Congenital Syndromes Involving the Lungs:
Pathogenetic Models Based on Chinese Medicine Theories

Jesse Li-Ling, M.D., Ph.D., 1,2 and Yiyang Wu, M.D. 1

Abstract

Background: Striking similarity seems to exist between the Jing-Luo and Zang-Fu theories of Chinese Medicine (CM) and clinical features of many so-called multiple congenital anomaly/mental retardation syndromes (MCA/MRs), as both may involve multiple organs and/or body systems.

Materials, methods, and results: Comparison of MCA/MRs involving the lungs and paths of 5 Jing-Mai traversing the organ has suggested that development of lung and radial ray (embryonic structure that gives rise to radial-side structures of the upper limb, in particular thumb and radius) are closely connected. The Lung Jing-Mai and those traversing the Kidneys may well explain combined malformations involving the lungs, radial ray, and the body’s developmental midline. Furthermore, Zang-Fu theories such as “The Lungs rule the skin and body hair,” and “The Lungs as a Zang pair with the Large Intestine” also seem to be in keeping with syndromes simultaneously affecting the lungs, colon, and skin. It may be deducible that the Jing-Mai, as described by CM, probably exists, and that the Jing-Mai and Zang-Fu theories have correctly summarized the connections between particular parts of the human body during embryonic development.

Conclusions: The CM theories therefore may provide important insights into the pathogenesis of relevant diseases as well as clues for development of new treatment for lung-related diseases.

Introduction

The practice of Chinese Medicine (CM) dates back to the prehistory era. The earliest description of the Jing-Luo system may be found in Huang-di Nei-jing (Inner Classic of the Yellow Emperor), a textbook compiled around 100 BC. 1,2 As viewed by CM, each Jing-Luo (variously translated as the Channel, Vessel, or Meridians) comprises a main trunk (Jing-Mai) and many primary and secondary collaterals (Luo and Sun-Luo). 3 There are 14 major Jing-Mai within the body, upon which almost all acupuncture points (Xue) are located. 4,5

Characteristically, each Jing-Mai connects certain internal Organs (Zang and Fu) with particular aspects of external body such as the head and neck, body trunk, limbs, and digits. (Figs. 1–5). This shows a striking similarity to the features of many so-called multiple congenital anomaly/mental retardation syndromes (MCA/MRs) as both can involve multiple organ/body systems. Comparison of described paths of Jing-Mai with characteristic features of many MCA/MRs has suggested that the former probably exists and has represented connections between various parts of the human body during embryonic development. Interestingly, the Kidneys (It should be noted that all CM terms are capitalized in the text since they might have referred to concepts, to some extent, different from the bioscience ones), as seen in CM, are the epicenter of development. The paths of 4 Jing-Mai connected with the Kidneys primarily traverse the midline structures and may therefore provide a more precise definition for the developmental midline (body parts thought to derive from early-formed structures [e.g., close to the primitive neural tube and ventral midline, malformations of which include oral clefts, neural tube defects, diaphragmatic hernias, and omphalocoeles]) of the body. 6

CM has classified the internal organs of the human body into Zang (Yin Organs), Fu (Yang Organs), and Qi-Heng Zhi-Fu (Curious and Constant Fu). There are 5 Zang (the Heart, the Liver, the Spleen, the Lungs, and the Kidneys) and 6 Fu (the Small Intestine, the Large Intestine, the Stomach, the...
Bladder, the Gallbladder, and the Triple Burner [also translated as Triple Energizer]). Together with the Pericardium, each Zang and Fu has its own pertaining Jing-Mai and connects with others via it.¹²

Through systematically correlating the 5 Jing-Mai traversing the Heart and developmental mechanisms of the cardiovascular system, Li-Ling⁷ had found a comprehensive correspondence between the 2 concepts, which may provide a crucial clue for delineating the nature of Jing-Mai as well as molecular networks regulating heart development. Notably, much evidence for the Jing-Mai has been found from the perspectives of biophysics and biochemistry during the past decades.⁸ Recently, Yang et al.⁹ further demonstrated time-dependent evolution of infrared radiant tracks along the Jing-Mai courses. Meanwhile, a group led by Langevin also discovered probable correspondences between the paths of Jing-Mai and connective tissue planes in the body,¹⁰ which seems in keeping with the former’s role in the development. The authors hypothesized that acupuncture points and Jing-Mai can be viewed as a representation of the network formed by interstitial connective tissue, which may function as a bodywide mechanosensitive signaling network.¹¹ Here, to test the hypothesis that clustering of clinical features, as described in anecdotal reports, are not just random but in keeping with CM theories, we have further summarized features of Jing-Mai traversing the Lungs and relevant congenital syndromes. Taken together with Zang-Fu theory, several models for the pathogenesis of such syndromes may be derived.

Materials and Methods

Case reports were retrieved from the PubMed database (www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed, as by May 1, 2007) using combined keywords including “lung,” “thumb,” “radial ray,” and “syndrome.” Features of congenital syndromes were derived from clinical synopses of relevant entries of the OMIM database (www.ncbi.nlm.nih.gov/sites/entrez?db=OMIM&itool=toolbar). Descriptions of paths of Jing-Mai were adapted from Kaptchuk⁵ with minimum modification. Clinical synopses of various syndromes provided by the OMIM database have been manually sorted from original reports by experts. In consideration of the highly variable nature of clinical pictures, strict statistics for the data were omitted.

Results

The lung–radial ray model

According to Kaptchuk, “The Lung Jing-Mai originates in the middle portion of the body cavity and runs downward, internally, to connect with the Large Intestine. Turning back, it passes upward through the diaphragm to enter its pertaining Organ, the Lungs. From the internal zone between the Lungs and the throat, it emerges to the surface of the body under the clavicle. Descending, the Lung Jing-Mai then runs along the medial aspect of the upper arm to reach the elbow crease. From there, it runs along the anterior portion of the forearm, passes above the major artery of the wrist, and emerges at the radial side of the tip of the thumb. Another section of the Lung Jing-Mai branches off just above the wrist and runs directly to the radial side of the tip of the index finger to connect with the Large Intestine Jing-Mai⁵ (Fig. 1).

Through the above translation of the original description from the Huang-di Nei-jing, it may be assured that (1) The Jing-Luo system described by the ancient Chinese does not entirely locate at the body surface; (2) There is a Jing-Mai connection between the lung and the radial ray (embryonic structure that gives rise to radial-side structures of the upper limb, in particular thumb and radius) of the upper limb.

Clinically, co-occurrence of lung and radial ray malformations has been rather common. Through reviewing 6 patients with unilateral lung agenesis, Osborne et al.¹² found hypoplasia of the ipsilateral thumb with various metacarpal and radial anomalies to be the most constantly associated limb abnormalities. Similarly, Mardini and Nyhan,¹³ Manouvrier,¹⁴ and Aggarwal et al.¹⁵ also reported on similar associations between lung agenesis and triphalangeal thumb, and proposed that such anomalies might have resulted from an insult around the fourth week of embryonic development. Benjamin et al.¹⁶ analyzed 21 patients with tracheal agenesis. Although no fixed patterns were found, associated features such as lung hypoplasia, respiratory tract obstruction, and skeletal malformations such as hemivertebrae and thumb abnormalities were noted. Frias and Felman¹⁷ reported on a case with absence of pectoralis major in association with aplasia of ipsilateral radius, thumb, diaphragm, and lung, which was queried as extreme Poland syndrome (Table 1). Clearly, these cases have all indicated that devel-
### Table 1. Clinical Features of Listed Congenital Syndromes

<table>
<thead>
<tr>
<th>Syndrome/Name</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alagille</strong></td>
<td>Failure to thrive, skull malformations, eye anomalies, nose malformations, peripheral pulmonary artery stenosis, cardiovascular malformations, rib anomalies, cholestasis, intra-/extrahepatic duct involvement, vertebral anomalies, short ulnae, short distal phalanges, mental retardation, absent deep tendon reflexes, urinary tract malformations, hepatocellular carcinoma, papillary thyroid carcinoma, hypercholesterolemia, hypertriglyceridemia, abnormal liver function tests</td>
</tr>
<tr>
<td><strong>Down</strong></td>
<td>Short stature, brachycephaly, facial anomalies, external ear deformity, conductive hearing loss, excess nuchal skin, cardiovascular malformations, duodenal stenosis/atresia, imperforate anus, Hirschsprung disease, vertebral/pelvis malformations, joint laxity, short broad hands, palmar crease anomalies, mental retardation, Alzheimer disease, hypotonia, leukemoid reactions, leukemia</td>
</tr>
<tr>
<td><strong>Ellis-van Creveld</strong></td>
<td>Short-limb dwarfism, cleft lip, defect in alveolar ridge, teeth anomalies, cardiovascular malformations, thorax malformations, urogenital malformations, pelvic malformations, fusion of carpal bones, genu valgum, tubular bones anomalies, cone-shaped epiphyses of phalanges, 2 to 5, talipes equinovarus, postaxial polydactyly finger/toes, nail dysplasia, mental retardation, Arnold-chiari malformation</td>
</tr>
<tr>
<td><strong>Goldenhar</strong></td>
<td>Skull malformations, external ear deformity, conductive hearing loss, branchial cleft remnant, cardiovascular malformations, lung hypoplasia, urogenital malformations, vertebral anomalies, mental retardation, hydrocephalus, Arnold-Chiari malformation, occipital encephalocele, agenesis of corpus callosum, hypoplasia of septum pellucidum</td>
</tr>
<tr>
<td><strong>Hermansky-Pudlak</strong></td>
<td>Nystagmus, eyes anomalies, epistaxis/gingival bleeding, cardiomyopathy, interstitial pulmonary fibrosis, restrictive lung disease, granulomatous colitis, inflammatory bowel disease, renal failure, skin pigment anomalies/albinism, thrombocytopenia, pigmented reticuloendothelial cells</td>
</tr>
<tr>
<td><strong>Holt-Oram</strong></td>
<td>Cardiovascular malformations, thorax malformations, absent pectoralis major muscle, vertebral anomalies, thumb malformations, carpal bone anomalies, upper extremity phocomelia, radial-ulnar anomalies</td>
</tr>
<tr>
<td><strong>Laterality</strong></td>
<td>Cardiovascular malformations, pulmonary stenosis, situs inversus viscerum, asplenia and/or polysplenia</td>
</tr>
<tr>
<td><strong>Marfan</strong></td>
<td>Tall stature, long arm span, earlier puberty growth, dolichocephaly, facial anomalies, eye anomalies, high-arched palate, cardiovascular malformations, pulmonary artery dilatation, emphysema, pneumothorax, thorax malformations, hernia, vertebral/pelvis malformations, joint anomalies, genu recurvatum, dolichostenomelia, feet malformations, decreased subcutaneous fat</td>
</tr>
<tr>
<td><strong>Poland</strong></td>
<td>Cardiovascular malformations, absence of pectoralis major muscle, absence of pectoralis minor muscle, hypoplasia of nipple/areola/breast, Sprengel anomaly, ribs anomalies, vertebral malformations, syndactyly/brachydactyly/oligodactyly, hypoplasia of latissimus dorsi/serratus anterior/infraspinatus/supraspinatus/deltoid muscles</td>
</tr>
<tr>
<td><strong>Townes-Brocks</strong></td>
<td>Skull malformations, external ear deformity, sensorineural hearing loss, eyes anomalies, cardiovascular malformations, duodenal atresia, anal malformations, rectovaginal/rectoperineal fistula, gastroesophageal reflux, umbilical hernia, urogenital malformations, thumb malformations/preaxial polydactyly, second metacarpal anomalies, absent/fusion of carpus, 2–3 and 3–4 finger syndactyly, 3–4 toe syndactyly, metatarsals malformations, absent/hypoplastic third toe, fifth toe clinodactyly, mental retardation, hypothyroidism</td>
</tr>
<tr>
<td><strong>VATER</strong></td>
<td>Large fontanels, cardiovascular malformations, choanal/nasopharynx/laryngeal stenosis, tracheal agenesis, thorax malformations, tracheoesophageal fistula, esophageal atresia, anal atresia, urogenital malformations, vertebral anomalies, radial aplasia/hypoplasia, radioulnar synostosis, thumb hypoplasia/preaxial polydactyly, triphalangeal thumb, syndactyly, tethered cord, spinal dysraphia, occipital encephalocele, single umbilical artery</td>
</tr>
<tr>
<td><strong>Zellweger</strong></td>
<td>Failure to thrive, skull malformations, facial anomalies, external ear deformity, sensorineural deafness, eyes anomalies, high arched palate, redundant skin folds of neck, cardiovascular malformations, pulmonary hypoplasia, thorax malformations, liver anomalies, pyloric hypertrophy, urogenital malformations, abnormal growth of bones, cubitus valgus, foot malformations, palm crease anomalies, metatarsus adductus, mental retardation, hypotonia/seizures, gynoid anomalies, alba anomalies, agenesis/hypoplastic corpus callosum/olfactory bulb, hypoplastic adrenal glands, breech presentation, early death</td>
</tr>
</tbody>
</table>
Down syndrome, MIM 18190685), eye anomalies (as in Marfan syndrome, MIM 154700), and ulnar ray malformations (developmental deficiency characterized by defects on the ulnar side of fingers, forearm, and elbow, typically seen in Ellis-van Creveld syndrome, MIM 225500) (Table 1). Specific correspondences were also found between the other 3 Jing-Mai connected with the Heart and syndromes featuring particular types of CHD. These include the Kidney Jing-Mai–conotruncal heart defects and other midline defects, the Spleen Jing-Mai–laterality sequence, and the Small Intestine Jing-Mai (together with one branch of Heart Jing-Mai) –co-occurrence of atrioventricular septal defect and intestinal malformations7 (Table 1).

The heart–lung model

As described by Kaptchuk, “The Heart Jing-Mai has three branches, each of which begins in the Heart. One branch runs downward through the diaphragm to connect to the Small Intestine. A second branch runs upward from the Heart along the side of the throat to meet the eye. The third branch runs across the chest from the Heart to the Lung, then descends and emerges in the underarm. It passes along the midline of the inside of the upper arm, runs downward across the inner elbow, along the midline of the inside of the forearm, crosses the wrist and palm, and terminates at the inside tip of the little finger, where it connects with the Small Intestine Jing-Mai” (Fig. 2).

The paths of the three branches of the Heart Jing-Mai seem to correspond with, respectively, associations between congenital heart defects and intestinal malformations (as in Down syndrome, MIM 18190685), eye anomalies (as in Marfan syndrome, MIM 154700), and ulnar ray malformations (developmental deficiency characterized by defects on the ulnar side of fingers, forearm, and elbow, typically seen in Ellis-van Creveld syndrome, MIM 225500) (Table 1). Specific correspondences were also found between the other 3 Jing-Mai connected with the Heart and syndromes featuring particular types of CHD. These include the Kidney Jing-Mai–conotruncal heart defects and other midline defects, the Spleen Jing-Mai–laterality sequence, and the Small Intestine Jing-Mai (together with one branch of Heart Jing-Mai) –co-occurrence of atrioventricular septal defect and intestinal malformations7 (Table 1).

The kidney–lung model

As described by Kaptchuk, “The Kidney Jing-Mai starts from the inferior aspect of the small toe, runs across the sole of the foot, and emerges along the arch of the foot to circle behind the inner ankle and pass through the heel. It then ascends the medial side of the lower leg to the medial side of the knee crease, climbs upward along the innermost aspect of the thigh, and penetrates the body near the base of the spine. This branch connects internally with the Kidney, its pertaining Organ, and with the Bladder, before returning to the surface of the abdomen above the pubic bone and running upward over the abdomen and chest. Another branch begins inside at the Kidney, passes upward through the Liver and diaphragm, and enters the Lung. This branch continues along the throat and terminates at the root of the tongue. A smaller branch leaves the Lung, joins the Heart, and flows into the chest to connect with the Pericardium Jing-Mai” (Fig. 3).

The lungs and the midline. In addition to the Kidney Jing-Mai, 3 other Jing-Mai (i.e., the Bladder, the Governing and the Conception Jing-Mai) also connect with the Kidneys. Intriguingly, the paths of these 4 Jing-Mai primarily traverse the midline structures of the body.6 Malformations commonly seen in congenital syndromes (e.g., those affecting the nasofrontal structure, eye, urogenital system, spinal column, central nervous system [CNS] and cardiovascular system) all seem to distribute along such Jing-Mai. Notably, the Kidney Jing-Mai “enters the Lung . . . continues along the throat and terminates at the root of the tongue.” Abnormal development along it may therefore induce disturbance along the Lung Jing-Mai. Together with the connection between the lungs and the radial ray, this may explain the common association of midline and radial malformations.

Maltz and Nadas19 reviewed 173 cases of unilateral lung agenesis, among which 23% had cardiovascular anomalies, 14% had gastrointestinal anomalies, 9% had urogenital anomalies, and 5% had fused or hemivertebrae. Osborne et al.12 noted that radial anomalies exist in many of such cases and that, remarkably, visceral and limb anomalies tend to be ipsilateral to the missing lung. Nazir et al.20 and Mardini and Nyhan13 both reported on similar cases with minor varia-
tion. Classical syndromes featuring such association may also include (vertebral, anal, tracheal, esophageal, and renal anomalies [VATER]/vertebral, anal, cardiac, tracheal, esophageal, renal, and limb anomalies [VACTERL]) associations (MIM 192350 and 276950), Townes-Brocks syndrome (also called Renal-Ear-Anal-Radial syndrome, MIM 107480), and many others (Table 1).

"The Kidneys rule the grasping of Qi (Natural Air)." Although the lungs are the main respiratory organ, the Kidneys may also have a close relationship with respiration. A smaller branch of the Kidney Jing-Mai "leaves the Lung, joins the Heart, and flows into the chest." Structurally, the Kidney Jing-Mai probably traverses the pulmonary artery and the aorta. Abnormal development along it may therefore result in conotruncal heart defects. Stenosis of the pulmonary artery is known to be the primary defect in the quadriad of Fallot tetralogy, the most common form of cyanotic congenital heart disease (CHD) featuring in addition ventricular septal defect (VSD), overriding aorta, and right ventricular hypertrophy. Abnormal development along the Kidney Jing-Mai in the chest may also result in malformations of trachea, larynx, and epiglottis.

The CM theories claim that "the Kidneys store the JING (Substance essential for development, growth, and maturation)," "the JING produces the Marrow," and "Brain is ‘Sea of Marrow.’"1,2 The Bladder and the Governing Jing-Mai, both connected to the Kidneys, traverse the brain.1,2 Development of the CNS may thereby have a close connection with the primordial kidneys. Imperfect formation of the brainstem can result in abnormal patterns of respiration. Furthermore, the Kidneys probably also connect with other endocrine organs via the Jing-Mai. It is known that certain hormones (e.g., prostaglandin) can influence lung maturation. These all seem to support the claim that "The Kidneys rule the grasping of Qi."

The Lung–Large Intestine–skin model

As described by Kaptchuk, "[t]he Large Intestine Jing-Mai begins at the tip of the index finger, and runs upward along the radial side of the index finger and between the thumb and index finger. It passes through the depression between the tendons of the thumb and then continues upward along the lateral aspect of the forearm to the lateral side of the elbow. From there, it ascends along the anterior border of the upper arm to the highest point of the shoulder. On top of the shoulder, the Jing-Mai divides into two branches. The first of these branches enters the body and passes through the Lungs and diaphragm before reaching the Large Intestine, its pertaining Organ. The second of these branches ascends externally along the neck, passes through the cheek, and enters, internally, the lower teeth and gum. On the exterior, it continues, curving around the upper lip and crossing to the opposite side of the nose"5 (Fig. 4).

The Lung as a Zang couples with the Large Intestine. Intriguingly, in a similar manner to all other Zang-Fu pairs, Jing-Mai connections between the Lung and the Large Intestine are doubled.7 Furthermore, the Large Intestine Jing-Mai primarily traverses the dorsal aspect of radial ray, just opposite the Lung Jing-Mai.

Clinically, Flye and Izant21 had noted lung sequestration in association with complete duplication of the colon. Mazur22 described hyperlucent lung syndrome in association with gastric and duodenal ulcers and sigmoid malformation. Pathogenetic connection between the lungs and the colon also seems feasible to expand to the entire respiratory system. Huang et al.23 had reported on association of laryngeal anomalies and colonic aganglionosis in addition to CHD and duplicated great toes in two sibs.

"The Lungs rule the Skin and body hair." The above claim may also find support from syndromes featuring combined anomalies affecting the lungs, colon, and skin. Garay et al.24 reported on 5 patients with Hermansky-Pudlak syndrome (MIM 203300, Table 1), among whom 2 had diffuse interstitial lung fibrosis, and 2 presented with inflammatory bowel disease with deposition of ceroid-like material in the colon. Sandberg-Gertzen et al.25 also reported on a case featuring oculocutaneous albinism, hemorrhagic diathesis, multisystem deposition of ceroid lipofuscin, mental retardation, gran-
ulomatosus colitis, and lung fibrosis. Schumacher et al.\textsuperscript{26} reported on a patient with multiple telangiectasias of the gastrointestinal tract, juvenile colonic polyps, and adenomas in association with multiple pulmonary arteriovenous malformations and atrial septal defect. A similar case was reported later by Inoue et al.\textsuperscript{27} Notably, occurrence of multiple cancers in the skin, lung, and colon were noticed by Takemiya et al.\textsuperscript{28} and Chaun et al.\textsuperscript{29} These cases all seem to suggest that the pathogeneses of the lungs, colon, and skin are interconnected, which conforms to the CM claims.

\textbf{The Lung–Liver model}

According to Kaptchuk, “Beginning on the top of the big toe, the Liver Jing-Mai traverses the top of the foot, ascending in front of the inner ankle and along the medial aspect of the lower leg and knee. It runs continuously along the medial aspect of the thigh to the pubic region, where it encircles the external genitalia before entering the lower abdomen. It ascends internally, connects with its pertaining Organ, the Liver, and with the Gall Bladder, and scatters underneath the ribs before pouring into the Lungs, where it connects to the Lung Jing-Mai. The entire cycle of the Jing-Mai system begins anew here. Reconstituting itself, the Jing-Mai follows the trachea upward to the throat and connects with the eye. Two branches leave the eye area, one descends across the cheek to encircle the inner surface of the lips, a second ascends across the forehead to reach the vertex of the head”\textsuperscript{16} (Fig. 5).

The paths of the Liver and the Kidney Jing-Mai overlap literally in between the Liver and throat. Involvement of the Liver Jing-Mai, however, seems to be more obvious in Alagille syndrome (MIM 118450, Table 1), where liver problems are strongly associated with peripheral pulmonary artery stenosis and various eye anomalies. In Zellweger syndrome (also called cerebro-hepato-renal syndrome, MIM 214100), though no structural lung malformation was listed, involvement of the lungs may be deducible from features such as apnea, cubitus valgus (elbow flexion/extension due to proximal migration of the radius), and transverse palmar crease on the hands (Table 1).
Discussion

Based on the above comparisons, the following hypotheses are presented.

1. Both Jing-Mai and Zang-Fu have a material basis and, as summarized by a Human Phenome model by Li-Ling, a close connection with embryonic development.

2. Such connections may be reflected by the co-occurrence of congenital anomalies and preferential metastasis of tumors, albeit with significant influence from natural selection and physiologic factors.

3. At the molecular level, such connections may be of shared gene expression, cell surface protein, and/or signaling pathway in nature.

4. Evidence of Jing-Mai and Zang-Fu may be obtained through combined approaches of gene expression analysis, knock-out experiments, and summary of congenital syndromes.

The above hypotheses may be further elaborated in the following aspects.

Embryonic development of humans as viewed by CM

Literature review has suggested that the CM concept of "JING" has probably referred to genetic material and its activities. Comparing CM theories with modern knowledge also suggests that the "Marrow" concept of CM has encompassed concepts such as hematology/immunity, CNS, and endocrinology. For features such as bone marrow dysfunction, mental retardation, and hearing loss associated with radial ray anomalies, CM theories such as "the Kidneys produce the Marrow," "Brain is Sea of Marrow," and "the Kidneys open into the Ears" seem to apply.

By correlating CM theories with embryology, it may be deducible that, during development, internal factors such as genetic mutations and/or external factors such as teratogens may first affect those earliest formed structures (i.e., those distributed along the 4 Jing-Mai connected with the Kidneys). The latter in turn may induce anomalies along other Jing-Mai. Such a "developmental midline–lung–radial ray" model may well summarize the features of many syndromes involving the lungs and stop the disagreements over eponymous categorization, which does not enable resolution of nosological problems. David et al. had described a term-born boy with severe pre- and postnatal growth retardation. The patient featured facial dysmorphism, cleft palate, velopharyngeal insufficiency, malformed ears and deafness, cervical vertebral anomalies, scapula asymmetry, hypoplastic scrotum, undescended testes, tripalangeal "floating" thumbs, flat feet, bowing knees, synkinetic movements of upper limbs, and absent left lung and kidney. The authors proposed this to be a unique anomaly of blastogenesis simultaneously affecting the arocralen, the mandibulofacial, and the cervicothoracic developmental fields: "It makes little sense to choose one association over another as the diagnosis, since our patient clearly presents as a compound of all of them (Nager AcroFacial Dysostosis, i.e., combination of facial anomalies of mandibulofacial dysostosis (Treacher-Collins-Francescetti) and a/hypoplastic or tripalangeal thumbs, MURCS (Mullerian duct aplasia, Renal aplasia, and Cervicothoracic Somite dysplasia), VATER, and Goldenhar facio-auroculo-vertebral spectrum)."

Connections beyond congenital malformations—"metastases"

The Jing-Mai connections between particular parts of the human body, apart from presenting as co-occurring malformations, may also be reflected by the preference of anatomical sites for metastasis. According to Drewes et al. and Kerin, acrometastases in patients with bronchial carcinoma is rare but well known. Lung tumors, however, seldom give rise to foot metastases. Wu and Guise reported on 6 patients with hand metastasis of tumors of breast, kidney, lung, colon, or humerus in origin. Affected areas included distal phalanges, carpal/metacarpal bones, nailed, and soft tissue of dorsum hand. All patients died within a few months. Metastases of lung/bronchogenic carcinomas to the thumb have also been described by many. Interestingly, hand metastases from cancers of colon and skin origins have also been described. Mendez Lopez et al. reported on a case with metastasis of colon cancer treated 4 years before to the first metacarpal. Gelberman et al. also reported on patients with hand metastasis of skin melanoma.

Metastases of reverse direction also seem to exist. Debruyne et al. had reported on a 76-year-old female who presented with chondrosarcoma of the distal right thumb. Ten (10) years after the surgery, the disease recurred at the trapezoid bone, followed by carpal joint and lung metastases. Wockel et al. reported on a girl with metastasis of a cornified squamous cell carcinoma developed in the nailbed of the right thumb. Lymph node metastasis and vein infiltration were found in the right axilla. The patient died 2 years later. Necropsy revealed diffuse tumor infiltration in the upper arm, axilla, shoulder, neck, and thoracic wall including the right breast. Thoracic para-aortic-abdominal and left-sided axillary lymph nodes and bilateral lungs and pleura were also involved. Karabela-Bouroupolou et al. also described wide metastasis of a chondrosarcoma developed in the proximal thumb in a patient with fatal outcome. These cases also seem to suggest that a connection between the lungs, large intestine, and skin, as summarized by CM theories, probably exists. Molecular features shared by such organs may have induced tumor metastasis in such cases.
Summary

For their compensatory ability and relative difficulties for measurement, the lungs are probably the most easily neglected viscera. CM regards the Lungs to be the Zang most vulnerable to “external pernicious factors.” In congenital syndromes, developmental anomalies of the lungs may often present as recurrent infections. Though Cunningham and Mann had proposed that “The association of pulmonary agenesis and ipsilateral malformations may shed light on its pathogenesis,” implications of patterned anomalies seen in various syndromes, however, have rarely been explored. As illustrated in this study, comparing with theories such as neural crest injuries, disruption of blastogenesis, developmental field defects, or abnormal development of embryonic aortic arches, CM theories can provide a much more specific explanation for such syndromes.

In addition to known mechanisms such as hematogenous dissemination or direct seeding, influences from the environment have recently been recognized as one important factor for organ-specific metastasis of colon cancer. Here, summary of metastases involving the lungs, colon, and the radial ray has suggested that, though seemingly odd, the Lung-Fu pairing between the Lungs and the Large Intestine, and claims such as “the Lungs rule the skin and body hair” are not just mechanistic. Genetically and/or biochemically, such organs are closely connected. It has been known that, in lower animals such as amphibians, skin is also used for (part of) the breathing.

Taken together, our study showed that both the Jing-Luo and Lung-Fu theories have a strong correlation with congenital organs involving particular organs and other body parts. As the mechanisms of such syndromes continue to be delineated, molecular mechanisms for CM may eventually be uncovered. This may be illustrated with the recent discovery of the dHAND–Shh–TBX5 pathway, which is involved in the development of heart and upper limb, in particular fingers. A recent Nature editorial had proposed that, through studying the interconnections between various aspects of an organism, systematic biology may provide an ideal tool for explaining the mechanisms of CM.

Conversely, CM theories have also provided a useful model for studying genetic syndromes, which may shed light on the organization, functions, and activities of the human genome, and development of more effective treatment.

Acknowledgments

This study has been sponsored jointly by grants from the National Natural Science Foundation of China (no. 60574040) and the Scientific Foundation for Returned Overseas Chinese Scholars, Ministry of Education, China.

References


Address reprint requests to:
Jesse Li-Ling, M.D., Ph.D.
Department of Medical Genetics
China Medical University
Shenyang 110001
China

E-mail: jliling2000@gmail.com