

Precision Medicine in Chinese Medicine

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Abstract. This article attempts to demonstrate the scientificity and clinical practicability of the meridian and acupoint system in Chinese medicine by explaining the analogy of the meridian and acupoint system, in addition to some experimental results of the biomedical engineering of Western medicine. Precision medicine in Chinese medicine is accomplished through the coordinated operation of the neurohumoral regulation system, the cell transduction system and the meridian system. Appropriate stimulation of acupoints on the human body can trigger certain targets in the body and produce the desired response, such as anti-inflammatory reactions or pro-inflammatory reactions. It can also change the homeostasis of the human body's internal environment, including endocrine, physiological, pathological, psychological and cellular states by controlling body temperature regulation within a certain range. There are many functions of meridians. In fact, the meridian system can not only respond to acupuncture stimuli, but also transmit the effects of drugs to the target. Different acupoints on the surface of the human body have the same or different functions, and through the transduction of the meridian system, the local targets or all of the body will produce the same or different responses. Several experiments with acupuncture and other mechanical stimuli have confirmed the existence of this fact. But the experiment can only show a small part of the full function of acupuncture. The functions of various acupoints are equivalent to the functions of receptors, channels, ion pumps and other structures on the cell membrane. It is just that there are macro and micro differences in the form of expression. Intracellular and extracellular signal transduction, cascade reactions, and neurohumoral regulation are closely related to the meridian system.

Keywords: precision medicine, Chinese medicine, acupuncture, meridian, acupoint.

1. Introduction

The precision medicine of Chinese medicine is embodied in the all-round diagnosis and treatment of internal or external, physiological or psychological of the human body through a dense and connected meridian net. When diseases or injuries come, many changes occur in the human body, such as fluctuations in pH and resting potential. Doctors can use drugs for targeted auxiliary rehabilitation and, at the same time, use acupuncture to properly stimulate the acupoints, purposefully actively trigger a series of controllable electro-chemical changes. These methods can produce therapeutic effects through meridians, nerve-humor regulation and intercellular signaling with the superposition of space and time. For example, depolarization triggers the action potential and improves the degree of the immune response. Some cold or heat-sensitive neurons and receptors of the human body are sensitive to the amplitude and frequency of stimulation. They emit impulses after being stimulated by acupuncture and act on the lesion site through meridians, nerve-humor regulation and intercellular signaling. Using the force and frequency of acupuncture to stimulate the acupoints can change the overall or local body temperature. Acupuncture stimulates some members of the TRP family to establish a positive and negative feedback mechanism between the feeling of sore/ numbness/ swollen/ pain and temperature changes, and achieve the purpose of clearing the pathogens and restoring homeostasis by regulating temperature.

2. Build a model to illustrate the theory of precision medicine in TCM

Precision medicine is the soul of Chinese medicine, the laws it follows, and the goal it pursues. For example, use different drugs for different people and different diseases. Doctors adjust the type

and quantity of drugs depending on the situation of different people, even they catch the same disease. Sometimes the same methods and drugs can be used to treat different diseases. After thousands of years of continuation and development, Chinese medicine has formed its own systems and concepts and has gradually integrated with modern science and technologies. Using modern scientific concepts and achievements to interpret and prove the precision medicine system in Chinese medicine can promote and expand the progress of modern medicine.

Chinese medicine believes that living species have relationships and a lot in common. The smallest known organism, prion proteins, are just a clump of protein particles that reveal the characteristics of life through their own composition and conformation. Proteins encapsulating nucleic acids can evolve into viruses; phospholipid membranes coating proteins and nucleic acids can become cells. Many cells form tissues and organs through catabolism and anabolism and then organically integrate and systematically coordinate, and eventually create a variety of multicellular species. They have both commonality and personality, and humans are one of them. Life multiplies in fission and inherits in fusion. Single-celled organisms evolved and made up humans, and man is made by cells in their own image. Humans cannot create the unknown, and neither can cells. Therefore, the human body has a similar structure and function to cells and can also be considered homologous and heterogeneous to a broad extent.

Cells are the epitome of the human body, and the human body amplifies cells. From the conformation of microscopic particles to cells, tissues, organs, systems, and the human body, even to the biosphere and the universe, the whole system is like a nesting doll layers upon layers. The skeleton of the cell is equivalent to the motor system of the human body; the function of the cytoplasm is consistent with the regulation of body fluids. There are thousands of various skeletons, channels, receptors and ion pumps on the cell membrane, and they correspond with various functions of meridians, nerves, acupoints, receptors and senses on the skin. Although the skin seems to change slowly, it is always in a state of flow and renewal. Organelles are equivalent to various organs of the human body—the nucleus is equivalent to the nerve center, exocytosis, and endocytosis are similar to food intake and excretion. Various physical and chemical reactions in cells are physiological changes in the human body—the absorption of the intestine and the secretion of glands are essentially cellular activities. Dolly sheep cloned from somatic cells is almost a perfect copy of the master copy, which can provide support for the nesting doll model and various forms of nesting doll relationships between the human body, systems, organs, tissues and cells.

All somatic cells in the human body have the same DNA but differentiate due to different expressions. Differentiation does not mean fragmentation. The inherent nature and mutual connection still exist. Specificity is not unique and is usually expressed completely or incompletely in various ways. With modern biological techniques, we can use viruses that carry insulin-producing RNA to infect human cells, making the infected cells express insulin. However, due to the inability of current technologies to control the virus, there is a danger of turning the entire human body into islets. Therefore, this wonderful technology cannot become gospel for diabetic patients for the time being. Nevertheless, this example makes a case for a conversion relationship between nesting doll models. For example, egg-laying dinosaurs went extinct 65 million years ago, but their fossil skeleton structure is very similar to that of today's animals, including humans, which supports that the nesting doll model is not only applicable to individuals but also to time and space.

In the Chinese medical concept, man and nature also have nesting doll relationships. Climate phenomena in different seasons correspond to human physiology and pathology changes. Sixty years per period, 24 solar terms per year, 12 time periods per day, 5-day and 7-day cycles, all of which are the rhythms and laws of resonance between life and nature. The nesting relationship and mutual adaptation between animals, plants, and nature are the basis of Chinese medicine's medical theory and pharmacology and the theoretical basis for drugs' function and targeted effect.

Modern genetic engineering provides strong evidence for the nesting doll model that humans share parts of the genome map with many species, proving that they share a common ancestor. The results and applications of animal experiments follow the principles of the nesting doll model. Clinical trials

and animal experiments based on the nesting doll model are the subjects of Chinese medicine. The nesting doll model is one of the manifestations of precision medicine in Chinese medicine. Its scientificity lies in deriving the hidden unknowns in other models through the explicit knowns in similar models, and drawing correct treatment measures according to the inferences.

The nesting doll model is closely related to the concept of the membrane system, which is a supplement and extension to the nesting doll model. The membrane system embodies the functions of eukaryotic cells, and organelles rely on the membrane system to perform their functions. Encapsulation, folding, fusion and transduction are the main functions of the membrane system.

As a human body made by cells, its activities are also essentially the encapsulation, folding, fusion and transduction of the membrane system, such as the sulci cerebri, the villi of the small intestine, the alveoli, the pericardium and the skin. Suppose the human body is approached from a three-dimensional to a two-dimensional structure and extended as much as possible. In that case, we can definitely obtain a very large multifunctional biofilm like a cell membrane with various structures coordinating and perfectly performing functions. Proper stimulation of one of these points will likely trigger a local or whole biofilm chain reaction. These allow us to explore the principles of acupuncture in precision medicine.

3. Modern scientific researches and analysis on precision medicine in TCM

The theoretical and practical effects of meridians in Chinese medicine prove that the meridians and the circulatory system, immune system and neuro-humoral regulation system of modern medicine all intersect with each other. In terms of excitation transduction, whether the meridians and acupoints have the functions of the sinoatrial node, intercalated disc, Purkinje cell, His bundle and Ranvier node is still in the process of experimental proof. External stimuli can change cells' physiological state, structure and function, and even trigger local or action potentials. The human skin is equivalent to the cell membrane, and the meridians and acupoints on the skin are equivalent to the skeleton, channels, receptors, ion pumps, etc. on the cell membrane. Appropriate stimulation of acupoints on the skin by acupuncture is also equivalent to stimulation of cell membranes, which can also change the physiological state and function of the body, and at the same time, trigger various local/overall changes, including immune responses even the participation of psychological motivation. A Harvard group reveals a neuroanatomical basis for acupuncture practice, showing that electroacupuncture stimulation can drive distinct autonomic pathways and modulate systemic inflammation in somatotopy-, stimulation intensity- and disease state-dependent manners. The vagal-adrenal anti-inflammatory axis evoked by low-intensity ES at the hindlimb ST36 acupoint operates in non-splenic tissues, whereas the spinal-sympathetic axis evoked by 3 mA ES at the abdominal ST25 acupoint can suppress splenic inflammation. 3.0 mA electroacupuncture stimulation at ST36 produced opposite effects at different disease states: anti inflammatory for electroacupuncture stimulation performed before lipopolysaccharide exposure and pro-inflammatory for electroacupuncture stimulation performed after lipopolysaccharide exposure(Liu et al., 2020). Activation of the vagal - adrenal axis can suppress systemic inflammation induced by lipopolysaccharide (LPS), a bacterial endotoxin(Liu et al., 2021).

Acupuncture stimulates acupoints, which can trigger pro-inflammatory or anti-inflammatory responses according to treatment needs and target diseases through the transduction of meridians. For example, it triggers the chemotaxis of white blood cells to gather to the target site and exert immune function. While the doctor changes another acupuncture method can produce anti-inflammatory effects. From the standpoint of acupuncture, signal transduction depends on the neuro-humoral regulation system and exists in various ways, including intercellular signaling. The action potential generated at one point of the cell membrane can spread throughout the entire cell membrane and trigger a series of physical and chemical changes inside and outside the membrane. The sinoatrial node's action potential can trigger all myocardium cells to generate an action potential. In the same way, the responses similar to action potential generated by acupoints in the human body are

transmitted to the required parts through the meridians, causing corresponding physiological and psychological changes, regulating local/overall physiological functions in the body, treating diseases or maintaining homeostasis.

The therapeutic principle of massage was demonstrated in experiments. Mechanically activated channels confer force sensitivity to cells and organisms by allowing the passage of ions across the membrane in response to a mechanical stimulus¹. Piezo1 and Piezo2 are mechanically activated ion channels that mediate touch perception, proprioception, and vascular development(Saotome et al., 2018). Mechanotherapy, application of mechanical loading to injured tissue, has been widely used as an alternative and complementary medicine and is known to improve rehabilitation of musculoskeletal tissues, possibly by increasing blood flow, reducing inflammation, and increasing mitochondrial biogenesis(Seo et al., 2021). Mechanosensitive ion channels are expressed in nearly all cell types and can respond to a diverse range of physical forces. Whereas the opening of mechanosensitive cation channels leads to membrane depolarization and triggers action potentials or neurotransmitter release, apply mechanical force to specific locations of a cell, including the nerve terminals or neurites, where mechanically activated ion channels are thought to be functioning(Ranade, Syeda, & Patapoutian, 2015). The application of mechanical force to a specific location in the human body can also activate various functions and work. For example, awake, behaving animals that lack Piezos had labile hypertension and increased blood pressure variability, consistent with phenotypes in baroreceptor-denervated animals and humans with baroreflex failure. Piezo1 and Piezo2 are the long-sought baroreceptor mechanosensors critical for acute blood pressure control(Zeng et al., 2018). This principle is also the mystery of acupuncture and massage for controlling and treating blood pressure.

Thermoregulation is the body's natural weapon to resist diseases. Acupuncture stimulates the skin's heat and cold receptors to induce the temperature-sensitive neurons of PO/AH to emit impulses, which can cause local or overall meridians, produce electro-chemical changes, and raise or lower body temperature, so that produces a therapeutic effect on the target. For example, the temperature rise or fall will cause changes in the polymerization and depolymerization of microtubules in cells, affecting functional activities such as cell division, conduction, morphology, and transportation.

Stimulating acupoints in different ways and levels can separately control the temperature of different body parts through meridian transduction. Animal experiments have shown that the hypothalamus, brainstem reticular structure and spinal cord contain temperature-sensitive neurons. Animal experiments have shown that the central nervous system such as the hypothalamus, brainstem reticular structure and spinal cord contain temperature-sensitive neurons, which are very sensitive to temperature changes, and the firing frequency changes when the temperature of the local tissue changes by 0.1° C, and there is no adaptation phenomenon. The temperature receptors are more sensitive to the rate of temperature change. The doctor decides acupuncture's frequency, strength, and depth based on the sensitivity of temperature-sensitive neurons and temperature receptors to the amplitude and rate of change. The pricking frequency, force, and depth can simulate fire frequency and amplitude changes.

Acupuncture can stimulate some members of the transient receptor potential (TRP) family to establish positive and negative feedback mechanisms between the feeling of sore/ numbness/ swollen/ pain and temperature changes, and promote metabolism, balance physiology and psychology, trauma repair and immunomodulation through fluctuations in electro-chemical equilibrium and temperature changes.

Primary afferent (somatosensory) neurons detect various physical and chemical stimuli, including temperature, pressure, and noxious irritants. The transient receptor potential (TRP) channel family has been shown to play a predominant role in these processes, particularly regarding thermosensitivity and chemosensitivity. Mammalian TRPA1 is expressed by primary afferent sensory neurons of the pain pathway, where it functions as a sensor of environmental and endogenous chemical irritants, and contributes to cellular mechanisms underlying inflammatory pain(Cordero-Morales, Gracheva, & Julius, 2011). TRP channels are polymodal in that they are activated by numerous stimuli including

voltage, temperature, and small molecules(Ranade et al., 2015). The most important ion channel family that detects and transmits noxious stimuli is the transient receptor potential (TRP) channel family(Gonzalez-Ramirez, Chen, Liedtke, & Morales-Lazaro, 2017). The 2021 Nobel Prize in Physiology or Medicine was awarded to David Julius and Ardem Patapoutian for their contributions to the discovery of temperature and haptic receptors.

There are vector differences between the concept of acupuncture and the discovery of David Julius in the understanding and utilization of the TRP family. Preclinical research has identified an array of ion channels in sensory neurons involved in the generation and transduction of pain as potential targets for pharmacological intervention(Szallasi, 2009). Acupuncture, on the other hand, needs to establish a conversion relationship between pain and temperature, linking pain, mechanical stimulation, and chemical signals with temperature switches, and through the physiological/psychological changes caused by the feeling of sore/numbness/swollen/pain, triggers the thermal changes, resulting in pro-/anti-inflammatory responses.

The TRP family is closely related to inflammation and temperature. Depending on the patient's condition, the mechanical stimulation of acupoints produces signals of sore/ numbness/ swollen/ pain, inducing the body's thermoregulatory system to change body temperature. In addition, since inflammation is usually associated with pain and heat, the local and targeted effects of inflammation, pain, burning and tingling caused by acupuncture will also induce the body temperature regulation system to respond. Therefore, the local, targeted or overall temperature of the human body changes. Sometimes the psychological effects also assist. A peripherally localized neuron preferentially sensitive to a noxious stimulus or to a stimulus that would become noxious if prolonged; capable of encoding stimulus intensities within the noxious range; may have a wide dynamic range of thresholds from innocuous to the noxious range but stimulus-response relationship peaks in the noxious range. These also include those not activated immediately but become responsive to heat and mechanical stimulation upon prolonged stimulation(Dubin & Patapoutian, 2010).

The various reactions of the human body are essentially the reactions of the cells. A diverse range of responses might occur, but that response is initiated by this simple chemical process of a ligand binding to a receptor. There are thousands or hundreds of thousands of receptors. All of them could potentially be receiving signals from a ligand or a chemical," second messenger" molecules that carry the signal further into the cell. They often involve networks of reactions, not just one enzyme but a series of enzymes that serve to amplify each other. So this pathway might not be the only one activated inside the cell at any given time. The cells integrate the information into a response through biochemical reactions.

There are also numerous receptors on the surface of the human body, and acupoints are the ones with stronger functions. Acupuncture is performed in various ways on the acupoints through appropriate techniques to achieve the cascading reactions required for system, organ, tissue and cell occurrence. Nociception is an important physiological process detecting harmful signals resulting in pain perception(Gonzalez-Ramirez et al., 2017). Activation of nociceptors requires that adequate stimuli depolarize peripheral terminals (producing a receptor potential) with sufficient amplitude and duration. This ensures that despite any attenuation and slowing of the receptor potential by passive propagation between the sites of transduction and action potential generation, information such as stimulus intensity will be encoded in the resulting train of impulses. The depolarizing receptor potential can be accomplished by multiple membrane conductance changes and electrogenic pump activity(Dubin & Patapoutian, 2010). There are many cellular mechanisms mediating hyperalgesia.

For example, producing plasma extravasation, causing the release of peptides and/or other bioactive substances from the terminal into the interstitial tissue. The released substances produce a myriad of autocrine or paracrine effects on endothelial, epithelial, and resident immune cells, leading to arteriolar vasodilatation and/or increased vascular permeability and plasma extravasation from venules. Liberated enzymes and blood cells further contribute to the accumulation of inflammatory mediators and neurogenic inflammation. A large variety of substances feed back onto nociceptors innervating the injured region and sensitize peripheral terminals by direct and indirect actions at ion

channels, receptors, and second messenger cascades (Dubin & Patapoutian, 2010). There are many ways for acupuncture and massage to use proper pain for treatment. By regulating the strength, time, frequency and amplitude of the stimulation of acupoints and meridians, doctors can produce targeted therapeutic effects. The most fundamental purpose is to induce the human body's own potential to eliminate the influence of disease and restore homeostasis.

4. Conclusion

Chinese medicine uses various macroscopic and microscopic structures, channels, positive and negative feedback mechanisms, receptors, regulators, meridians and acupoints of the human body to control the overall/local changes in the human environment to inhibit/eliminate diseases, improve the physiology/psychology of the human body and weaken or eliminate the conditions for diseases. Every species is the fruit of the same evolutionary tree of life, and the common ancestor is the basis for animal experiments and natural laws in the clinical treatment of humans. After 4 billion years of evolution, cells remain the template for the human body. If the human body is extended in the form of a biofilm, it will present a perfect reflection of the structure and function. The meridians and acupoints are like the skeletons, channels, receptors and ion pumps on the cell membrane, distributed in the biofilm of the human body, forming a dense and connected web with the tissues, organs and systems of the human body through this dense and connected web of the directional/extensive transduction of appropriate stimuli. The biofilm will use the experience and capabilities accumulated over 4 billion years to play a precise regulatory function, resist internal and external harm, and maintain the human body's homeostasis.

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