Research article Available online www.ijsrr.org ISSN: 2279–0543

International Journal of Scientific Research and Reviews

APhysicochemical Approachtowards Understanding the Mechanism ofStem Cell Therapy

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ABSTRACT

Stem cells (abbreviated as SCs) are important for living organisms to grow. In a blastocyst, a few days old embryo, the inner cells are responsible for the generation of heart, lungs, skin, sperm, eggs and other tissues. In adult tissues like bone marrow, muscle, and brain, discrete populations of adult SCs replace cells that are lost through normal causes, injury, or diseases. The SCs have unique regenerative abilities for treating many acute diseases like diabetes, heart problems and many other disorders. Though the stem cell therapy is becoming popular, present understanding how SCs use their potential forcell-based therapiesto treat disease is still in a rudimentary state. Laboratory studies of SCs cells enabled scientists to learn about the stem cells' essential properties what made them different from the other specialized cell types. Stem cells have already been used in the laboratory to find new drugs and to develop model systems to study normal growth and identify the causes of genital defects. Researchers working withSCsare always inquisitive to know how an organism develops from a single cell and how healthy SCsapproach towards the damaged/diseased cells and repair/regenerate then in adult organisms. So far very little progress has been made to elucidate the mechanism how SCs repair and regenerate the desired cells. In the present article, we have proposed a simple physicochemical mechanism to describe how a stem cell regenerate /repair a diseased cell , for instance, a dead pancreas cell from the consideration of charges and dipolar interaction associated with the cells. The proposed mechanism might further enhance our knowledge about cell-communication and cell signaling processes.

KEYWORDS: Stem cells, Cell-cell interaction, Electrostatic interaction, Stromal cells, Cell signaling, Cell-cell communication

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INTRODUCTION

Stem cells are the body's raw materials from which all other cells with specialized functions are generated. Under the right conditions and environment, available in the body or in the laboratory, stem cells might proliferate, differentiate and grow to form more cells called daughter cells.These daughter cells either become new stem cells (self-renewal) or become specialized cells (differentiation) having specific functions, such as blood cells, brain cells, heart muscle or bone cells. No other cell in the body has the unique natural ability to generate different new cell types.Multipotent stem cells have the power to regenerate bone, cartilage, collagen, blood vessels, tendons and ligaments, and more to repair the injury. Exclusive protocols use our own body's growth and healing factors to accelerate the healing cascade within our body.

Diseased cells of organs or tissues are repaired or regenerated by the process of tissue engineering where stem cell or progenitor cell engraftment, differentiation, and long term replacement of damaged or dead tissue are performed. In this process multipotent stem cells differentiate into a specific cell type (say, for instance, pancreas cell, considered in our present discussion) in the laboratory or in the site of injury. These cells then integrate into the site of injury, replacing or repairing the damaged tissue, and thus facilitating improved function of the organ or tissue. An example of this process is the use of cells to replace cardiomyocytes after myocardial infarction[1-3]. For diabetic treatment, SCs after isolation[4,5] can be infused into the body through veins. After treatment, the C-peptide determines how well beta cells are working and maketheir improvements. As a consequence, dose of insulin intake can be reduced. The HbA1c may also drop in some cases. Stem cells can regenerate new insulin-producing cells to produce more insulin and hence lower the high blood sugar levels.

It is to be noted that the cells have the capacity to release several molecules such as cytokines, chemokines, and growth factors which act in a paracrine or endocrine manner to repair the cells. These factors facilitate self-healing of the organ. The delivered stem cells (via local or systemic administration) remain viable for a relatively short period (days-weeks) and then die. It is assumed that the cells naturally secrete the relevant therapeutic factors, or which undergo epigenetic changes or genetic engineering that causes the cells to release large quantities of a specific molecule. Examples include cells that secrete factors which facilitate angiogenesis, anti-inflammation, and anti-apoptosis.[3,6,7]This model uses adherent stromal cells or mature endothelial cells to treat peripheral artery disease[7,8].There is no proposed model which could explain the mechanism by which a stem cell repairs the diseased cell (a cell which has lost its function like cell signaling, cell to cell communication etc.) orregeneratesa new prototype.The stem cells can live and grow in special

media(growth factor and nutrients) in test tubes or Petri dishes in laboratories. But the mechanism of regeneration of wounds or repair special cell types is yet to clarify.

A schematic model representing how pluripotentstem cells generally derived[8] fromcord blood or bone marrow might repairorregeneratea new pancreas cell, for example,to cure diabetes has been attempted in this article. Our plan is mainly to suggest a probable model describing how stem cells actually perform the cell therapy or regenerate new cells replacing the diseased / dead ones of a particular organ like pancreas, as mentioned above.

SUGGESTEDMECHANISM Of STEMCELL REMEDIATION

2.1. Existing Theories

There is actually no confirmed theory explaining how SCs becomes active and start to regulate their functionsto cure the pancreas (in case of diabetes) or other diseased organs/cells. There are three proposed old ideas to explain how stem cells cure diseases by repairing diseased cells. As mentioned above, let us consider the case of Type 1 diabetes with a suicidal death/damage of the pancreas (due to a breakdown of tolerance by giving these cells).The SCs could regenerate or restore some of the tolerance leading to an improvement. First theory is the homing effect theory proposed by Hess and his group[9]. According to this theory, when stem cells reach the pancreas, exert some kind of stimulations causingdefective part of the pancreas to regenerate or grow[9].It appears that the cells homing to the damaged pancreas somehow provided with the desired medicinal cues and as a consequence there is indication of an improvement in insulin production. The large numbers of stem cells are supposed to be capable of differentiating to other cells, like pancreatic insulin producing cells which is the second idea. According to the third theory or idea,SCs can regulate the immune system, that is, immunoregulatory T-cells. Some preliminary data suggested that there was an increase and improvement in regulatory T-cells after infusion of the drugs. After infusion, there might be an improvement in regulatory T-cells.But the unanswered question how SCs are capable to recognize and regenerate/repair the specific diseased pancreas cells. Here, we consider, some electrochemical interaction might be invoked.

2.2. Present Proposed Theory

The macromolecules including proteins and nucleic acids are considered to be ionic in the aqueous media carrying a multitude of charged groups (both cationic and anionic groups) for instance, negatively charged Glu^- and positively charged Lys^+.A charge distribution on the stem cell can be schematically represented as in Figures 1a and 1b.Before interaction between a stem cell and a diseased pancreas cell (DPC, in our present case, or the cell to be repaired or regenerate), charge

distributions on the surfaces of both SC and DPC are schematically represented as shown in Figure -1band 1c.

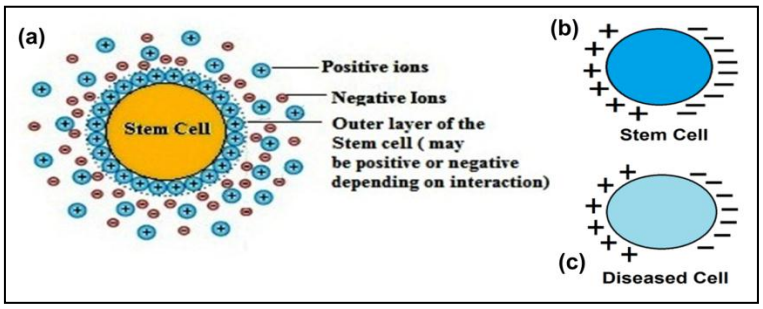

Figure-1.Schematic representations of the proposed charge as distributed on a stem cell(a),just before interaction positive and negative charges are re-arranged around the normal stem cell (b) and the diseased pancreas cell (c).Because of less liquid content, the charge density is more in the diseased SC (i.e. more polar in character) as a consequence SCs are attracted towards the diseased SCs. After interaction, they are rearrangedasrepresented schematically in Figures 2 and 3.

In between the initial and the final regeneration processes of the DPC by SCs, there are many possible states of gradual remediation of the DPCs with different charge distributionsand SC concentration surrounding the DPC as shown in Figures2 and 3. In figure 2, the first state (bluish one) represented the condition where the pancreatic insulin producing beta cell (PC) is almost dead (no cell to cell communication or cell signaling occurs).

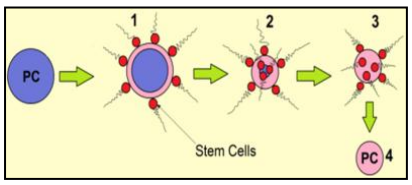

Figure-2. A suggested mechanism of transformation of stem cells into pancreas cells to make the dead or partially dead (or strained) pancreas cell (PC, not producing insulin) active (alive). There are different intermediate stages (1-3) of transformation of the stem cells into active PCs or remediation of dead/diseased PC. The final cured PC is represented by (2 in Fig.1a and IV in Fig.3, respectively).

In the whole remediation process (1-4 and I-II,respectively, in Figures 2 and 3), the SCs are first attracted and targeted towards the dead DPCsurfaceand arrest them (gradually surrounds the whole surface of the DPC). At the remediation states, different electrostatic interactionstake place between DPC and SC via surface charges and all the SCs gradually used up to regenerate the cure PC (states 4 and IV in Figures 2 and 3, respectively). The whole process of remediation is schematically represented by Figure -3.

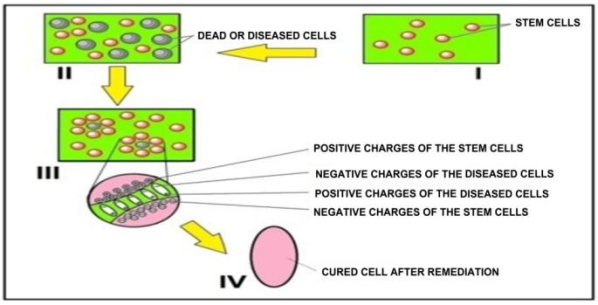

Figure-3. Four important intermediate stages of cell remediation: I. Stem cells approaching towards the dead cells. II. SCs surround the dead cells for repair. III. Electrostatic interaction taking place between SC and DPC. IV. The repaired alive PC(after remediation).

To elucidate why SCs will be active to repair the diseased cell one may support the following conjecture. The SC –DPC interaction is always favored compared to those of DPC-PDC and SC-SC interactions. This is because of thefact that due to the dead/non alive character of DPC,it contains less fluid and as a consequenceits surface is little bit more polar (means difference of +veand – ve charges are not uniformly distributed over the DPC). Because of less fluid content, the dead cell surface possesseshigher dielectric permittivity(stronger dipolar interaction) as compared to that of the live one.The DPC wall contains less fluidcompared to that of the normal living PC (as more conducting cells with more water contents havelower dielectric surface charges) and hence SCs are attracted electro-statically by the DPCs. The living cells with higher conductivity have uniform and symmetric charge distribution is not attracted by the SCs electrostatically or by other means (like Coulomb interaction). That is, there is strong interaction (dipolar nature) between the DPCs and the stem cells.

2.3. Physicsand Information TheoryBehindFunctioning of The Stem Cells

It is to be noted that information theory is very much involved with cell -cell communication process. Along with electrochemical interaction, entropy(associated with the ordering of the molecules) and information theory (associated with the cell-cell communicationprocess) also take part in the healing process using SCs. It is to be noted that entropy and information are inter related functions associated with the functioning of SCsand curing/regenerating the diseased cell. In biological system, there is strong correlation among entropy, information and cell signaling process.It had already been established that information (Shannon theory of information[10] and entropy are equivalent and interdependent (one increase with the decrease of the other). This is similar to the case of equivalence of mass (M) and energy (E) from the relation $E=Mc^2$, where c is the velocity of light~ $3x10^{10}$cm/sec (according to Einstein's mass–energy relation). A minimum unit of information may be called a bit of information carried by an ordered SC and this information is

related to the entropy of the system. In entropy unit this information (a bit) is equal to ~$k_B$ln2 or ~1.3x10 $^{-16}$ erg/K (where K is degree Kelvin, body temperature~300K and $k_B$is the Boltzmann constant) which is very small energy (or information) transferred from the SCto cure a diseased cell. This means, the minimum energy a pluripotent SC carrying healing information (in unit of bit) is equivalent to ~1.3x10 $^{-16}$ erg/K in entropy (or energy) unit. If a SC carry more energy in multiple of bits (in case of higher dilution) then the charges surrounding the SCs have higher degrees of freedom and it becomes more active (with longer mean fee path and higher velocity) with increased entropy content. This information or energy/K carried by the SCis transferred (cell signaling or cell-cell communication process[11]) to the brain (through neurons and electrochemical reaction) and the brain sends the necessary information to cure the diseased cell (having different proteins with capabilities of receiving the information which acts as medicine). Modern Biology also explains the cell to cell signaling/communication process by communication theory [13] which in turn related to the entropy acquired by the cells. It is to be noted that different small molecular weight chemicals are secreted by the cells while cell to cell commutation/signal takes place[12]. The said entropy change during cell-cell communication is associated with these secreted small molecular weight chemicals.

DISCUSSION

As mentioned above,during cell growth and cell to cell communications and growth, cells secrets some low molecular weight chemicals[12]. Such molecules are adsorbed by the DPCs as in the case of other living cells and interaction between SC and DPC takes place. SCs receive information about the diseased cell from these adsorbedsmall molecular weight molecules and accordingly rearrange the above mentioned asymmetric charge distribution. The interaction and the charge distribution are, therefore,diseased-cell specific (i.e. SCs receive different type of information from different types of diseased cells to be repaired/regenerate and start repainting work accordingly). While repairing/generating a typical cell, SC receives signals from the said adsorbed molecules and the nature of charge distributions. The signals received by the SC is electronic/and or chemical in nature which helps SC to understand the signature of what type of cell regeneration is to be carried out.

The force of ionic or the DPC-SC interaction can be described by Coulomb's low. The energy of interaction between to ions witheffective charges e_1(in the present case SC) and e_2(DPC) is given by

$$U_{ion} = (e_1e_2/€_r) \qquad (1)$$

where r is the separation between SC and the diseased cell (DPC or PC); € is the dielectric constant of the medium in between the two cells.Ionic bonds are formed, in particular, between

inorganicgroups in proteins (e.g.negatively charged Glu^-andpositively charged Lys^+), between such groups and small interactions, between phosphate groups in nucleic acids,cations etc. The dipolar interactions of the charges associated with the SCs and the DPCs are, in general, attractive.Thedipolemoment p of a small molecule or atomic group or ions is equal, in order of magnitude, to the product of the electronic charge (4.8×10^{-10}esu) by the length of chemical bond. The traditional unit for dipole moment is the Debye (D); $1D= 10^{-18}$esu. The energy of orientation interaction between two dipoles is inversely proportional to the cube of their separation:

$$U_{or}=(1/r^3)[\mathbf{p_1}\mathbf{p_2}- 3(\mathbf{p_1}\mathbf{r})(\mathbf{p_2}\mathbf{r})/r^3] \qquad (2)$$

For adequate functioning of thestem cells, the dipoles should line up in a tail-to-tail fashion, i.e. all the three vectors$\mathbf{p_1}$, $\mathbf{p_2}$ and **r**are needed to be collinear, and then

$$U_{or} = -2[p_1p_2/r^3] \qquad (3)$$

The SCs, because of their specificity, can recognize the signature (knowing different modes of vibrations of a specific cell to be repaired due different charges)of the specific DNA structure of the DPCs to be repaired /regenerate and gradually transform by rearranging the charge distribution toregenerate the vibrations of the PCs and finally regenerate/repair the diseased/dead PCs (or the beta cells) as shown in Figure -4. The process is, of course, slow and effective but depends on various factors including pressure, temperature and above all, surrounding *in-vivo*environment of the SCs and DPCs. Second possible casemay also arisewhen the PCs are partially dead/strainedso that it cannot function properly like normal ones. Here also,being attracted by similar electrostatic interaction, the SCs surround the DPC, as in the previous case (Figure-3). The non-functioning part of the DPC which is more polar in nature than the normal one, there is strong interaction with the SC which energies/cure the DPC by releasing its strain and the inactive part is slowly repaired/re-vitalized as normal one. In this way the whole dead or partially dead/strained DPCs might ultimately be cured or regenerated by the SCs (Fig.4) and function normally.

CONCLUSION

We have proposed for the first time a phenomenological model to demonstrate how SCs repair/regenerate the diseased cells of an organ like dead or partially inactive pancreas. The proposed mechanism is complicated involving the cell-cell communication process, entropy of the system and cell signaling path ways. Similar mechanism might also be applicable in case of regeneration or repairof other diseased cells using stem cells.Present study also indicated that some interesting cues about the proliferation of cancer “stem cells” and the control of cancer cell growth and proliferation might be possible by using stem cells applying the technique of electrochemical interaction. More elaborate study in this direction might be interesting.

ACKNOWLEDGEMENT

One of the authors (BKC) is grateful to Dr C R Santraand Professor S C Sarkar (CRCR, JU)for fruitful discussion.

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