Traditional Chinese Medicine as a Useful Complement to Omics Initiative

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1. Synapsis
With the advancement of microarray chip, next-generation sequencing and mass spectrometry, and the realization that most, if not all, life phenomena are complex by nature, many biological researches have turned to simultaneous measurement of the full collection of the subjects, e.g., the genome, transcriptome, proteome, metabolome, etc. Such collections of life substances, in turn, will react with nutrients, drugs, and other chemical substances from the environment.

Traditional Chinese Medicine (TCM) views the human body from the perspective of Jing-Mai (variously translated as the Channel, Vessel or Meridians) and Zang-Fu (Yin and Yang internal organs). For its unique correlation with the presentation of genetic syndromes and types of treatment (acupuncture, moxibustion, and Chinese herbal medicine), the TCM may provide an important complement for Omics approach for the understanding and treatment of human diseases. In this article, two important perspectives of the TCM, i.e., the Phenome and the Tropisms of herbal medicine, are introduced as the crucial components for the Omics initiative.

2. The Human Genome Project (HGP)
In the mid 19th century, Charles Darwin hypothesized the theory of evolution to explain the adaptation and variety of species. Shortly after, Gregor Mendel discovered the basic laws of genetics during his experiments on breeding garden peas. Subsequently, researchers discovered nucleic acid and chromosomes, and proved that deoxyribose acid (DNA) is the basic genetic building block of life. In 1953, Francis Crick and James Watson worked out the double-helix structure of DNA\textsuperscript{[1]}, which led to the discovery of genes and the invention of DNA sequencing techniques. In the 1990s, the Human Genome Project (HGP) was initiated, and by 2003 researchers have finally decoded the complete DNA sequence of \textit{Homo sapiens}\textsuperscript{[2]}. At this stage, researchers appeared to have reached the very bottom of life phenomena - further down there are lifeless molecules and atoms. Undoubtedly, above achievements have great implications. DNA is the blueprint of life, and to decode its sequence will shed light on the basics of all life activities, which may provide clues for the treatment of many of mankind’s most perplexing diseases.

3. The Era of Omics
The completed DNA sequences of human and many other species have made the structural information of genetic materials available. For the next step, functional information of such genomes (time, site and strength of expression of individual genes and genetic networks), is to be delineated.

With the realization that most, if not all, life activities are controlled by multiple genes or genetic networks rather than single genes, many researchers have started to look at genes from a more holistic angle, i.e., the Omics approach, in order to obtain comprehensive information and derive more reliable answers\textsuperscript{[3]}. For many researchers, their initiative of research has changed from the “DNA ~ RNA ~ Protein” to “Genome ~ Transcriptome ~ Proteome”. And this has been coupled with technological advances including microarray chip, next-generation sequencing and mass spectrometry.

4. The Genotype ~ Phenotype Enigma
From the very beginning, the Genotype ~ Phenotype correlation has been the core question for genetic research. Gene has been defined as a DNA sequence with certain functions, and genetic mutations are thought to underlie the evolution and onset of various diseases. So far researchers have
already discovered genetic mutations underlying several thousand types of diseases. Established in the early 1960s, the Online Mendelian Inheritance in Man (OMIM) database has collected the most comprehensive and authoritative information on the genetic bases of human diseases.

Defined as “what an organism looks like as a consequence of the interaction of its genotype and the environment”, “phenotype” has been the key to the interpretation of the functions of genes. To fulfill the goal of functional genomics, the phenotypes of genetic conditions need to be systematically interrogated.

As they explored the Genotype ~ Phenotype correlation, researchers have encountered several challenges. These have included variability of phenotype (individuals carrying the same mutation may show different features), pleiotropy (a mutation may cause abnormalities of multiple sites) and genetic heterogeneity (a condition may be caused by different mutations).

Another important yet puzzling feature of genetic diseases has been that many such diseases have presented clinically as “syndromes”, i.e., a group of diseases showing a collection of symptoms and signs including multiple body systems. This also conforms with the laboratory data that the expression of genes are usually not restricted to a particular body system. This has revealed an important conceptual inconsistency, i.e., the body systems defined by Western medicine do not conform to gene expression and embryonic development.

5. Discoveries about Traditional Chinese Medicine (TCM)

Throughout the history of human civilization, the East and West seem to have represented two extremes. The West, inspired by the birth and development of rational Western philosophy, has tended to be more analytical and to explore the fundamentals of phenomena. The East, inspired by native transcendental religious and philosophical ideas, has tended to emphasize summary and abstraction in order to grasp the whole picture.

Modern Western medicine has largely been a product of Enlightenment ideas and 18th and 19th century European and North American practice. These ideas viewed the world in rational terms and attempted to understand the world by breaking it into parts. Consequently, modern Western medicine places great importance upon studying the whole of the human body by dissecting it (anatomy) and delineating the functions of its structures (physiology). Based on anatomical structures and functional relevance, the human body has been divided into respiratory, circulatory, digestive, urinary, neurological, musculoskeletal, reproductive, endocrine, integumentary, and hematological systems. These divisions have laid the foundation for modern clinical specialties. Meanwhile, physiological experiments and inventions such as the microscope have promoted advances in pathology. Discoveries of cells and subcellular structures have further advanced medical research to the realm of molecules.

In contrast to its Western counterpart, Traditional Chinese Medicine (TCM) has appeared to be primitive, static or unscientific. Similar to other traditional ethno-medical systems from around the world, TCM has prehistoric roots and probably developed through trial and error in a Chinese religious, environmental and social context. The fundamental theoretical basis for TCM has been based on principles of balance and harmony. In this system, the human body contains Jing-Mai and Zang-Fu.

Figure 1 The Heart Jing-Mai as described by TCM

According to Huang-di Nei-jing (The Inner Classic of Yellow Emperor)[8], the Heart Jing-Mai has three branches, traversing respectively from the Heart to the Small Intestine, the ulnar side of the upper limb, and underneath the eyes via the throat, which respectively correlate with the co-occurrence of heart - intestinal malformation as seen in Down syndrome, heart - hand malformation as seen Ellis van Creveld syndrome, and heart - eye malformation as seen in Cat eye syndrome and Marfan syndrome.

During my PhD search on genes underlying congenital syndromes such as DiGeorge syndrome and Velo-cardio-facial syndrome, I have discovered a striking correlation between the features of such syndromes and the paths of Jing-Mai and the Zang-Fu described by TCM (Figure 1). Such correlations are systematic and comprehensive, and
may be expanded to many other syndromes, which strongly suggested that the human body concepts of TCM may have in fact reflected the mechanisms of embryonic development[4-7]. Above discoveries may provide crucial clues for gene research as well as uncovering the mechanisms of TCM.

6. TCM Theories as a Useful Component for Omics Approach

As the blueprint of life, DNA certainly has a close relationship with embryonic development. To grow from a single cell to a system as complex as a newborn baby, every step must be precisely controlled. The large number of genes hidden in human DNA will give guidance and direction to each of these steps. Understandably, various genetic mutations can all impact the embryonic development and lead to structural defects of the human body, which in turn may manifest as diseases. Therefore, embryology is the stepping stone for understanding the genetic basis of such diseases.

Figure 2 Human Phenome based on the TCM concepts. Triangles in the figure represent musculoskeletal system. Roman numbers (I ~ V) and Arabian numbers (1 ~ 5) refer to fingers and toes, respectively. Thick lines in the right half of the figure represent the route of the Jing-Mai. Various genetic defects may be regarded as injury to the JING, which may result in 1) abnormal development of the genitourinary system; 2) abnormalities along the four Jing-Mai connected with the Kidneys (midline defects); and 3) abnormalities along other Jing-Mai. JING injury may also result in Marrow deficiency, resulting in abnormalities of blood/immunity (BL/IM), endocrine (ENDO), central nervous system (CNS), and bone (including cranium and spine (CNS)) formations. BL: Bladder; CNS: central nervous system; G: reproductive system; GB: Gall Bladder; LI: Large Intestine; r: radial ray; SI: Small Intestine; ST: Stomach; TE: Triple Energizer; u: ulnar ray.

For its consistency with the patterns of gene expression and congenital syndromes, the fundamental concept of TCM may provide at least two step stones for a full understanding of the functions of the Human Genome, i.e., the Human Phenome based on TCM concepts (Figure 2) and the Tropisms of Chinese herbal medicine.

Incidentally, the TCM also has a concept called “JING” which corresponds with the Western term “gene”. It has been stated that “the JING is the substance most closely associated with life itself; it is the source of life and of individual development. Although it is undifferentiated material, it is the Substance that gives organic life its specific character. It contains the possibility of birth, maturation, decay, and death...”. Apparently, the two medical systems seem to have very similar views in this respect, except that the TCM concept is more holistic.

The TCM also classified the internal organs as part of the Five-Element theory (Table 1). According to this theory, each herb will “enter” one or more Jing-Mai, which has formed the Tropisms of Chinese herbal medicine.

The above theories have formed the basis for TCM treatment, as many diseases are regarded as results of JING deficiency or depletion. And based on the symptomatic patterns of patients, particular acupoints along the Jing-Mai may be chosen for acupuncture and/or moxibustion treatment. Alternatively, combined remedies of Chinese herbs may be prescribed for deranged functions of particular Zang and/or Fu.

In TCM, the prescriptions for herbal remedies usually comprise a combination of medicinal substances. This also drastically differs from modern Western medicine, where most drugs are single chemicals developed through laboratory experiments and clinical trials. However, it should always be born in mind that, in real life, what we eat, drink or contact are rarely single chemicals. Instead, it will be a complex reaction between a myriad of substances and a variety of cells and proteins, which in turn are coded by networks of genes. Clearly, the Tropisms of TCM has provided a guide to navigate through these super-complex reactions between omic levels of substances and life molecules or cells.

7. Summary

The 2012 Annual Meeting of the American Society of Human Genetics held in San Francisco, California has set the theme as “Getting Ready for the Human Phenome Project”[9]. As researchers pointed out, understanding the genetic contribution to both rare single-gene Mendelian disorders and more complex common diseases will require integration of research efforts among many fields and better defined phenotypes.

With its unique correlation with the patterns of gene expression and congenital syndromes, the TCM theories will make a significant contribution to the understanding of the phenotypes of human
diseases and treatment of such conditions. Clearly, rationalization of data derived from databases including the OMIM, medicinal herbs, chemical drugs, and food in the light of TCM theories can certainly complement the current approach for the “Omics” research.

Acknowledgement
This work was jointly supported by the National Natural Science Foundation of China (81473446) and the Natural Science Foundation of Chongqing (cstc2013jcyjA1587).

References

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