

Concepts of Dhatu Siddhanta W.S.R. To Theory of Tissues Formation, Differentiation and Theory of Stem Cell

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ABSTRACT

To preserve health and to cure illnesses through Rasayana (rejuvenation) remedy in conjunction with principal remedy is the unique technique of Ayurveda. The basic constituent unit of a dwelling being is usually a functional cellular. Query arises from where it's far generated? The way it attains its very last specific differentiation form? As age progresses, diverse modifications occur at every cellular stage and cell undergoes to adaptation hence. Microenvironment for cell nourishment diminishes with age or as disease condition persists. In this context, Acharyas had contributed and documented various facts and theories through their insight wisdom. Hidden secretes in the basic principles of any medical system are needed to be explained in terms of contemporary knowledge. Contemporary research areas should be opened to include various explanations of different fields of ancient thoughts to support these new doctrines, if any. This evaluate can be helpful to open the door of future studies area inside the field of opposite medical method of Ayurveda inside the context of Dhatu Siddhanta (concept of tissues formation and differentiation) and idea of stem cell.

Keywords: Aging, Dhatu Siddhanta, Rasayana, stem cell theory.

I. INTRODUCTION

At the time of fusion of wholesome Purush Beeja (spermatozoa) and Stree Beeja (ovum) in the presence of Jeeva (soul - a life factor) fertilization takes place,[1] and a new life comes in the shape. Ayurveda believes Garbha (fetus) attains its maturity in mother's womb through numerous inter-changes by

the influence of Pancha Mahabhuta (five basic elements)[2] and then it differentiates into all types of specific cell lineages. Thus, a single fertilized human egg (ovum) differentiates and develops into an embryo, and then into a fetus, after birth in an infant, a child, and finally an adult.[3] This business of cell differentiation and development persists during prenatal and postnatal life of an individual to maintain health. The cell attains differentiation and specification cell type by the response of some unspecific and undifferentiated mother cell known as stem cell. There are two types of sources of stem cells; embryonic stem (ES) cells and adult stem cells. Stem cells have attracted the attention of biologists and medical scientists for a long time. These provide materials for regenerative medicine.[4] In 1998, researches in the US found a way of harvesting stem cells, a type of primitive cells, from embryos and maintaining their growth in the laboratory, and thus started the era of stem cell researches.[5] Theory of stem cell has arrived in the current trend of life sciences. This seems to be more similar to Dhatu Siddhanta (theory of tissues formation and differentiation) of ancient wisdom. Normal functioning of the cell is always influenced by various factors such as stress, chemical agents, diseases and environmental hazards. Yet, the cell survives and continues the function by means of adaptation.[6] As age progresses, various changes occur at every cell level. To prevent the aging through Rasayana (rejuvenation) therapy is a unique approach of Ayurveda.

Doctrine of Dhatu Siddhanta

The basic theory of Ayurveda is based on the state of equilibrium of Tridosha, Saptadhatu and Trimala.[7] All these are nourished well initially by the influence of potency of individual Jatharagni (digestive energy) after consuming the food. Then, the productive nutrients (Ahara Rasa) are passed into each level of Dhatu (bodily tissues) for nourishment. Ultimately, necessary nutrients for the formation and development of all tissues are supplied by one stream of pool. They carry their support to the site, where Dhatus are located. The nourishment of all Dhatus is influenced by the function of respective Dhatvagni (metabolic energy of each tissue). To motivate the formation of self-clone of respective tissue and depended tissues (Upadhatus) are major functions of each Dhatvagni. Dhatvagni of each Dhatu also provides the necessary supplements to subsequent tissues to potentiate their cloning. Thus, Rasa, Rakta, Mamsa, Meda, Asthi, Majja and Shukra Dhatus develop sequentially and nourish further Dhatus. For example Rasadhatvagni plays an important role in the formation of Rakta Dhatu from Rasa Dhatu which further nourishes the Mamsa Dhatu by the influence of Raktadhatvagni. Whenever potency of any level of Dhatvagni diminishes or elevates the business of production of next Dhatu may be affected. During this process, some metabolic wastes are produced which are known as Dhatumala (tissue excreta). A same phenomenon of differentiation and development of Dhatu is sustained throughout life for everyone. Any Avarana (obstruction) or Dushti (vitiation) in different Srotas (microcirculation of tissue) may lead to deformity of the next tissue. In Ayurveda, some theories of tissue formation and development (Dhatu Pushti Nyaya) are elucidated in this regard. These theories are Khale Kapota Nyaya, Ksheera Dadhi Nyaya, Kedara Kulya Nyaya and Ek Kala Dhatu Pushti Nyaya. In the nourishment process from Rasa to Shukra Dhatu, Dhatvagni of respective Dhatu substantially divide to essential elements into three fractions, that is, Sukshma, Sthula and Mala Bhaga. Tissue-specific stem cells sustain organs for a lifetime through self-renewal and generating differentiated progeny.[8]

Serenity of Stem Cell Theory

The term stem cell appears in the scientific literature as early as 1868 in the works of

the eminent German biologist Ernst Haeckel. In 1908 by the Russian histologist, Alexander Maksimov was postulated the existence of hematopoietic stem cell.[9] Each type of cell in the body has a specialized structure and function that differs from that of its precursor unspecialized cells. Such unspecialized precursor cells are known as stem cells. Stem cells are often called “master cells” because they are a class of undifferentiated and unspecialized cells having potency to differentiate into specialized cell type.[10] Stem cells are defined by two fundamental properties.[11] They self-renew, and every time they give rise to a cell with an identical stem cell program. They have the capacity to generate all the cells in the tissue they arise from. Stem cells are maintained the entire tissue during a lifetime. There are different types of stem cells along with different expectations of their biological activity.[12] To be classified as a stem cell, a cell must satisfy three main criteria. One, it can divide without limit whole the life, sometimes after long periods of inactivity. Second, it can renew the stem cell pool: During cell division each daughter cell can choose whether to commit to differentiation into a single cell type or remain as stem cell.[13] When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a muscle cell, a red blood cell (RBC), or a brain cell.[14] Third, under certain physiologic or experimental conditions, they can be induced to become tissue - or organ - specific cells with special functions.[14] On the basis of potency stem cells are classified into totipotent, pluripotent, multipotent, oligopotent, and unipotent types. Totipotent stem cells have the ability to differentiate into all possible cell types, e.g. fertilized egg, which is independently capable of giving rise to all embryonic and extra-embryonic tissues. While unipotent stem cells have the ability to only produce cells of their own type, but have the property of self-renewal required to be labeled a stem cell, e.g. muscle stem cells. ES cells are considered pluripotent because they do not have the ability to become part of the extra-embryonic membranes or the placenta. Studies have shown that, mesenchymal stem cells can differentiate into cells normally associated with the ectoderm and endoderm, these are nerve cells, muscle cells, skeletal cells and cardiomyocytes.[15,16,17] RBC and several types of white blood cell are arise from the same unspecialized precursor cells in red bone marrow.[18]

Cell Cycle and Developmental Fate

The cell is the structural and functional unit of the living matter and is capable of carrying on the processes of life independently.[19] As the evolution of multicellular organisms has progressed, various cell groups organized into tissues and organs.[20] One group of cells takes up one particular work and undergoes the necessary change in structure and mode of life.[18,19] This process of adaptation of a cell, for the purpose of doing a particular function, is called differentiation or specialization.[19] The cell cycle is the period of time between the birth of a cell and its own division to produce two daughter cells. Cell cycle is divided into four distinct phases, which are known as G1, S, G2, and M. G1 is the period when cells respond to growth factors directing the cell to initiate another cycle; once made, this decision is irreversible. Cells that retain the capacity for proliferation have entered a phase called G0 which described as quiescent even though they may be quite active physiologically. Growth factors can stimulate quiescent cells to leave G0 and re-enter the cell cycle.[18] Stem cells are mostly dormant, have a low metabolic rate, low growth factor requirement and live a long life. They rarely enter the cell cycle, but when they do, for instance in response to cellular loss or damage, they exhibit a tremendous potential to regenerate the entire tissue.[11] According to Ayurveda, fate of Dhatu is decided through the potency of respective Dhatvagni. Even all Dhatus get their nutrition for growth from one stream of the pool, but on the basis of their need and demand they fulfill their requirements. Hence, the rate of cell division is tightly coupled to the demand for growth and replacement.

Binding Bridge Between Dhatu Siddhanta and theory of Stem Cell

Theory of Dhatu Siddhanta and stem cell seems similar due to the concept of aging and Rasayana therapy. In Ayurveda, the concept of Rasayana with respect to Dhatu and Stem cells is initially introduced by Prasad BS.[21] He logically explained the age old concept of “Dhatu Siddhanta” (theory of tissue formation and differentiation) in the light of modern understanding of stem cell theory. Tissues formation and their equilibrium state are difficult to maintain whole life. On the basis of stem cell type potency, this development is continued whole life. The bone marrow contains at least two kinds of

stem cells. One population, called hematopoietic stem cells, forms all types of blood cells in the body. A second small population called non-hematopoietic stem cell can generate bone, cartilage, fat and cells that support the formation of blood and fibrous connective tissue (skeletal stem cells). In some organs, such as the gut and bone marrow, stem cells regularly divide to repair and replace worn out or damaged tissues. In other organs, however, such as the pancreas and the heart, stem cells only divide under special conditions.[11] Mesodermal progenitor cells are found throughout the body, they can differentiate to form multiple cell types (e.g. osteocytes, adipocytes, chondrocytes, fibroblasts, and smooth muscle cells) and they have a limited ability to self-renew.[22] Rasa Dhatu may have all types of cell differentiate lineage responsible for the development of all Sapta Dhatu, may be known as pluripotent. Recent studies suggest that the spermatogonial stem cells can be reprogrammed to become ES-like cells to acquire pluripotency.[23] Wholesome Shukra Dhatu may be considered as pluripotent, because it is responsible for the transmission of genetic information from an individual to the next generation. Thus, each Dhatu carry the potency to regenerate further Dhatu, because each Avayava (organ) is formed by composition of many Dhatus.

II. DISCUSSION

For meeting the objective of healthy progeny, Ayurveda scholars felt the importance of six procreative factors (Shad Garbhakara Bhavas) such as Matrija (maternal), Pitrija (paternal), Atmaja (soul), Rasaja (nutritional), Satmyaja (wholesomeness), and Sattvaja (psych/mind).[24] Each procreative factor is assigned with a certain organogenesis/functional/ psychological phenomenon, to develop in the forthcoming baby, during its intrauterine life.[24] The Ayurvedic principles are more focused on proper preparation of the parents, an essential prerequisite for a healthy progeny.[25] Pancha Mahabhutas plays the important role in the friction and growth of a fertilized ovum and formation and development of organs.[26] Ultimately, in the presence of soul, the process of new birth takes place with the union of Shukra (sperm) and Andanu (ovum).[27] The fertilized ovum (zygote) divides at first into two cells, these again into two more, and so on-until a large mass of embryonic cells is formed by the influence of Pancha Mahabhutas. The first few

cells are believed to be totipotent, which means that, each one of them has got the potency of creating a complete individual.[5]

The cell is the functional unit of the body. According to modern medicine, metabolic processes, divisions and multiplications go on in all the cells of our body from birth to death. In the conjunction and disjunction of cells, the activating factor is Vata.[28] In Sushruta Samhita, one can see how the organs are formed from various Dhatus.[29] For these constant processes in all cells, a biological energy is constantly essential, without which the survival of our body is quite impossible. The same biological energy is provided by Agni, which is one of the unique concepts of Ayurveda. This Agni provides two types of biological energy, that is, potential and kinetic in the cells of the human body.[30] Jatharagni (digestive energy) plays an important role in between food and health. Good nutrition means “maintaining a nutritional status that enables us to grow well and enjoy good health”.[31] Food is not only responsible for development and growth, but also imports strength, complexion, health and proper functioning of senses.[32] In the entire process of tissue transformation, the Dhatvagni of respective Dhatu works steadily at every level of tissue formation and development. If Dhatvagni is good, it will increase the potency, otherwise drug (s) or food will not work in the proper way. On the basis of need and demand, it nourishes the Dhatu in Sukshma (carry the next Dhatu materials), Sthula (develop the same Dhatu) and Dhatumala. The former is taken for nourishment while the latter one is thrown out, which otherwise defile the body if it stays longer. Patterns and rates of cell division within the tissues vary considerably. In many epithelia, such as the crypts between intestinal villi, the replacement of damaged or effect cells by division of stem cells can be rapid. The rate of cell division is tightly coupled with the demand for growth and replacement. In the healing of wounded skin, cell proliferation increases to a peak and then returns to the normal replacement level.

Aging is a process that involves all organs and tissues of the human organism. Cells and tissues are impacted by aging in differing degrees, depending on their regenerative potential and sensitivity to outside stimuli.[33] As age progresses, various changes occur at every cell level and cell undergoes to adaptation accordingly. It is clear that aging does not occur simultaneously

in all the tissues. Different body tissues are affected naturally due to aging at different periods of time. The classics have divided age into immature, mature and old, which extend from birth to 30 years, 30–60 years and above 60 years, respectively. Sapta Dhatu is involved in the aging process adapting some age related degenerative changes in an individual. Each Dhatu has some specific role in maintaining the healthy body and those will be degenerated in a gradual manner with the advancement of age. Depletion (Kshaya) of quality and quantity of each Dhatu is gradually evident in aging. It seems that stem cell may not be able to express their fate to jump in cell cycle. Growth factor cannot able to stimulate quiescent cells to leave G0 phase. Microenvironment for cell nourishment diminishes as age or disease condition persists.

In aging Dhatukshaya (tissue emaciation or loss) is universally accepted as one of the main reasons to initiate pathogenesis. There is inevitable metabolic dysfunction (Dhatvagninasana), out of which all Sapta Dhatus are lost. Ultimately, deterioration of immunity (Ojakshaya) is evident. All Dhatus get increased by the use of substances having similar properties and they get reduced by the use of those having opposite properties. Therefore, among other Dhatus of the body, the muscle (Mamsa Dhatu) increases by the administration of meat, blood by blood and so on. Similarly, Samanya which is responsible for the increase of Dhatus is related to both the attributes Gunas and the categories (Jati) of substances.[34] Acharya Charaka has been quoted that by the medicine, only these bodily tissues attain their equilibrium state, e.g. when there is a deficiency of semen, with a view to promote it, milk, ghee and such other substances known to be sweet, unctuous and cold should be administered.[35]

In the present scenario, Ayurveda must not remain silent to rationalize its therapeutic approach.[36] Ayurveda has not only paid attention towards healing of ailments, but also retarding of aging and healthy longevity for which multi-dimensional strategy known as Rasayana has been introduced. However, one difficulty is always faced with the overlapping between aging and disease. Both the aging process and diseases can cause changes in the body, which affect life span. At this juncture incorporation of Ayurvedic regimen in the treatment may be a hope-finding solution and requires appreciation with scientific reasoning.[37]

Ayurveda observes that Vata Dosha remains dominant naturally in old age, which leads to dominancy in different pathology. Nanatmaja Vikara, Anubhanda, Gata Vata and Avarana are different pathologies explained in Ayurveda.[38] Vata Vyadhi can manifest either due to Dhatukshaya or Avarana.[39] When Dosha or Dhatu obstructs a particular Dosha then, it will give rise to increased signs and symptoms related to the function of that particular Dosha or Dhatu which has obstructed.[40,41] In fact the knowledge of Avarana plays an integral part in understanding the Samprapti of many diseases.[38] The treatment of Avarana should aim towards cleaning the Srotasus with medicaments which possess Anabhishyandhi, Snigdha, Kapha Pitta Aviruddham and Vatanulomana property.[42] Rasayana Chikitsa play an integral role in the management of Avarana. Rasayana drugs are commonly used to improve health and longevity by balancing between Tridosha, Saptadhatu and Trimala.

Rasayana Chikitsa of Ayurveda is in vogue since antiquity. The specific actions of Rasayana drugs in the Poshaka Rasa level (nutrient supplement), Agni level (metabolic appreciation) and Srotas level (tissue nourishment) are well acceptable.[43] Some Rasayana drugs may act directly on specific Dhatus, e.g. Vrishya, Balya drugs directly acts on Shukra Dhatu and results in the production of Shukra. Organ and tissue specific Rasayana drugs are explained in Ayurveda classics. For example Medhya Rasayanas are specific for brain tissue. Such Rasayanas retard brain aging and help in generation of neural tissues besides producing anti-stress, adaptogenic and memory enhancing effect.[44] Same as, Hridya Rasayana for heart, Chakshusya Rasayana is used for eyes and others. Screening of such drugs that modulate stem cell self-renewal and differentiation, or protect cell death, can be helpful in developing new drugs to treat human neurodegenerative diseases. In one of the review papers, introduced drugs and natural products that modulate stem cell fate to neurons or glia is established.[45] In the near future, more progress in identifying new drugs that regulate stem cell proliferation and differentiation will be used in neurodegenerative diseases.

Good numbers of Rasayana drugs have shown immunomodulatory activity to boost up or restore functional immunity in response to defense

mechanism.[46] The Rasayana drugs have also shown tissue and disease specific immunomodulatory activity.[47] These Rasayana drugs not only play a role in immunity but also exhibits its anti-stress, inotropic and antioxidant activity which helps in the quality-of-life (QOL) improvement as observed in patients. Hence, QOL may be increased by better or proper care/nourishment to bodily tissue. Rasayana drugs may act as adjuvant drug in stem cell therapy to patients. Recent studies have also revealed that Ayurvedic Rasayana Ashwagandha and Shilajeet therapy could modulate the immune profile in patient.[48] Rasayana drugs may be helpful to develop microenvironment (niche) in which cell or tissue grows. The stem cell niche concept was firstly introduced in 1978[49] and it represents the natural microenvironment that surrounds stem cells. Niche can be defined as an anatomical and functional entity that plays a crucial role in maintaining tissue homeostasis, repair and regeneration in case of injuries.[50] It is believed that the stem cell niche provides a complex array of physical signals, including cell-cell contacts and cell-matrix adhesions, and biochemical signals, such as growth factors to the stem cells in a temporal and spatial manner.[51,52] The integration of both local and systemic cues in the niche guides these cells to proliferation and fate specification.[51,52]

III. CONCLUSION

Cells and tissues go through modifications by using getting old in differing levels; depending on their regenerative ability and sensitivity to out of doors stimuli.[33] getting older is a system that involves all organs and tissues of the human organism. Technique to heal a disease and rationalize growing older method via Rasayana Chikitsa is one of the unique standards of Ayurvedic device. By means of reciprocal addition of ideas of Dhatu Siddhanta, Rasayana capsules of Ayurveda and stem cellular remedy of modern science may be helpful for future scientific researchers.

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