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Hypothesis

The five elements of the cell

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ABSTRACT

Everything in the surrounding universe can be attributed into five elements. Human organs can be also linked to the five elements. Cells, the smallest unit of the human body, consist of cellular organelles as little organs. Here, we extended the concept of the five elements to a cellular level via the human organs, theoretically re-evaluating the overall association of cellular organelles in maintaining the homeostasis of cellular functions.

1. Introduction

Similar to how Greek philosophers have discussed the origin of all things in the universe, ancient philosophers in China also debated on how the origin and consequence of all things can be explained and cycled. They postulated that the universe is composed of five fundamental elements, and then they developed the theory of how the universe was created and it undergoes a cycling process. The 'five elements theory' not only defines the character of each element, but also emphasizes the mutual interaction and rotation of the elements under an interactive system.

The five elements (五行), or five phases, are orderly classified by five materials as follows: wood, fire, earth, metal, and water.[1] Each element has its own literal and philosophical meaning. The wood-type is represented by a tree that grows straight and is abundantly spreading out. The fire-type is represented by a state of combustion that generates heat. It is likely that the earth-type will establish a foothold to newly change an outdated system. The metal-type is represented by the formation of hard crystal. Lastly, the water-type is represented by a stream that seems to run out of a solid melting.[1–5] The attributions of each element in itself do not reveal their identities, but rather, reveal their color when under reciprocal interaction. There are two flows among the five elements, i.e., the mutual nourishment cycle (相生) and mutual restrain cycle (相剋), which have organically positive or negative influences on each other.[5,6]

1.1. *The characteristics of the five elements*

On the concept of five elements, everything, including forms

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of matter or even spirit, can be classified, and arranged into each of the five elements. Following the examples of the five phases, either the features or the appearance of all things can be used to categorize them into their own unique five phases. In terms of shape, the wood-type appears as long sticks, fire-type is symbolized by an inverted triangle, earth-type stands for wide ground, metal-type describes images of sharp edge, and water-type depicts the shape of a running stream. In addition to shapes, color is also applied to the five phases. Blue is a symbol of the wood-type; red is representative of the fire-type; yellow represents feeling comfortable and symbolizes soil, not only fostering but also supporting, the earth-type; white is the metal-type color of polished iron and silver; and black, which represents the ability to hide, is associated with the water-type.[1,5]

1.2. *The practical application of the five elements*

Doctors who practice traditional Chinese medicine (TCM) have put the five elements theory into practice, extending it to clinical practice as a form of five element acupuncture (FEA), which was introduced by a British acupuncturist, Dr J.R. Worsley.[7] FEA is now a popular alternative treatment worldwide, including in Europe, Australia, and the United States. According to Dr Worsley, human bodies are composed of a combination of the five elements.[7] A deficiency among the five elements are thought to cause illness. Thus, practitioners diagnose the deficient elements in the patients and treat illness by supplying the deficiency using FEA.[8,9] There is also another FEA method, called Sa-Ahm acupuncture, in Korea. In Sa-Ahm acupuncture is applied on points called Five-Shu (五輸), which is five flows of qi(氣) divided by five elements at limb distal part below elbow or knee joint.[10] Thus, even if there are differences among countries, the five elements theory can be practically applied to alternative medicine in the worldwide.

1.3. *The five elements and human organs*

Prior to the introduction of functional organs under anatomical system, TCM had already established the human organic system, applying the above concept to human organs, consequently categorizing human organs according to the five elements, during China's Warring States Period (770–221 BC). The classical book of Huangdi Neijing (also called the Inner Classic of the Yellow Emperor) connected each organ to five elements linked to natural phenomena, particularly weather; however, they lacked an explanation for causal relationships.[11,12] Although it is still ideological theory, which is yet to be proven, TCM has developed this theory and applied it to functional organs and anatomical systems. TCM divides the human organic system into five organs, i.e., the liver, heart, pancreas (including spleen), lung, and kidney, which correspond to wood-, fire-, earth-, metal-, and water-type, respectively. The liver plays a role as the first of the five-phase cycle, supplying energy originating from glucose, fatty acids, and amino acids to the whole body, and even converting extra energy to glycogen storage, hormones, and proteins. Oriental medicine refers to the heart as the ruler of the human body, circulating blood, oxygen, nutrients, and waste. It is tied to the impression of furious flames. The pancreas is part of the digestive system. It produces insulin, which induces target cells to absorb glucose as an energy source that supplies the body. This function has been likened to that of the earth-type, which fosters crops. As the lid of the body, the lung is a respiratory organ for breathing, or the exchange of gas. The exchange of carbon dioxide and oxygen occurs in the lung, giving it metal-type attributes. Finally, the kidney plays a role in filtering the body's waste for removal and producing urine. Water, excreted from the kidney is reminiscent of the flow of a river; therefore, the kidney has a water-type attribute.

1.4. *The five elements and cellular organelles*

The cell is functionally and structurally the smallest unit of the human body. By maintaining communication between extracellular and intracellular environments, cellular organelles perform the diverse functions required for cells to grow, divide, synthesize, package, and survive. The cellular organelles include the endoplasmic reticulum (ER), Golgi apparatus (GA), mitochondria, lysosome, and plasma membrane (PM), which envelopes the cell. Considering the concept of the fractal theory, i.e., typical self-similar patterns, cellular organelles may correspond to human organs. Thus, it then follows that cellular organelles can be classified as little organs.[13] As explained above, since the five organs can be based on five phases, this can also be applied to the five cellular organelles. This means that human cellular organelles can also be orderly divided into five parts, where the ER, GA, lysosome (including vacuoles), mitochondria, and PM, correspond to wood-, fire-, earth-, metal-, and water-type, respectively. The ER is composed of three kinds of structural forms: cisternae, vesicles, and tubules. The ER can be structurally and functionally divided into the rough ER and smooth ER. The rough ER is involved in the synthesis of protein due to the many ribosomes lining its inside, while the smooth ER is involved in lipid, glycogen, and steroid synthesis.[14,15] Thus, the main function of the ER is synthesis. Proteins that are synthesized at the ER are modified to direct them to their destinations. Like packaging in the post office, the GA acts as a central transport system and plays an important role in modifying, sorting, and packaging macromolecules for transportation. Each molecule cannot perform its functions until it has matured at the GA.[16] Although each molecule completes its function at its destination, the by-products that are generated by metabolic processes need to be eventually recycled or removed. As the cellular digestive organelle, the lysosome contains hydrolase enzymes in its acidic compartment that can digest metabolic products or waste. In addition to the lysosome, vacuoles are also able to help process cellular waste. The function of vacuoles is to contain waste or water to isolate harmful contents from the cell. Like the lysosome, some vacuoles also have digestive function through maintaining an acidic internal pH and containing hydrolytic contents.[17,18] Mitochondria provide the cell with energy (i.e., adenosine triphosphate) via oxidative respiratory phosphorylation, using oxygen, to carry out diverse metabolic tasks, such as apoptosis, calcium signaling, cellular metabolism, etc.[19,20] Finally, the PM, acts as a selective filter, and separates the internal part of cell from the outer environment. It selectively transports ions, inorganic, and organic molecules through the membrane. The

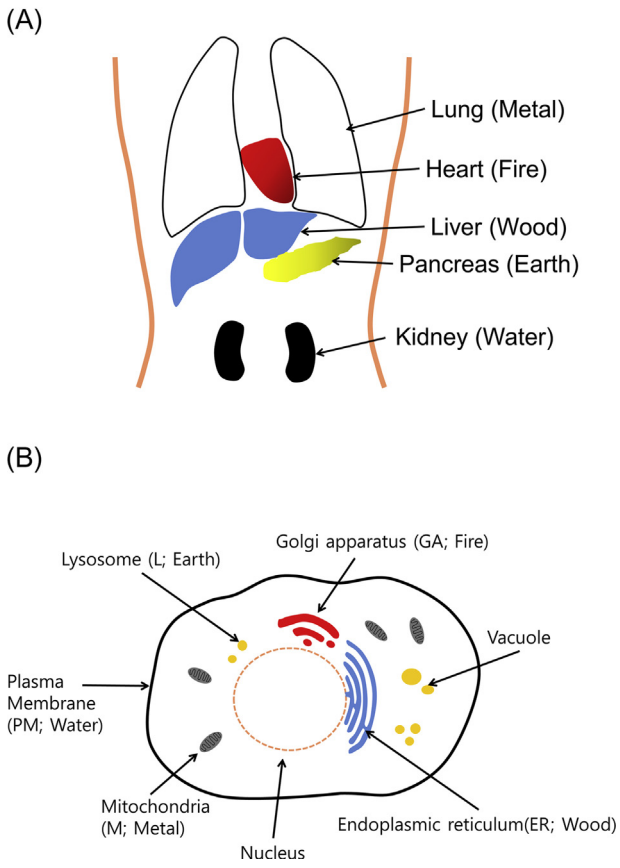

Fig. 1 – Diagram of human organs and cell structure. Major human organs comprising the circulatory system like the lung and heart, digestive system like the liver and pancreas, and urinary system like the kidney (A). Representative cellular organelles include the nucleus, endoplasmic reticulum (ER), Golgi apparatus (GA), mitochondria (M), lysosome (L), vacuoles, and plasma membrane (PM) surrounding the cytosol of cells (B).

materials can be transported through the cell membrane by several mechanisms: 1) passive diffusion, 2) active transportation through transmembrane channels and transporters, 3) endocytosis, and 4) exocytosis.[21–23] Thus, cellular organelles seem to have the attributes of little organs of the human body. Importantly, the nucleus, which is the control center of cell, could not be included in the five cellular organelles, because it corresponds to the brain, the control organ of the body, which is excluded from the list of five organs corresponding to the five elements. Overall, the ER, GA, lysosome, mitochondria, and PM, correspond to the liver, heart, pancreas, lung, and kidney (Fig. 1). Certain aspects of oriental medicine, like the relationship between the organs and the five elements, may also be extended to the five elements (Fig. 2). That is, based on the fractal theory, the five cellular organelles may be linked to the five elements that correspond to the five organs. The synthetic function of the ER makes itself have the characteristics of the wood-type, as does the liver. Similarly, the GA, lysosome (vacuole), mitochondria, and PM also correspond to fire-, earth-, metal-, and water-type, respectively.

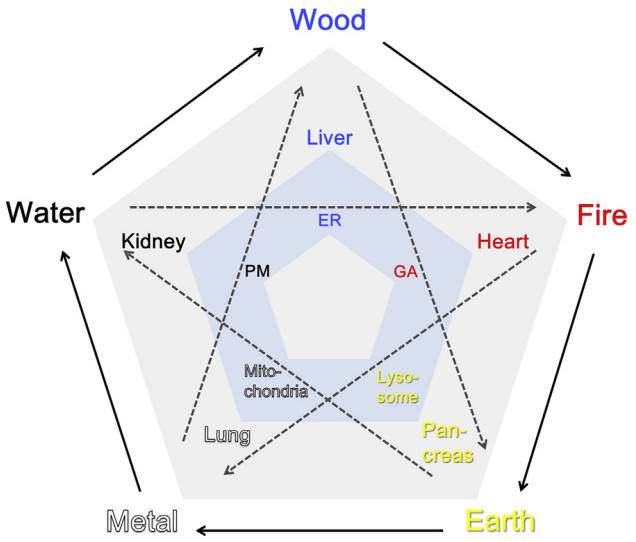

Fig. 2 – Diagram of linkage between cellular organelles extending to organs and five elements. The clockwise rotation of five elements is order, circulates from the wood- to water-type. The human organs, which are connected to the five elements, also rotates along with them. The innermost pentagon indicates cellular organelles as microcosms of the five elements. Arrow-lines present mutual nourishment cycle, arrow-dashed lines indicate mutual restrain cycle. Pc indicates pancreas.

1.5. *Relationships of cellular organelles in the theory of five elements*

As introduced above, there can be cycles of mutual nourishment and mutual restrain. The mutual nourishment cycle is the so-called win-win relationship that forms a circulation in the order of the ER, GA, lysosome, mitochondria, and PM (shown in Fig. 2). The mutual restrain cycle, however, is a balance of relationships that forms a circulation in the order of ER, lysosome, PM, GA, and mitochondria.

A representative example of the mutual nourishment cycle is the transportation of synthesized molecules, such as proteins and lipids, from the ER via the GA into the lysosome. The mutually beneficial relationship between the lysosome and mitochondria is exemplified by the steady-state removal of reactive oxygen species formed in the process of mitochondrial respiration.[24] The mitochondria-derived vesicles budding from the mitochondria can selectively carry reactive oxygen species to the lysosomes. The mitochondria supply the PM with energy to perform active transport across the membrane, in and out of various molecules through transporters. In relation to the circulation between the PM and ER, the PM, being tightly associated with the ER, can regulate Ca^{2+} signaling as well as organelle morphology through the interplay of the stromal-interaction molecule proteins.[25]

In the mutual restrain cycle, the typical balance of processes is seen in the formation of autophagosomes, a double-membrane compartment that usually manifests under unfavorable starved conditions. This process involves mitochondria, the ER, GA, and lysosomes. Cells remove dam-

aged molecules or waste products and organelles through the process of autophagy. The core of this process is the formation of the autophagosome, which eventually fuses with lysosomes, degrading its contents and forming the autolysosome.[26] Autophagosomes are initially formed at ER-mitochondria contact sites, i.e., mitochondria-associated ER membrane.[27] Interestingly, the GA is known to be involved in autophagy as a potential membrane source.[28] The balanced relationship between the lysosome and PM can be explained by both endocytosis and exocytosis,[29] whereas the balanced relationship between the PM and GA is mainly observed in exocytosis.

As explained above, both the outer and inner circles are linked to the five elements in an intriguing manner, which corresponds to the relationships of the five cellular organelles (i.e., the ER, GA, lysosome, mitochondria, and PM). These relationships between the organelles have central roles in maintaining homeostasis in both intra- and extra-cellular environments and metabolism, which is like the mutual nourishment and restrain cycles of the five elements (Fig. 2).

1.6. *Perspective study of cellular organelles on the theory of five elements*

It may be too obvious that the latest theories in biology have not taken into account the idea of conceptual and reciprocal of five elements theory, as it has evolved through the interpretation of results through experimental and analytical methods. Thus, efforts to identify the mutual nourishment or restrain cycle between microscopic cellular organelles in a systematical and experimental manner have not been considered. However, since stem cell research has recently become more prominent, pluripotent stem cells might provide a resource to prove the cellular five elements, with the hypothesis that the interaction between cellular organelles, or mutual nourishment or restrain of cellular organelles, will also be experimentally verified in terms of cell type. For example, in the case of pluripotent stem cells, there is a difference in the number of mitochondria before and after differentiation,[30–32] which is a simple example showing that the role of cell organelles can change with different cell types. In addition, cancer cells can produce energy by the Warburg effect by mitochondrial respiration defects due to mitochondria abnormalities. Although mitochondrial metabolism can play an important role in chemotherapy, other organelles such as ER (mutual nourishment of mitochondria) and GA (mutual restrain of that) can also be targeted by chemotherapy. Thus, mitochondria can be considered to either be a part of the mutual nourishment cycle or restrain cycle (Fig. 2).

2. Conclusions

So far, most researchers have primarily studied cell biology based on individual cellular organelles without considering the overall association between each organelle. However, traditional oriental medicine has long emphasized the linkage between the systems. Regarding the human body systemically as the principal of the universe, using the five elements theory, it is evident that cellular organelles are organically, or functionally connected to each other as the circle of the five elements. Furthermore, matching the ER, GA, lysosome (vacuole), mitochondria, and PM to the wood-, fire-, earth-, metal-, and water-types, respectively, through the possibility of the existence of the cellular five elements, we have re-evaluated the relationship between each cellular organelle. These relationships could have a mutual nourishment or restrain cycle among the ER, GA, lysosome (vacuole), mitochondria, and PM. This new concept on relationships between five indispensable cellular organelles and essential organs in body would provide an upgraded version of homeostatic functioning and/or pathophysiological conditioning in a cell or even in a body.

Conflict of interest

The authors declare no conflict of interest.

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