

Advancement in Stem Cell Therapy for Ischemic Myocardial Cell: A systematic Review

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ABSTRACT

Background: Cardiac muscle possesses a limited capacity to regenerate its tissue on its own. It is less likely to reverse the altered cardiac functioning to its normal physiological state after a major myocardial infarction. Stem cell transplantation provided a unique therapeutic approach in managing such injuries. There has been a substantial debate about the complexity, scope and medical application of stem cell transplantation in past few years.

Materials and Methods: An extensive review of medical literature was conducted to establish the consensus about the possible mechanism of cell renewal, associated complications and risks of failure of this technique. Twenty cases of mammalian animals and twenty-four cases of stem cell transplantation in human subjects were reviewed.

Results: Most common associated complication was re-stenosis of coronary artery. Few clinical trials reported the failure in improving cardiac functioning. The success rate of stem cell transplantation was remarkable in the literature related to experimental animal subjects.

Conclusion: It was concluded that renewal of the cardiac cell is a result of induction of angiogenesis and prolonged cell survival. This topic still requires an immense amount of research to fill the gap in adequate knowledge.

Keywords: Mesenchymal stem cells (MSCs), Myocardial infarction (MI), Cardiomyocytes, Hematopoietic stem cells (HSCs)

INTRODUCTION

Recent classification of stem-cells has divided it into three generations. First generation includes skeletal myoblasts (SMs), bone marrow mononuclear cells (BMMNCs), hematopoietic stem cells (HSCs), endothelial progenitor cells (EPCs) and mesenchymal stem cells (MSCs). Second generation has cardiopoietic MSCs (cpMSCs), cardiac progenitor cells and induced pluripotent stem cells (iPSCs). Next generation therapy includes cell enhancement approaches and cell-free approaches¹. Mesenchymal

stem cells or bone marrow cells are multipotent adult stem cells that have potential to differentiate into a variety of lineages². Cardiac tissue possesses a transient regenerative capacity which eventually ends up with scarring of damaged tissue. But MSCs are capable enough to differentiate into endothelial cells, vascular smooth muscle cells and perhaps even cardiac myocyte. Origin of the cells in the forming myocardium was determined by expression of EGFP. Its expression was combined with the labeling protein specific for myocytes, endothelial cells and

smooth muscle cells. The percentage of new myocytes, endothelial cells and the smooth muscle cells expressing EGFP was 53% (n=7), 44% (n=7) and 49% (n=7), respectively³.

A study conducted by Nagaya N et al. demonstrated in a rat model that after intravenous infusion, preferential site of attraction for MSCs were ischemic myocardial tissue. It differentiated into vascular endothelium cells and cardiomyocytes. The possible mechanism behind the reduction of infarct size, improved cardiac functions after acute MI and increment in capillary density was the induction of angiogenesis and myogenesis. It was believed that von Willebrand factor has a positive role in induction of new myocardial tissue⁴. Biodistribution of MSCs depends upon the route of administration. Endocardial (EC), intracoronary (IC) and intravenous (IV) infusion are common courses to deliver stem cells. A study on porcine MI model concluded that IC and EC infusion of MSCs in post-MI subjects resulted in increased engraftment when compared with intravascular infusion⁵.

Stem cell transplantation has been emerging as a new therapeutic intervention for different fields of medicine. But, a major dilemma in stem cell therapy for ischemic heart diseases is the low survival of transplanted cells in the peri-infarcted region. Number of pilot studies on MSCs transplantation demonstrated the failure of such intervention. Some studies reported the failure of transplantation within a week, while other reported that most implanted cells may die within 4 days after infusion into the ischemic heart. Electron microscopy revealed that dead cells had features of both irreversible ischemic injury and apoptosis^{6,7}.

The purpose of our study is to assess the advancements in stem cell transplantation, causes of its failure and the associated adverse outcomes.

MATERIALS AND METHODS

Several different methods can be found in the vast literature on stem cell therapy, but only particular introduction methods of cardiac stem cell were highlighted in the literature from past few decades.

Most common deployment techniques are introduction of stem cell via catheter or a 22-gauge needle which are minimally invasive techniques. However, different sites of implantation are found in literature review.

In one study conducted in 2004, Shao-liang C et al. injected autologous mesenchymal cells into coronary artery along with normal saline. It was introduced 12 hours after PCI was done and showed much improvement in left ventricular function⁸. A double-blind, randomized, controlled trial conducted in 2006 discussed 3 separate methods of MSC introduction in swine. Stem cell was delivered via IV infusion in ear vein catheter, intracoronary infusion after balloon inflation and an endocardial infusion into the infarcted areas. IC infusion showed much promising results as compared to EC and IV methods⁵. In another method discussed in 2003, transendocardial delivery of MSCs was performed using NOGA catheter after left heart catheterization⁹. A prospective randomized study done in 2005 used novel epicardial technique to deploy autologous MSCs via 22-gauge needle. Autologous MSC tissue was extracted from iliac crest bone marrow¹⁰. To the best of our knowledge, no non-invasive technique is currently present to transplant cardiac stem cells.

RESULTS

After the approval of this study from the Ethical Review Board of Jinnah Medical and Dental College, literature search was conducted on Pub-med, Embase and Google scholar on the literature which was published from January 1999 to January 2017. Details are given in Table 1 and Table 2. No limitation of age in human subjects and type of animal in mammalian subjects was established. The research was limited to humans and other mammalian animals. Only English medical literature was included in our review. The key MeSH and non-MeSH terms used were 'Mesenchymal stem cells (MSCs)', 'Myocardial infarction (MI)', 'Cardiomyocytes', 'Hematopoietic stem cells (HSCs)'.

Table 1: Reported cases of stem cell transplantation in animal subjects

Author/ Year of Publication	Animal Subject	Method of MI Induction	Type of Stem Cells Injected	Follow-up	Hemodynamic status	References
Dai, W., et al/ 2005	Rat	Left coronary artery ligation	MSCs	6 months	LVEF: improved After 4 week = 43.8% At 6 months= 41.8%	(35)
Nagaya, N., et al/ 2004	Rat	Left coronary artery ligation	MSCs	4 weeks	LVEF= improved About 53%	(4)
Silva, G.V., et al/ 2005	Dog	Left coronary artery ligation	MSCs	60 days	LVEF: improved 30 days after intramyocardial injection At rest= 48% With stress=27%	(36)
Bel, A., et al/ 2003	Sheep	Left circumflex artery	BM-MNC	8 weeks	LVEF= improved from 13% to 65%	(37)
Davani, S., et al/ 2003	Rat	Left coronary artery ligation	MPC	30 days	LVEF= improved About 43%	(38)
Ghostine, S.d., et al/ 2002	Sheep	Circumflex coronary artery catheterization	Skeletal myoblasts	1 year	LVEF= improved about 48%	(39)
Jian-an, W., et al/ 2005	Rabbit	Left coronary artery ligation	HMSCs	4 weeks	LVEF: improved Before operation=0.79+/- 0.07% After operation=0.66+/- 0.04 %	(40)
Brasselet, C., et al/ 2005	Sheep	Left coronary artery ligation	Skeletal myoblast	8 weeks	LVEF= improved From 47% to 54%	(41)
de Silva, R., et al/ 2008	Pig	LAD	BM-MNC	6 weeks	LVEF= improved From 24% to 29%	(42)
Doyle, B., et al/ 2008	Pig	Left circumflex artery	EPC	8 weeks	LVEF= improved about 49%	(43)
Memon, I.A., et al/ 2005	Dog	LAD	Skeletal myoblasts/BM-MNC	4 weeks	LVEF= improved About 47%	(44)
Moelker, A.D., et al/ 2006	Pig	Left circumflex artery	BM-MNC	4 weeks	LVEF= improved About 46%	(45)
Tang, J., et al/ 2006	Rat	Left coronary artery ligation	MSCs	4 weeks	LV function: improved LVSP=110mmHg LVEDP=13mmHg	(46)
Berry, M.F., et al/ 2006	Rat	Left coronary artery ligation	MSCs	8 weeks	LV function: improved Max left ventricular pressure=52mmHg	(47)
Min, J.-Y., et al/ 2002	Pig	Left coronary artery ligation	hMSCs & hfCs	6 weeks	LV function: improved At rest: LVSP=75mmHg LVEDP=10.4mmHg With stress: LVSP=36mmHg LVEDP=15mmHg	(48)
Yang, Y., et al./ 2002	Rat	Left coronary artery ligation	EDCs	6 weeks	LV function: improved LVSP=70% LVEDP=140%	(49)
Tomita, S., et al/ 1999	Rat	Cryoinjury to left ventricular free wall	BMCs	5 weeks	LV function: improved	(11)
Sakakibara, Y., et al/ 2002	Rat	Left coronary artery ligation	cardiomyocytes	4 weeks	LV function: no change LVEDP=9.4mmHg	(13)
Nagaya, N., et al/ 2005	Rat	Myocarditis induced by immunization with porcine cardiac myosin	MSCs	4 weeks	LV function: improved LVEDP=12mmHg	(12)
Fujii, T., et al/ 2005	Rat	Left coronary artery ligation	MNC AM AM-MNC	4 weeks	LVEDP: improved in AM- MNC only MNC=12mmHg AM=8mmHg AM-MNC=5mmHg	(50)

Table 2: Cases reported on human trials of stem cells transplantation

AUTHOR/ YEAR OF PUBLICATION	AGE	PRESENTING COMPLAIN	TYPE OF STEM CELLS INJECTED	FOLLOW-UP	PATIENT'S OUTCOME	INTERVENTION/ DRUG THERAPY	REFERENCE
Stamm, C., et al/ 2003	64	Anterior septum MI	AC133+ stem cells	10 months	SVT and pneumonia	PCI	(26)
Stamm, C., et al/ 2003	73	Infero-lateral MI	AC133+ stem cells	8.5 months	Bronchitis	PCI	(26)
Stamm, C., et al/ 2003	54	Inferior wall MI	AC133+ stem cells	7.7 months	None	PCI	(26)
Stamm, C., et al/ 2003	69	Anterior septum MI	AC133+ stem cells	6 months	Bleeding from left internal mammary artery	PCI	(26)
Stamm, C., et al/ 2003	75	Inferior wall MI	AC133+ stem cells	3.5 months	None	PCI	(26)
Stamm, C., et al/ 2003	55	Lateral wall MI	AC133+ stem cells	3 months	None	PCI	(26)
Strauer, B.E., et al/ 2001	46	Anterior septum MI	Autologous MSCs	10 weeks	None	PCI	(51)
Patel, A.N., et al/ 2005	56	Mild MI	CD34+ stem cells	6 months	None	PCI	(10)
Patel, A.N., et al/ 2005	76	Moderate MI	CD34+ stem cells	6 months	None	PCI	(10)
Patel, A.N., et al/ 2005	72	Mild MI	CD34+ stem cells	6 months	None	PCI	(10)
Patel, A.N., et al/ 2005	65	Mild MI	CD34+ stem cells	6 months	Hematoma at bone marrow harvest site	PCI	(10)
Patel, A.N., et al/ 2005	57	Moderate MI	CD34+ stem cells	6 months	None	PCI	(10)
Patel, A.N., et al/ 2005	61	Moderate MI	CD34+ stem cells	6 months	None	PCI	(10)
Patel, A.N., et al/ 2005	66	Mild MI	CD34+ stem cells	6 months	None	PCI	(10)
Patel, A.N., et al/ 2005	61	Mild MI	CD34+ stem cells	6 months	None	PCI	(10)
Patel, A.N., et al/ 2005	60	Moderate MI	CD34+ stem cells	6 months	None	PCI	(10)
Patel, A.N., et al/ 2005	74	Moderate MI	CD34+ stem cells	6 months	None	PCI	(10)
Kang, H.-J., et al/ 2004	64	Antero-lateral wall MI	Peripheral blood stem cells	6 months	None	PCI/Aspirin+ clopidpgrel, β -blockers, ACE inhibitors	(27)
Kang, H.-J., et al/ 2004	60	Anterior septum MI	Peripheral blood stem cells	6 months	Coronary artery restenosis	PCI/Aspirin+ clopidpgrel, β -blockers, ACE inhibitors, HMG CoA inhibitor	(27)
Kang, H.-J., et al/ 2004	67	Inferior wall MI	Peripheral blood stem cells	6 months	Coronary artery restenosis	PCI/Aspirin+ clopidpgrel, β -blockers, ACE inhibitors	(27)
Kang, H.-J., et al/ 2004	57	Antero-lateral wall MI	Peripheral blood stem cells	6 months	Coronary artery restenosis	PCI/Aspirin+ clopidpgrel, β -blockers, ACE inhibitors	(27)
Kang, H.-J., et al/ 2004	74	Antero-lateral wall MI	Peripheral blood stem cells	6 months	None	PCI/Aspirin+ clopidpgrel, β -blockers, ACE inhibitors, HMG CoA inhibitor	(27)
Kang, H.-J., et al/ 2004	63	Anterior septum MI	Peripheral blood stem cells	6 months	Coronary artery restenosis	PCI/Aspirin+ clopidpgrel, β -blockers, ACE inhibitors	(27)
Kang, H.-J., et al/ 2004	55	Inferior wall MI	Peripheral blood stem cells	6 months	Coronary artery restenosis	PCI/Aspirin+ clopidpgrel, β -blockers, ACE inhibitors, HMG CoA inhibitor	(27)

Inclusion and exclusion criteria

Studies reported the stem cell implantation in human and non-human subjects (mammals) with myocardial damage were included in our study,

whereas stem cell transplantation in tissues which were other than cardiac origin was excluded from our review.

FREQUENCIES AND PERCENTAGES

Table 1: Twenty different cases of stem cell transplantation in animal subjects were reviewed. The animals (n=20) consisted of 10 rats (50%), 4 pigs (20%), 3 sheeps (15%), 2 dogs (10%) and 1 rabbit (5%). All mammals were included because of close resemblance of cardiac anatomy to human heart. Induction of MI was performed in all subjects by coronary artery ligation except for two cases in which cryoinjury was performed¹¹, while the other one had myocarditis induced by immunization with porcine cardiac myosin¹². The duration of follow-up varied from 4 weeks to one year. All subjects showed improved cardiac function except one in which no change¹³ was reported before and after implantation of stem cells.

Table 2: Data of 24 cases of stem cell transplantation in human subjects are collected in Table.2. Patients were within the age range of 46 to 76 years old. Most of the patients presented with anterior wall (n=8) or inferior wall MI (n=5). All patients received PCI as an initial intervention. The duration of follow-up was varying from 3 months to 10 months. The most frequent complication of stem cell transplantation was coronary artery restenosis (n=5). Moreover, few cases showed minor complications like pneumonia, bronchitis, bleeding from internal mammary artery and bleeding from marrow harvest site.

DISCUSSION

Clinical and theoretical studies on evaluation of MSCs have been the topic of ongoing discussion for some decades. Although the pilot studies of autologous mesenchymal precursor cells have shown trophic capacity to regenerate myocardium, many practical and clinical aspects are still controversial. The focus of our review is to assess the physiology and molecular mechanism of stem cell intervention, post-infusion adverse outcomes and failure of therapy. Clinical human trials and experimental studies on mammalian animals reported in past two decades are also part of our discussion.

MOLECULAR SCIENCE OF STEM CELL THERAPY

Both animal and clinical trials have provided the evidence of improved cardiac function after MSC transplantation. A comparative study was conducted by Xinyang Hu et al. on rats with permanent MI to evaluate the possible mechanism. Normoxic and hypoxic stem cells were injected within endocardium around the peri-infarct region after 30 minutes of MI. In vitro and in vivo assessment of MSC death, angiogenesis, infarct size and cardiac function was observed after 6 weeks of transplantation. Hypoxic stem cell induces pro-survival and pro-angiogenic factors including hypoxia-inducible factor 1, angiopoietin-1, VEGF, Flk-1, erythropoietin, Bcl-2 and Bcl-xL. Cell death and caspase-3 activation in hypoxic group were significantly lower compared to those of in normoxic stem cells both in vitro and in vivo. Transplantation of hypoxic versus normoxic MSCs after MI resulted in increment of angiogenesis as well as enhanced morphologic and functional benefits of stem cell therapy. Mild to moderate degree of hypoxia induces pro-survival and pro-angiogenic factors within the MSCs, contributing to the enhanced tolerance of H-MSCs to apoptosis and increased angiogenesis after transplantation¹⁴.

It is hypothesized that IGF-1 has a key role in attracting stem cells to damaged tissue, their differentiation via release of paracrine factors and activation of molecular pathway for cell survival. It was observed that ex-vivo over expression of IGF-1 resulted in elevated SDF-1 alpha levels, a potent chemo-attractant of stem cells, both in vitro and after transplantation in the infarcted heart¹⁵. SDF-1 increases expression approximately 3-fold in MSCs which leads to significant reduction in cardiac myocyte death, increased vascular density, and improvement in cardiac function following the intravenous infusion of MSCs in 24 hours after MI¹⁶. Mesenchymal stem cells express SDF-1; thus their engraftment could sustain myocardial SDF-1 levels in the infarct border zone to a time at which cardiac myocytes express CXCR4^{16,17} and ischemic preconditioning leads to the early expression of CXCR4 by cardiac myocytes¹⁸. Growth factors, like FGF-2, that signal through phosphatidylinositol kinase-3 can lead to synergistic up-regulation of CXCR4 in the setting of hypoxia^{19,20}. SDF-1: CXCR4 axis is not the only pathway active in stem cell based

myocardial repair. Interleukin 10²¹, thymosin beta 4²² and other non-CXCR effects by variety of growth factors have all been demonstrated the induction of myocardial repair²³.

Embryonic stem cells (ESCs) hold great promise for cardiac regeneration but are susceptible to various concerns. A study by Mohsin K et al. demonstrated that mouse ESC-derived exosomes (*mES Ex*) possess the ability to augment cardiac function in infarcted hearts. *mES Ex* enhanced neovascularization, cardiomyocyte survival and reduced fibrosis after myocardial infarction consistent with resurgence of cardiac proliferative response. Importantly, *mES Ex* augmented cardiac progenitor cell (CPC) survival, proliferation and cardiac commitment concurrent with increased c-kit⁺ CPCs in vivo 8 weeks after in vivo transfer along with formation of bonafide new cardiomyocytes in the ischemic heart. The underlying basis for the beneficial effect of *mES Ex* was tied to delivery of ESC specific miR-294 to CPCs, promoting increased survival, cell cycle progression and proliferation²⁴.

OUTCOME OF STEM CELL THERAPY

Similar human clinical trial was conducted in 2004, in which left ventricular ejection fraction was assessed after successful PCI. Intracoronary infusion of bone marrow stem cells showed improved LVEF by 0.7% in the control group and 6.7 % in the bone marrow cell group. Transfer of bone marrow cell enhanced left ventricular systolic function in myocardial segments adjacent to infarcted area²⁵. In vivo studies demonstrated the induction of angiogenesis after BMC transplantation in cryoinjury-derived scar. At 3 weeks after injury, fresh BMCs (n=9), cultured BMCs (n=9), 5-aza-induced BMCs (n=12) and medium (control, n=12) were transplanted into the scar. After 8 weeks of myocardial injury, cardiac-like muscle cells which stained positively for myosin heavy chain and troponin I were observed in the scar tissues of 3 BMC transplanted groups. Only 5-aza-treated BMC transplanted hearts had higher systolic function (P<0.05) than that of the control hearts¹¹.

Similarly, as discussed in Table 1, in our review of literature, hemodynamic status after stem cell therapy was assessed in terms of left ventricular ejection fraction or left ventricular function in mammals. Out of 24 cases, 23 showed an

improvement in LVEF or LV function, and only one case study failed to show any improvement in left ventricular function¹³.

SAFETY PROFILE

In past few decades, stem cell transplantation has emerged as a relatively safe and successful intervention in treating patients with acutely damaged myocardium. But some studies reported minor adverse outcomes related to this therapy. A study conducted by Stamm C et al. reported 6 cases of autologous MSC transplant; of whom 3 developed bronchitis, supra-ventricular tachycardia with pneumonia and bleeding from internal mammary artery²⁶. Similarly, hematoma of bone marrow at the harvest site of BSCs was also observed¹⁰. In a randomized clinical trials on 27 patients, few developed restenosis of coronary artery after intracoronary infusion of peripheral blood stem cells²⁷. In vivo studies on mammalian animals also demonstrated some poor outcomes. An experimental trial related to intracoronary infusion of MSCs in dogs provided evidence of acute myocardial ischemia with the induction of micro-infarction²⁸. Clinical application of MSC-based therapy is restricted because of the poor survival of implanted cells, and this poor survival remains poorly understood. A study by Mao J showed using a tumor necrosis factor (TNF)- α -induced bone marrow (BM)-MSC injury model in vitro and a rat MI model in vivo, miR-23a was involved in TNF- α -induced BM-MSC apoptosis through regulating caspase-7 and the injection of BM-MSCs over-expressing miR-23a could improve left ventricular (LV) function and reduce infarct size in the rat MI model²⁹.

The overall safety profile of stem cell-based therapy is excellent as evident by our case review; only 5 out of 24 cases showed coronary artery restenosis as a result of stem cell transplant (Table 2).

CHALLENGES FACED IN STEM CELL THERAPY

Stem cell therapy faces several challenges. It is difficult to grow, preserve, and transport stem cells before they are administered to the patient. Synthetic analogs for stem cells represent a new approach to overcome these hurdles. In a study by Lan Luo et al., they successfully fabricated a synthetic MSC (syn-MSC) therapeutic particle and

demonstrated its regenerative potential in mice with acute myocardial infarction. They packaged secreted factors from human bone marrow-derived mesenchymal stem cells (MSC) into poly (lactic-co-glycolic acid) micro-particles, and then coated them with MSC membranes. Syn-MSC exhibited a factor release profile and surface antigens similar to those of genuine MSC. Syn-MSC promoted cardiomyocyte functions and displayed cryopreservation and lyophilization stability *in vitro* and *in vivo*. In a mouse model of acute myocardial infarction, direct injection of syn-MSC promoted angiogenesis and mitigated left ventricle remodeling³⁰.

Similar studies conducted by Reinecke H et al. believed that the fundamental reason of transplantation failure is the delay in seeking medical attention³¹. Hematopoietic stem cells (HSCs) possess the greatest capacity of transdifferentiation into multiple cell lineages. Despite the fact, another study by Reinecke H et al. reported the failure of hematopoietic stem cell therapy in 175 subjects³². Such failure raises concerns about stem cell therapy which requires further investigation to establish an evidential consensus about its therapeutic efficacy.

ETHICAL CONSIDERATION

Ethics in stem cell therapy is another vital component of modern medicine. It is a topic of immense value. We have discussed some common ethical aspects faced during stem cell-based therapy. A research by Anne M in 2001 highlighted the point that using fetal stem cell might be an unethical because fetus cannot provide informed consent which is required for the extraction of stem cells.⁽³³⁾ According to new FDA guidelines for stem cell-based therapy released in 2006, each patient should be informed about the risk of acquiring any infections or genetic from donor tissue, rejection of implanted tissue, contamination or damage to the donor tissue, purity and potency of stem cells, safety and effectiveness *in vivo* of stem cell therapy³⁴.

CONCLUSION

From review of evidence, we observed that induction of angiogenesis, prolonged cell survival and paracrine factors are essential for successful stem cell transplantation. Most frequent patient-related adverse outcome was restenosis of coronary

vessels, but the overall safety profile was significant. Human trials conducted in past few years showed as remarkable improvement in overall cardiac functioning as experimental trials in different mammals. Long-term success rate of MSCs therapy is debatable as some failures of intervention were also reported in medical literature. Ethically, embryonic stem cell transplantation is the most controversial topic which requires a detailed assessment.

ABBREVIATION

AM=Adrenomedullin
 Bcl-2=B- Cell Lymphoma 2
 Bcl-xL= B-Cell Lymphoma-extra large
 BM-MNC=Bone marrow mononuclear cells
 CPC=cardiac progenitor cell
 CXCR4 =C-X- C chemokine receptor type 4
 EC=Endocardial
 EDCs=Explant derived cardiac stem cells
 EGFP=enhanced green fluorescent protein
 EPC=Endothelial progenitor cells
 Flk-1=a receptor for VEGF
 hMSCs=Human mesenchymal stem cells
 IC=intracoronary
 IGF1=Insulin like growth factor
 IV=intravenous
 LAD=left anterior descending artery
 LVEDP=Left ventricular end diastolic pressure
 LVEF=Left ventricular ejection fraction
 LVSP=Left ventricular systolic pressure
 mES Ex=mouse ESC derived exosomes
 MNC=bone marrow derived mononuclear cells
 MPC=Mesenchymal precursor cell
 SDF-1=stromal cell derived factor 1
 SynMSC =synthetic MSC
 TNF- α = tumor necrosis factor
 VEGF=vascular endothelial growth factor

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