The Impact of Advanced Glycation End-Products (AGEs) on Proliferation and Apoptosis of Primary Stem Cells: A Systematic Review

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Stem cell-based regenerative therapies hold great promises to treat a wide spectrum of diseases. However, stem cell engraftment and survival are still challenging due to an unfavorable transplantation environment. Advanced glycation end-products (AGEs) can contribute to the generation of these harmful conditions. AGEs are a heterogeneous group of glycated products, nonenzymatically formed when proteins and/or lipids become glycated and oxidized. Our typical Western diet as well as cigarettes contain high AGEs content. AGEs are also endogenously formed in our body and accumulate with senescence and in pathological situations. Whether AGEs have an impact on stem cell viability in regenerative medicine remains unclear, and research on the effect of AGEs on stem cell proliferation and apoptosis is still ongoing. Therefore, this systematic review provides a clear overview of the effects of glycated proteins on cell viability in various types of primary isolated stem cells used in regenerative medicine.

1. Introduction

Regenerative therapies, including stem cell treatments, hold a high potential for treating patients with a spectrum of diseases. Stem cells can stimulate endogenous tissue repair mechanisms or replace damaged, necrotic tissue [1]. Stem cells are defined as undifferentiated cells with unlimited self-renewing capacity. They have the potential to form identical clones throughout the symmetrical division but can also differentiate into multiple cell types depending on the stem cell potency [1]. The source of stem cells is diverse as they can be found throughout the body in embryonic, fetal, and adult stages [2]. Because stem cells are the building blocks of organs and tissues, they are interesting candidates for regenerative medicine in order to repair multiple types of injuries [3]. For example, mesenchymal stem cells (MSCs) have the potential to differentiate into adipose, bone, or cartilage tissue, which makes them attractive candidates for the regeneration of these tissues in multiple diseases or injuries such as metabolic bone diseases or osteoarthritis [4–6]. Neural stem cells (NSCs) are adult precursor cells, therapeutically relevant in diseases of the brain and central nervous system, such as Alzheimer’s disease or stroke [7]. Adipose tissue-derived stem cells (ADSCs), a specific type of MSCs isolated out of the adipose tissue [8], have been found to modulate inflammation, thereby promoting chronic wound healing [9]. Endothelial precursor cells (EPCs) are found in the bone marrow or blood and are capable of migrating towards lesions due to tissue ischemia or traumatic injury [10]. In addition, EPCs are involved in endothelial repair in patients with diabetes and atherosclerosis. Finally, blood-derived stem cells (BDSCs) are used in the clinic to restore the hematopoietic system in the blood and bone marrow malignancies or in autoimmune diseases [11]. However, despite their promising paracrine effects, differentiation, and migration capacities for repairing injured tissue, transplantation of stem cells remains challenging due to low cell engraftment, low cell survival, and suboptimal transplantation conditions [12].
Oxidative stress, presence of inflammatory cytokines, and/or advanced glycation end-products (AGEs) contribute to the generation of the harmful environment in which stem cells need to be transplanted and survive.

AGEs are a heterogeneous group of glycated proteins. They are formed when reducing sugars or aldehydes nonenzymatically react with proteins and lipids during posttranslational modifications [13]. Highly reactive dicarbonyl compounds, such as glyoxal or methylglyoxal, which can be oxidized by aldehydes and ketones, are also AGEs precursors [14]. AGEs can be endogenously formed in our body during hyperglycemia via the Maillard reaction and in situations of increased oxidative stress, such as increased levels of hydroxy radicals or decreased antioxidants, typically seen in an injured tissue. In addition, AGEs can also be absorbed via dietary compounds, especially when food is rich in both fat and proteins or cooked at high and dry heat [15].

2.1. Literature Search Identification. The primary objective of this systematic review was to assess the impact of AGEs on stem cell viability and proliferation of different primary stem cell types, by identifying the PICO elements (P = population: primary stem cells, I = intervention: AGEs, C = comparison: to control, and O = outcome: stem cell viability, proliferation, and apoptosis) [33]. In this systematic review, databases were searched for articles published from inception until the 27th of October 2020. The electronic databases PubMed and Web of Science were used with the following mesh terms 'Glycation End Products, Advanced' OR 'Stem Cells' and the following keywords: (Advanced Glycation End Product OR Advanced Glycation End Products OR Advanced Glycation End-Product OR Advanced Glycated End Product OR Advanced Glycated End Products OR Advanced Glycated End-Product OR Advanced Glycated End Products OR Glycated Protein OR Glycated Proteins) AND (Stem Cell OR Stem Cells OR Progenitor Cell OR Progenitor Cells).

2.2. Inclusion and Exclusion Criteria. After database searching in Pubmed and Web of Science, 339 abstracts of articles were included in the screening procedure. Articles were excluded based on different criteria: (1) articles with AGEs, RAGE, or stem cells as outcome measurements; (2) effects on other cell types than stem cells or progenitor cells; (3) articles about RAGE or diabetes and not AGEs; (4) articles with AGEs used as a diabetic model; (5) reviews; (6) book chapters; (7) announcements; (8) retracted papers; and (9) articles written in other languages than English. 75 full-text articles were assessed for eligibility. When experiments were performed on primary stem cells, but on stem cell lines or when stem cells are provided and material and methods lack isolation procedure, articles were excluded. When outcome measurements were different from viability, proliferation,
or apoptosis, articles were also excluded. Finally, 37 studies were included in this review.

2.3. Data Extraction, Analysis, and Quality Assessment. Results of the search were manually screened and are shown in Figure 1. Literature searches were independently performed by two reviewers (LE and HB). In case of disagreement, a consensus-based decision was made by the two reviewers to include/exclude an article. Data about the effect of AGEs on proliferation and apoptosis of different types of primary stem cells were analysed. Data were grouped based on stem cell type/isolation source: blood-derived stem cells (Table 1), endothelial progenitor cells from the bone marrow (Table 2), mesenchymal stem cells (Table 3), adipose tissue-derived stem cells (Table 4), and neural stem cells (Table 5). Because there is no standardized protocol for quality assessment for in vitro studies, the study quality of the selected full-text articles was assessed by two reviewers (LE and HB). When both reviewers judged the quality of study design to be inappropriate, articles were removed. Due to the high heterogeneity of the data (i.e., outcome measures, AGEs exposure duration, AGEs concentration, and experimental protocols), a meta-analysis could not be generated.

3. Results

3.1. Study Selection and Flow Diagram. The electronic databases PubMed and Web of Science were used to identify all articles regarding the impact of AGEs on primary stem cell proliferation and apoptosis. Study selection and flow chart diagram are shown in Figure 1. 222 and 262 articles were identified through database searching in PubMed and Web of Science, respectively. 145 duplicates were removed ending up to 339 articles being screened. 264 articles were excluded after screening. Then, 75 full-text articles were assessed for eligibility, resulting in the exclusion of 38 more articles. 20 articles about stem cells derived from cell lines or provided stem cells (with methods of isolation lacking) and 18 articles in which experiments about stem cell viability, proliferation, or apoptosis were not assessed were excluded. 37 studies were therefore included in this review.

3.2. Study Results

3.2.1. Blood-Derived Stem Cells. Blackburn et al. [34] investigated the effect of AGEs on peripheral blood mononuclear cells (PBMCs, Table 1). PBMCs were isolated from peripheral blood samples of healthy humans and cultured on 1 mM methylglyoxal- (MGO-) modified collagen gels for 4 days. Culturing PBMCs on MGO-modified collagen gels led to a decrease in cell number. In addition, endothelial progenitor cells (EPCs), a specific type of PBMCs, were investigated [1]. Isolation of EPCs from blood samples was performed by gradient density centrifugation [35–43] (Table 1). Regarding the origin of blood, one study isolated EPCs from umbilical cord blood [37] while in all other studies peripheral blood was used [35, 36, 38–44]. The concentration of AGEs application ranged from 2 μg/ml to 400 μg/ml. In addition, stimulation time varied from 1 up to 7 days. The effect of AGEs on EPCs from the blood are inconsistent. Bhatwadekar et al. [35], Chang et al. [36], Chen et al. [44], Li et al. [38], Liang et al. [39], Shen et al. [41], and Sun et al. [42] reported a decrease in cell proliferation and/or an increase in apoptosis of EPCs after exposure to AGEs. As opposed to these findings, Scheubel et al. [40] observed an increased EPCs proliferation after stimulation with a low dose of AGEs (20 μg/ml). However, at higher concentrations (200 μg/ml), AGEs caused a decrease in proliferation together with an increase in apoptosis. Zhu et al. [43] reported AGEs to have no effect on EPCs apoptosis but caused a decrease in proliferation, while Chen et al. [37] observed no effect of AGEs on EPCs proliferation but an increase in EPCs apoptosis. Concisely, compared to control conditions, all studies show that AGEs alter proliferation or stimulate apoptosis in EPCs derived from the blood.

3.2.2. Endothelial Progenitor Cells Isolated from Bone Marrow. Isolating EPCs from the bone marrow is a standardized procedure [45–52] (Table 2), in which the tibia or femur of rodents (rats or mice) were flushed with media or PBS. AGEs were applied to EPCs in a fixed [46, 49] or dose-dependent [45, 47, 48, 50] manner, with concentrations ranging from 50 to 500 μg/ml. The EPCs exposure time of 24 hours was the same in all studies, except for Zeng et al. [51], in which EPCs were stimulated for 48 hours. Wang et al. [52] stimulated in a time-dependent manner up to 48 hours. An increased apoptosis [16–18, 20–22] associated or not with a decrease in cell proliferation [16–19, 22, 23] as a result of AGEs exposure was reported in these studies. In short, AGEs negatively impact cell proliferation and increase apoptosis of EPCs isolated from the bone marrow.

3.2.3. Mesenchymal Stem Cells. Nine articles have studied the effect of AGEs on mesenchymal stem cells (MSCs, Table 3) derived from BM, tendons, periodontal ligament, or the pancreas. Despite differences in the concentration (25 up to 800 μg/ml) and duration (6 hours up to 19 days) of AGEs exposure, a decrease in proliferation associated or not with an increase in apoptosis, was observed in 7 out of 9 studies [53–60]. In contrast, Sakamoto et al. [56] observed a trend of decreased proliferation of MSCs by AGEs, but results did not reach significance. Duruksu and Aciksari [61] investigated MSCs isolated from pancreatic islet explants and cultured the cells on plates coated with modified collagen. In contrast with other studies, pancreatic MSCs showed an increase in proliferation when cultured on AGEs-modified collagen.

3.2.4. Adipose Tissue-Derived Stem Cells. Five publications reported the effect of AGEs on adipose tissue-derived stem cells (ADSCs, Table 4). ADSCs are a type of MSCs, isolated from adipose tissue samples of humans [62–64], mice [65], and rats [66] by enzymatic dissociation with collagenase. Irrespective of the differences in concentration (20 up to 1600 μg/ml) and duration (8 hours up to 7 days) of AGEs application, Li et al. [62] and Wang et al. [63, 64] reported an increase in apoptosis. Li et al. [65] and Zhang et al. [66] reported a decrease in proliferation. Taken together, AGEs have deleterious effects on ADSCs viability.
3.2.5. Neural Stem Cells. Neural stem cells (NSCs) were investigated in four articles (Table 5). Brain tissues were isolated from rats to obtain cultures of proliferative neurospheres. Fleitas et al. [67] cultured NSCs for 6 days with 50 μM MGO or glyoxal- (GO-) modified proteins. Meneghini et al. [68] and Wang et al. [69, 70] applied AGEs in concentrations ranging from 25 to 400 μg/ml for 3 up to 7 days to NSCs. Fleitas et al. [67] observed apoptosis in NSCs due to modified proteins. The articles from Wang et al. [69, 70] reported a decrease in proliferation of NSCs after AGEs application, while Meneghini et al. [68] observed an increased proliferation.

4. Discussion

4.1. Effect of AGEs on Primary Stem Cell Proliferation and Apoptosis. According to this systematic literature review, AGEs cause a significant decrease in proliferation or an increase in apoptosis of BDSCs, ADSCs, and EPCs. In MSCs, a reduced stem cell viability was observed in 8 out of 9

**Figure 1:** Flowchart summary of the search and selection of the included articles. AGEs: advanced glycation end-products; RAGE: receptor for AGEs; PC: progenitor cells; SC: stem cells; BM: bone marrow.
studies. In NSCs, we can conclude that glycated proteins induce a decrease in proliferation or increase in apoptosis in 3 out of 4 articles. In short, our study reveals that AGES are deleterious and alter the proliferative capacity of primary isolated stem cells in 35 out of 37 articles.

Compared to the results of other studies examining the effect of AGES on MSCs, the controversial results of Duruksu and Aciksari [61] are likely due to the low concentrations of AGES products used, i.e., 10 μg/cm²-modified collagen, while the concentration of AGES in other in vitro studies is

| Study name         | Year | Isolation SC/PC | AGES application Concentration | Duration | Effect on outcome |
|--------------------|------|-----------------|--------------------------------|----------|------------------|
| Bhatwadekar et al. [35] | 2008 | Human EPCs–peripheral blood, DGC | Fibronectin coated with 10, 50, & 100 μM MGO | 24 hours | ↘ |
| Blackburn et al. [34] | 2017 | Human PBMC–peripheral blood, DGC | Collagen type I gel +1 mM MGO | 4 days | ↘ |
| Chang et al. [36] | 2017 | Human EPCs–peripheral blood, DGC | 500 μg/ml | 24 hours | ↘ |
| Chen et al. [37] | 2009 | Human EPCs–umbilical cord blood, DGC | 50, 100, 200, & 400 μg/ml | 24 hours | - ↘ |
| Chen et al. [44] | 2019 | Human EPCs–peripheral blood, DGC | 200 μg/ml | 48 hours | ↘ |
| Li et al. [38] | 2016 | Human EPCs–peripheral blood, DGC | 50, 100, & 200 μg/ml | 24, 48, and 72 hours | ↘ |
| Liang et al. [39] | 2009 | Human EPCs–peripheral blood, DGC | 50, 100, & 200 μg/ml | 7 days | ↘ |
| Scheubel et al. [40] | 2006 | Human EPCs–peripheral blood, DGC | 2, 20, & 200 μg/ml | 7 days | Low conc. ↗, high conc. ↘ |
| Shen et al. [41] | 2010 | Human EPCs–peripheral blood, DGC | 2, 20, & 200 μg/l | 24, 48, and 72 hours | ↘ |
| Sun et al. [42] | 2009 | Human EPCs–peripheral blood, DGC | 200 μg/ml | 24 hours | ↘ |
| Zhu et al. [43] | 2012 | Human EPCs–peripheral blood, DGC | 15 to 3704 μg/l or 250 to 1000 μg/l | 24, 48, and 72 hours | ↘ |

SC: stem cell; PC: progenitor cells; ↘: decrease; ↗: increase; -: no effect; EPCs: endothelial PC; PMBC: peripheral blood mononuclear cell; DGC: density-gradient centrifugation; MGO: methylglyoxal.

| Study name         | Year | Isolation PC | AGES application Concentration | Duration | Effect on outcome |
|--------------------|------|--------------|--------------------------------|----------|------------------|
| Chen et al. [45] | 2010 | Rat–bone marrow, DGC | 50, 100, 150, 200, & 400 μg/ml | 24 hours | ↘ |
| Chen et al. [46] | 2016 | Rat–bone marrow, DGC | 400 μg/ml | 24 hours | ↘ |
| Jin et al. [47] | 2018 | Mice–bone marrow, DGC | 100, 200, & 400 μg/ml | 24 hours | ↘ |
| Kim et al. [48] | 2018 | Mice–bone marrow, DGC | 250, 500, 600, & 750 μM | 24 hours | ↘ |
| Li et al. [49] | 2017 | Rat–bone marrow, DGC | 200 μg/ml | 24 hours | ↘ |
| Li et al. [50] | 2012 | Rat–bone marrow, DGC | 50, 100, 200, & 500 μg/ml | 24 hours | ↘ |
| Zeng et al. [51] | 2017 | Rat–bone marrow | 200 μg/ml | 48 hours | ↘ |
| Wang et al. [52] | 2019 | Rat–bone marrow, DGC | 100, 200, & 400 mg/l | 12, 24, and 48 hours Low conc. ↗, high conc. ↘ |

PC: progenitor cells; ↘: decrease; ↗: increase; DGC: density-gradient centrifugation.
generally ranging up to 500 μg/ml. This was confirmed by Scheubel et al. [40] and Wang et al. [52]. Low concentrations of AGEs induce cell proliferation in EPCs, whereas at higher concentrations, they decrease the proliferative capacity of these cells. The concentrations of AGEs used in several in vitro studies are varying but generally reflect the physiological concentration of AGEs found in samples of patients. Indeed, AGEs-albumin concentration in diabetic patients has been shown to range from 50 to 400 μg/ml [71, 72]. In patients suffering from cardiovascular diseases, AGEs levels can rise to concentrations up to 200 μg/ml [73]. Other studies report lower AGEs concentrations in vivo in the range of several ng/ml, for example, in patients with early-stage Alzheimer’s disease [74]. However, estimation of reliable AGEs concentrations in vivo is challenging, because of the heterogeneity of different types of AGEs and the different analytical methods used for measuring these AGEs [75].

Therefore, investigating a broad range of AGEs concentrations in vitro is necessary. Furthermore, in in vitro experiments, stem cells are exposed to AGEs in short term, while in several diseases, stem cells are exposed to AGEs for months or years. Therefore, subjecting these cells to higher concentrations of AGEs in vitro compared to the in vivo situation remains relevant [48]. In the same line of controversial results, Meneghini et al. [68] reported an increase in NSC proliferation after AGEs application, with concentrations ranging from 25 to 100 μg/ml. A possible explanation for these controversial results could be, as stated in their article, that AGEs and other ligands of the RAGE receptor like HMGB1 and S100 calcium-binding protein B, are enhancing stem cell proliferation. Due to traumatic or ischemic brain injury, the binding of these specific ligands to the RAGE receptor can activate the NF-κB signaling pathway, thereby inducing endogenous

| Study name          | Year | Isolation SC                  | AGEs application           | Duration       | Effect on outcome |
|---------------------|------|-------------------------------|----------------------------|----------------|------------------|
| Durusku et al. [61] | 2018 | Rat–pancreatic islets explants | Modified collagen 10 μg/cm² | 24, 48, & 62 hours | ↗               |
| Fang et al. [53]    | 2020 | Human–periodontal ligament    | 100 μg/ml                  | 1 to 7 days    | ↘               |
| Kim et al. [54]     | 2013 | Rat–bone marrow               | 300 μg/ml                  | 24 hours       | ↗               |
| Lu et al. [55]      | 2012 | Human–bone marrow             | 25, 50, 100, 200, 400, & 800 μg/ml | 6, 12, 24, 48, 72, & 96 hours | ↘               |
| Sakamoto et al. [56]| 2016 | Rat–bone marrow               | 500 μg/ml                  | 7, 11, 13, 16, & 19 days | -               |
| Sun et al. [57]     | 2013 | Rat–bone marrow               | 50, 100, 200, & 400 μg/ml AOPPs | 24, 48, & 72 hours | ↘               |
| Weinberg et al. [58]| 2014 | Rat–bone marrow stromal cells | 50, 100, 200, & 400 μg/ml | 16 hours       | ↗               |
| Xu et al. [59]      | 2019 | Rat–Achilles tendons          | 100, 200, & 400 μg/ml      | 24 hours       | ↗               |
| Yang et al. [60]    | 2010 | Rat–Bone marrow               | 25, 50, 100, & 200 μg/ml   | 6, 12, & 24 hours | ↘               |

SC: stem cells; AOPPs: advanced oxidation protein products; ↘: decrease; ↗: increase; -: no effect.
4.2.1. AGEs Activate the Intrinsic and Extrinsic Apoptosis Pathways

How AGEs interfere with the various apoptosis pathways is depicted in Figure 2. Wang et al. [69, 70] reported a decrease in proliferation of NSCs via PPARγ inhibition. PPARγ is responsible for blocking the caspase cascade in both the extrinsic and intrinsic apoptosis pathways (Figure 2) [78]. AGEs downregulate PPARγ protein expression, which causes a release of caspase blockage, resulting in apoptosis stimulation. AGEs can interact with RAGE in order to activate multiple cellular signaling cascades, including MAP kinase (MAPK) pathways [79]. PPARγ phosphorylation is therefore increased, resulting in a decrease of PPARγ transcriptional activity. Indeed, it has been shown that PPARγ agonists like rosiglitazone [39] or pioglitazone [59], added to in vitro cultures of EPCs and MSCs, respectively, reverse the deleterious effects of AGEs via PPARγ activation. This is also confirmed in other cell types like chondrocytes [79], macrophages, or endothelial cells [80].

Apoptosis can also be induced via the intrinsic mitochondrial pathway (Figure 2) [78]. Bax, a proapoptotic, and Bcl-2, an anti-apoptotic regulatory protein, are involved in this pathway. Li et al. [49] identified that this intrinsic pathway was activated in MGO-stimulated EPCs via the reduction of miRNA-27. miRNA-27 is antagonizing this intrinsic apoptosis pathway. If AGEs downregulate miRNA-27, the apoptotic pathway is stimulated in an indirect manner. These data were confirmed by Jin et al. [47]. Another indirect way of inducing apoptosis is via Akt signaling. Chen et al. [37] showed that AGEs downregulate Akt, which is normally responsible for the inhibition of caspase activation [81]. AGEs exposure can also lead to increased Bax expression and to a reduction of Bcl-2 expression, stimulating apoptosis in EPCs [44].

4.2.2. RAGE Activation Leads to MAP Kinase Activation and Generation of ROS

Figure 3 shows how activation of RAGE can induce apoptosis and reduce proliferation through the activation of several MAPK pathways. Zhang et al. [66] and Wang et al. [63, 64] reported activation of the AGEs/RAGE signaling pathway in ADSCs after exposure to AGEs. Binding of AGEs to their receptor RAGE activates the JNK and p38/MAPK pathways (Figure 3). Phosphorylation of JNKs and p38 causes upregulation of proapoptotic transcription factors in the nucleus, leading to an increase in apoptosis [82, 83]. In EPCs [41, 42, 46] and MSCs [53, 54, 58, 60], JNK/MAPK pathways are also activated by AGEs, leading to an increase in apoptosis. In addition, AGEs activate the MAPK pathways via excessive ROS generation. AGEs can decrease the availability of antioxidant enzymes, leading to increased oxidative stress [36, 38, 45]. Furthermore, RAGE activation by AGEs can directly induce activation of NADPH oxidase, leading to formation of ROS [84]. Next to the damaging effects of ROS on DNA and proteins, oxidative stress can also be a trigger for activating apoptosis via the JNK and p38/MAPK pathways. In MSCs and EPCs, excessive ROS production is thought to be responsible for the inhibitory effect of AGEs on stem cell proliferation [51, 55, 57].

Zhu et al. [43] investigated the effect of AGEs on the ERK/MAPK pathway. The ERK/MAPK pathway, in contrast to the JNK and p38/MAPK pathways, is responsible for cell growth (Figure 3) [85]. Activation of ERK via phosphorylation causes translocation to the nucleus where it induces transcription of factors related to cell growth and proliferation [86]. Zhu et al. [43] reported that AGEs caused less activation and phosphorylation of ERK, leading to decreased activation of growth transcription factors, resulting in a reduced proliferation.

4.2.3. AGEs Induce Changes in Extracellular Matrix Composition and Stem Cell Attachment

Blackburn et al. [34] suggest that changes in extracellular matrix (ECM) proteins play a key role to induce stem cell dysfunction. AGE-modified ECM has been shown to support less adhesion and retention of the stem cells, thereby causing detachment of stem cells which results in cell death [34]. In addition, the inhibitory effect of AGEs on EPCs derived from blood repair [68]. By increasing stem cell proliferation via the NF-kB axis, damaged neurons and glia cells are replaced to repair the injured regions after brain injury. In line with these findings and hypothesis, Romanko et al. [76] and Jin et al. [77] also reported that neural progenitor cells in the subventricular zone proliferate and replace damaged neural cells after moderate brain insults.
is also due to the modification of cell attachment and decreased capacity to adhere [40]. A possible underlying mechanism is that, at the site of injury, the recruited progenitors need to adhere to the preexisting vascular cells. AGEs block the RGD domain, a peptide sequence which is recognized by cell surface integrins. Therefore, EPCs cannot
attach, spread, or migrate, leading to a decrease in their proliferative capacities [35].

4.2.4. Alternative Signaling Pathways Affected by AGEs. According to Fleitas et al., [67] AGEs inhibit the processing from probrain-derived neurotrophic factor (pro-BDNF) to mature BDNF. BDNF is involved in neurotropic signaling including differentiation, survival, and synaptic plasticity of various populations of nerve cells, involved in tissue repair. Therefore, an increase in AGEs possibly cause an increased pathogenicity.

In addition, activation of RAGE can lead to the synthesis of miRNAs in stem cells known to regulate apoptotic signaling via intracellular ROS production. Li et al. [62] have found that miR-5591-5p is upregulated in ADSCs, when stimulated with AGEs. In the future, more insights on miRNA-mediated effects on stem cells is necessary, as it has been shown that microRNAs are key regulators in self-renewal processes in different types of stem cells [87].

4.3. Different Strategies to Improving Viability of Stem Cells by Tackling AGEs. AGEs have detrimental effects on the viability of various primary stem cell types. However, tackling the deleterious effects of AGEs on stem cells is until now neglected but could potentially improve stem cell retention and viability. This could be achieved by several strategies, suggested by several studies [88], which are summarized in Figure 4. A first option is blocking RAGE with different synthetic small molecules [89], RAGE inhibitors such as FPS-ZM1 [90] or anti-RAGE antibodies [91]. Consequently, downstream pathways in the RAGE axis are not activated. Thereafter, directly blocking proteins involved in the apoptotic or RAGE pathway could be a way to interfere in the molecular pathways activated by AGEs. For example, MAPK can be targeted in order to block cellular signaling [92]. However, clinical trials reveal issues which relate to limited drug efficacy and toxicity of these compounds. AGEs and their precursors can also be directly inhibited or scavenged [93]. By increasing sRAGE, AGEs are trapped, RAGE is not activated, and the mediated signaling is attenuated. In addition, AGEs can also be broken down or AGEs formation can be suppressed [94]. Finally, ROS scavengers or antioxidants like N-acetylcysteine (NAC) can reduce oxidative stress levels and might interfere in the AGEs pathway. By these interventions, stem cell properties and viability could be improved. Such approaches require scientific proof but could open new therapeutic insights into stem cell transplantation as an effective regenerative therapy.

5. Conclusion

AGEs are increased in a lot of pathological situations and have detrimental effects on various tissues and cell types. In this systematic review, we show that AGEs impair the proliferation and apoptosis on different types of primary stem cells in vitro. These effects can be executed throughout several underlying mechanisms such as activation of RAGE or apoptotic pathways and excessive ROS generation. In the future, tackling this negative impact of AGEs on stem cells could improve stem cell properties, retention, and viability. Such approaches require solid scientific proof but could open new therapeutic insights into stem cell transplantation as an effective regenerative therapy.

**Abbreviations**

- **ADSCs**: Adipose tissue-derived stem cells
- **AGEs**: Advanced glycation end-products
- **AOPPs**: Advanced oxidation protein products
- **BDNF**: Brain-derived neurotrophic factor
- **BDSCs**: Blood-derived stem cells
- **BM**: Bone marrow
- **CML**: N(6)-carboxymethyllysine
- **DGC**: Density-gradient centrifugation

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**Figure 4**: Strategies to tackle the effect of AGEs (88). AGEs lead to an increase in apoptosis or a decrease in proliferation via different pathways. This process can be tackled by different cellular approaches including scavenging, breaking down, or inhibiting AGEs and their precursors. RAGE can be directly blocked, or the downstream effectors can be inhibited. Oxidative stress can be reduced by antioxidants and ROS scavengers.
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