changes accumulating from the earliest passages rather than abruptly at the end [2]. A lot released at passage 4 therefore differs quantitatively from the same donor's cells at passage 2, and the marker panel must resolve a continuum, not a binary senescent/not-senescent call [3,4]. This review asks what the serial-passage literature has measured — replicative limits, telomere attrition, cytological markers, karyotypic drift, DNA-methylation change, functional decay — how dispersed it is, and which could serve as a release specification or potency-assay input.

The Replicative Limit Is a Distribution, Not a Constant

In bone-marrow MSC from eight healthy donors, Wagner and colleagues recorded 6-16 cumulative population doublings after the colony-forming step, plus an estimated 7-9 during colony formation — roughly 13-25 in total. Proliferation lasted 43-77 days in one medium and 74-104 days in a commercial formulation, so medium alone moved the endpoint by weeks [2]. A 12-donor cohort from the same group, stratified by age (four donors 21-25 y, four 44-55 y, four 80-92 y), gave 7-22 doublings post-colony, again plus 7-9, and senescence at 50-90 days [5].

Bonab and colleagues, in eleven bone-marrow donors (five female, six male; mean age 25 y, range 2.5-63 y), reported about 30 doublings over 130 days, range 26-32, mean culture duration 118 days, mean terminal passage 9; nine of the eleven survived 100-164 days, two arrested at 63-95 days [6]. Adipose preparations sit higher and wider. Schellenberg and colleagues found growth arrest in fourteen donors at 53.8 ± 14.4 doublings after 138 ± 20 days, one outlier reaching 85.9 doublings at passage 32 after 185 days [7]. Estrada and colleagues recorded 25.09 ± 1.6 doublings over 23 passages in five adipose preparations [8], and Legzdina and colleagues 14.69-28.97 doublings at senescence in the five of eight cultures that expanded, the other three arresting at 8.02-10.19 [9].

The spread within adipose tissue alone — 8 to 86 cumulative doublings — exceeds any reported adipose-marrow difference, so tissue source predicts expansion capacity weakly relative to donor and protocol. Some cultures fail before they senesce: the three Legzdina preparations stopping near 8-10 doublings are not late-passage cells, and pooling them with successful expansions would inflate the apparent variance of senescence [9]. Passage number is not a doubling count. Bonab and colleagues recorded 7.7 doublings before the first passage and 1.2 at the tenth [6]; a late passage carries roughly one sixth of the replicative content of an early one, so two lots labelled "passage 5" from different donors and seeding densities need not be biologically comparable.

Telomere Attrition and Cell-Cycle Inhibitors as Mechanistic Anchors

Human MSC lack detectable telomerase — Siegel and colleagues found none in 24 preparations from a cohort of 53 donors aged 13-80 y [10] — making progressive telomere loss the default. Attrition is modest. Bonab and colleagues reported mean telomere length of 9.19 kbp at passage 1 falling to 8.7 kbp at passage 9, roughly 100 base pairs lost every two passages [6]. Legzdina and colleagues, measuring relative length in adipose cultures at

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senescence, saw larger first-to-last-passage losses — 52.3 % in one culture, 35.8 % in another [9]. Baxter and colleagues concluded that even minimal-expansion protocols induce rapid ageing of marrow stromal cells, with losses of about half their total replicative lifespan [11]; no per-doubling rate is asserted here.

Table 1: Cumulative population doublings at growth arrest reported for human MSC by tissue source; the Wagner values include an estimated 7-9 doublings during initial colony formation [2,5,6,8,9,7].

Study	Tissue	N	Cumulative PD
Wagner 2008	Marrow	8	13 to 25
Wagner 2009	Marrow	12	14 to 31
Bonab 2006	Marrow	11	30 (26 to 32)
Estrada 2013	Adipose	5	25.09 +/- 1.6
Legzdina 2016	Adipose	5	14.7 to 29.0
Schellenberg 2011	Adipose	14	53.8 +/- 14.4

Telomere length is nonetheless a poor single-lot discriminator. Wagner and colleagues found only a weak tendency toward age-dependent shortening and no subpopulations with accelerated attrition [5], and Bertolo and colleagues no significant correlation between telomere length and an independent senescence readout across 16 bone-marrow and 6 adipose donors [12]. A signal of a few hundred base pairs against inter-donor variation of kilobases cannot be a release specification.

Shibata and colleagues established that p16INK4A tracks closely with MSC senescence and is potentially silenced by DNA methylation during expansion [13], and Bertolo and colleagues confirmed a significant late-passage rise in p16INK4A ($p = 0.017$) alongside significant declines in CDCA7, CDC2, p18INK4C and E2F1 ($p = 0.012$) [12]. Reported fold-changes for p16INK4A vary widely and none is quoted here; induction is reproducible in direction, but epigenetic as well as transcriptional regulation complicates use as a quantitative gauge.

Cytological Markers: What SA-beta-Galactosidase Actually Reports

Senescence-associated beta-galactosidase, introduced as a marker of senescent human cells in culture and ageing skin [14] and later standardised [15], remains the workhorse assay, with a large dynamic range in MSC. Estrada and colleagues measured 4.23 ± 1.6 % positive cells at passage 2 rising to 90.48 ± 3.29 % at passage 20 in five adipose preparations, while hTERT-transduced counterparts showed no activity even at late passage [8]. A roughly twenty-fold rise is a strong signal, but the trajectory saturates: at 90 % positive the assay can no longer distinguish degrees of exhaustion, and early in culture the difference between 4 % and 8 % is within donor-to-donor scatter. Choudhery and colleagues illustrate that scatter: 5.2 ± 1.9 % positive cells in adipose donors under 40 y versus 12.2 ± 1.1 % in donors over 50 y ($p < 0.05$) at comparable passage [16] — a baseline shift due to donor rather than expansion.

Morphometric readouts move in parallel. Legzdina and colleagues found large cells two- to three-fold larger than small ones (approximately 109-177 versus 47-59 arbitrary units) [9], and Yang and colleagues tracked the small-cell fraction from 86.7 % at passage 3 to 31.4 % at passage 8 in DMEM and from 85.5 % to 65.1 % in alpha-MEM in a single-donor series [17]. Siegel and colleagues found mean cell diameter of 20.9 ± 0.8 um in female versus 22.0 ± 1.1 um in male donors [10].

Bertolo and colleagues showed intrinsic autofluorescence correlating with X-Gal positivity (Kendall tau-b 0.672, $p < 0.001$), C12FDG fluorescence (0.703, $p < 0.001$), side scatter (0.839, $p < 0.001$) and cell volume (0.698, $p < 0.001$) across 16 bone-marrow donors of mean age 48 y (range 17-78) plus 6 adipose donors, eight with paired early (P1-P4) and late (P6-P15) passages [12]. Read on live, unstained cells, it suits in-process control.

Genomic Drift and the Transformation Literature

Estrada and colleagues quantified aneuploidy by interphase FISH from passage 2 to passage 20 in five adipose preparations: chromosome 8, 8.07 ± 0.89 % to

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18.65 ± 3.13 %; chromosome 11, 9.15 ± 0.76 % to 22.05 ± 2.73 %; chromosome 17, 11.74 ± 1.39 % to 27.56 ± 2.90 % [8]. Redaelli and colleagues observed one marrow donor accumulating trisomy 7 in 52 % of metaphases at passage 9 and 50 % at passage 12 [18]. Tarte and colleagues reported that aneuploidy arises during clinical-grade production without transformation [19], the frame the field has settled on.

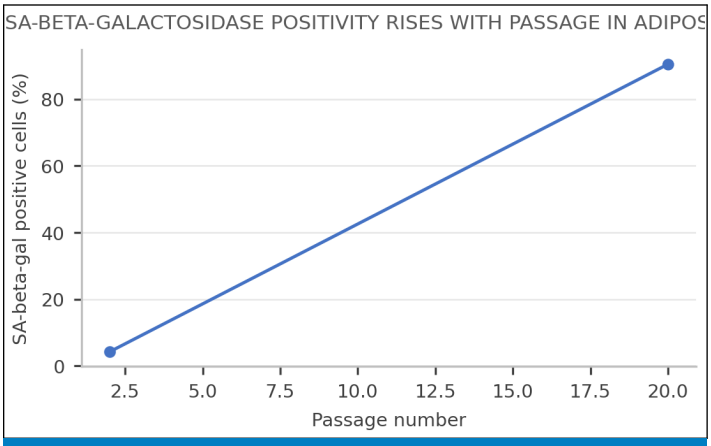

Figure 1: Senescence-associated beta-galactosidase positivity in adipose-derived human MSC rises from 4.23 +/- 1.6 % at passage 2 to 90.48 +/- 3.29 % at passage 20 [8], n = 5 independent cultures.

That frame required a correction of the record, frequently misstated since. Rubio and colleagues reported spontaneous transformation of human adult stem cells in long-term culture [20]; that paper was retracted, the retraction relation carrying the date 15 August 2010. Rosland and colleagues subsequently reported frequent spontaneous malignant transformation in long-term marrow MSC cultures [21]. That paper was not retracted. Its own authors corrected it in a 2010 letter to the same journal, attributing the phenotype to cross-contamination [22]. Conflating the two understates the corrected record's reliability and overstates the transformation risk of expanded MSC. What survives: expansion produces measurable karyotypic drift, drift is not transformation, and a karyotype specification is a poor gate but a reasonable characterisation endpoint.

Methylation Drift as a Quantitative Passage Meter

Schellenberg and colleagues, assaying 27,578 unique CpG sites, identified 517 consistently differentially methylated with senescence, 156 hyper- and 361 hypo-methylated; in passage 5 versus passage 10 alone, 233 sites were more than 15 % hyper-methylated and 186 more than 15 % hypo-methylated, the changes correlating with repressive histone marks [7]. Bork and colleagues had shown that long-term culture and donor ageing produce related but distinguishable patterns [23], and Franzen and colleagues that senescence-associated methylation is acquired stochastically in subpopulations rather than uniformly [24] — hence a bulk readout behaves like a continuous dose measure rather than a threshold.

Koch and colleagues distilled this into a six-CpG signature whose hyper- and hypo-methylation are linear in cumulative population doublings, regressed to predict a culture's doubling count [25,26]. The prediction error of that model is not quoted here. The signature is a mitotic clock, distinct from chronological DNA-methylation age estimators across human tissues [27]; a manufacturing assay wants expansion history, not donor age.

What This Means for Release Criteria and Potency Assays

Clonogenicity collapses before growth arrest: Schellenberg and colleagues found CFU-f frequency near 20 % at early passage and below 1 % after two months in the same 14-donor adipose cohort [7], and Legzdina and colleagues found colony counts correlating negatively with passage number ($p < 0.05$) [9]. DiGirolamo and colleagues showed that colony formation identifies samples with the greatest capacity to propagate and differentiate [28]. Differentiation output falls in step: in the single-donor Yang series, adipogenic LPL fell from 5865-fold at passage 4 to 356-fold at passage 8, PPAR-gamma from 16.1-fold to 6.7-fold, and osteogenic ALP was 14.3-fold higher at passage 4 than at passage 8, while CD146 fell from 95.1 % to 49.7 % [17]. Donor age moves the same endpoints

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before culture begins — Choudhery and colleagues found osteogenic Von Kossa staining of 20.0 ± 1.7 %, 15.2 ± 1.3 % and 8.9 ± 2.2 % and Alcian blue absorbance of 0.51 ± 0.06, 0.26 ± 0.04 and 0.17 ± 0.02 across young, adult and aged adipose donors [16] — and Stenderup and colleagues showed decreased maximal lifespan and accelerated senescence of marrow stromal cells with donor age [29].

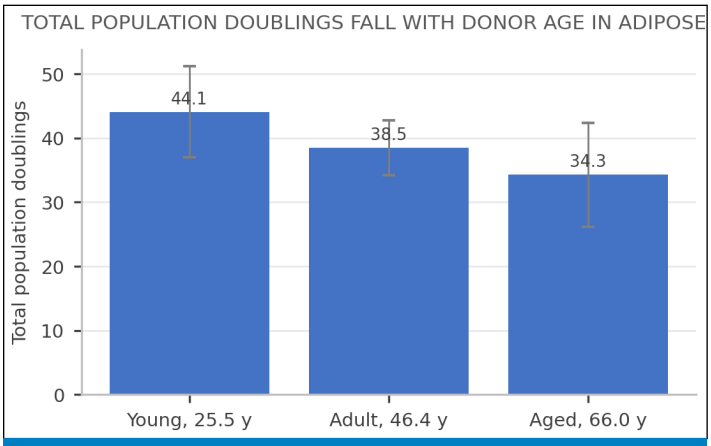

Figure 2: Total population doublings achieved by adipose-derived MSC stratified by donor age, mean +/- SD [16], n = 8 young, 10 adult and 11 aged donors.

For immunomodulatory products, Loisel and colleagues found that senescing clinical-grade marrow and adipose MSC inhibit T-cell proliferation less efficiently, through proteasomal degradation of indoleamine 2,3-dioxygenase, while their effect on NK and B cells is preserved [30]. Senescent MSC also secrete: the senescence-associated secretory phenotype is general to senescent cells [31], and Severino and colleagues showed that IGFBP4 and IGFBP7 released by senescent cells drive premature senescence in neighbouring MSC [32], so a partially senescent lot may propagate the phenotype.

Passage number should not be a release criterion: it is not a doubling count [6], and the limit varies several-fold between donors [7,9]. Cumulative population doublings, recorded prospectively, is better but still ignores the pre-passage colony-forming phase contributing an estimated 7-9 doublings [2,5]. A defensible panel would pair a continuous expansion-history readout — the six-CpG methylation clock [25], or live-cell autofluorescence for in-process control [12] — with a potency assay measured on the lot: for immunomodulatory products, the immune functional assays the International Society for Cellular Therapy has proposed as release criteria for advanced-phase trials [33]; for structural products, CFU-f plus a quantitative differentiation endpoint [28]. SA-beta-galactosidase belongs in characterisation, not release: informative in the middle of its range and uninformative at both ends [8,14].

Conclusion

Expansion capacity spans roughly 8 to 86 cumulative population doublings across cohorts, telomeres shorten measurably but weakly relative to inter-donor variation, SA-beta-galactosidase rises about twenty-fold but saturates, aneuploidy roughly doubles without progressing to transformation, and methylation drift accumulates linearly enough to be regressed on doubling count. Function — clonogenicity, differentiation output, and IDO-dependent T-cell suppression — declines earlier and more steeply than growth arrest. On every axis, within-source between-donor dispersion is as large as any between-source difference, which is why a fixed passage ceiling cannot substitute for a lot-specific measurement [3]. Table 2 sets the candidate readouts side by side with what each measures and the limitation that bears on its use as a specification. Release criteria should rest on a continuous measure of expansion history and a potency assay matched to the product's proposed mechanism; the remaining gaps — SASP output in MSC specifically, DNA-damage focus counts across passage, and the prediction error of epigenetic passage estimators — are what would make the specification enforceable rather than merely reasonable.

Table 2: Candidate senescence readouts in serially passaged human MSC, the quantity each measures, the passage-resolved change actually reported, and the limitation that bears on its use as a release criterion [8,6,7,25,12].

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Readout	Measures	Reported change with passage	Limitation as release criterion
SA-beta-galactosidase	Lysosomal senescence stain	4.23 +/- 1.6 % (P2) to 90.48 +/- 3.29 % (P20), n = 5	Saturates near 90 %; early range within donor scatter
Telomere length	Cumulative replication	9.19 kbp (P1) to 8.7 kbp (P9), n = 11	About 100 bp per two passages, far below inter-donor spread
Aneuploidy, chr 17 (FISH)	Genomic drift	11.74 +/- 1.39 % (P2) to 27.56 +/- 2.90 % (P20), n = 5	Roughly two-fold only; drift is not transformation
CFU-f frequency	Clonogenic potency	About 20 % early to below 1 % after two months, n = 14	Collapses well before growth arrest; no fixed cut-off set
Six-CpG methylation clock	Cumulative population doublings	Six CpG sites linear in cumulative doublings	Prediction error not established here
Autofluorescence	Live-cell senescence surrogate	Kendall tau-b 0.672 vs X-Gal, 0.839 vs side scatter, n = 16 + 6	Correlative only; no correlation with telomere length

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