

Tightly regulated distribution of family members of proteins is related to social property in the open body system (Review)

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Abstract. Environmentally mediated systemic involvement of autoimmunity, allergy and carcinogenesis are very common by clinical and epidemiological investigation. However, there is an unknown relationship between environment and environmentally mediated systemic involvement of autoimmunity, allergy and carcinogenesis. This unknown molecular communication or response conducts the primary injury sites of the skin, and surface mucosa in the respiratory, alimentary, or reproductive tracts, to the secondary sites or even the whole body under some physiological and pathological conditions. Also, this unknown molecular communication or response involves a variety of molecular events, detectable in systemic differentiation, overexpression, hyperplasia, carcinogenesis, allergies or autoimmunity. The family members of proteins and their relatives are almost ubiquitous, and distribution is tightly regulated at all three administrative levels to form an interacting multiprotein complex. The key question is whether there is unknown communication or response among the family members and, if there is, is it associated with some social property of the proteins in the open body system?

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1. Introduction

Proteins are the basic functional units of the body. At the primary structural level, the amino-acid sequence shows a distinct domain organization. At the secondary and tertiary structural level, the multidomain organization forms elusive allosteric functional conformations or motifs that play dominant roles in activation, inactivation and communication. The sharing of one or more very similar domains or motifs constitutes a protein family. Like the well-studied members of von Willebrand factor A (vWFA) and collagen families, the majority of members in these families are located in the extracellular matrix with expression restricted to a specific tissue in an organ, or a specific tissue in many organs, or in circulated blood (1,2). The members in the cell membrane, cytoplasm, or nucleus are involved in cellular functions such as gene transcription, DNA repair, ribosomal and membrane transport, and proteasome activity (2). Why is the distribution of family members so tightly regulated? The family members may form a multiprotein complex (2). If there is any unknown potential communication or response among the family members, any local protein of family member activity may have a potential communication or response in distal sites by sharing the same or similar motifs of other family members. In fact, there are so many different kinds of family members of proteins that cooperate together and play molecular structure-related roles in a microenvironmental community that even an individual protein may have more than one family membership. It is unlikely that there is only one individual protein or group of proteins responding to the physical, chemical or biological

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factors, even the extremely fine acupuncture needle. If there is any unknown potential communication or response among family members, protein molecules would play important roles to conduct the local stimulation or injury to the distal organ or even the whole body under some physiological and pathological conditions (1). The proteins in the body consist of a highly ordered and subtly controlled society. This society has a potential communication or response by some physiological or pathological conditions. These potential communications or responses may be related externally and internally to environmental factors. The external environmental factors may be physical, chemical or biological challenges. The internal environmental factors may be ionic strength, pH, temperature, circulated molecules and stress or depression of psychotic challenges. The mechanism regulating the activation and inactivation state of individual proteins is emerging from structural investigation. Since the activity of individual protein molecules in local communities and their conduction to distal sites is invisible by current scientific tools, the tightly regulated distribution of family members and potential communication or response among the family members remains to be investigated. In this report, we aim to review family membership, local community, society and regularity of distribution. We also collected evidence from clinical observation, manifestation of some idiopathic diseases; 'non-scientific evidence' of traditional Chinese medicine, acupuncture and other Chinese medicines. Some of those aforementioned phenomena support our hypothesis; there is some unknown communication or response among the family members. This unknown communication or response among the family members may be associated with some social property of proteins in the open body system. Investigation of this mechanism considering the above notion would provide insights into understanding the relationship between the local lesion and multiorgan or multisystem of systemic disorders.

2. Family memberships, the local community and society of proteins

Although there are countless proteins in the body, each individual multidomain protein has several different family memberships, which interact with its surroundings, form highly ordered multiprotein complexes, participate in the local community, and communicate messages to neighbor proteins, cells or tissue, or even to the whole body. The family relatives are almost always ubiquitous and exert multifarious functions. In order to investigate the memberships and their relative proteins, we chose two distinctly different proteins, cartilage matrix protein of matrilin-1 and pulmonary collectin of surfactant protein A (SP-A) as the examples; mainly focusing on well-studied vWFA and collagen family memberships.

Matrilin-1 is a member of the matrilin family and a member of the family of vWFA, as well as the epidermal growth factor (EGF), and thus has at least three different family memberships. In the matrilin family there are four members, matrilin-1, -2, -3 and -4 (3). In the vWFA family membership, on March 24, 2002, the SMART non-redundant database showed there are 948 proteins containing 1196 vWFA domain (2). They include vWFA collagens, integrins, plasma complement factors, von Willebrand factor, trypsin inhibitors

and their relatives, anthrax toxin receptor family, hemicentins, polydrom, cochlin, vitrin, calcium channel $\alpha 2\delta$ family, CLCA family of putative chloride channel subunits of extracellular proteins, and also include Rpn10-26S proteasome regulatory subunit, TFIIP44, Ku70/80 DNA helicase family, ATPases associated with diverse cellular activities (AAA)-vWFA proteins, Sec-23, and copines of intracellular proteins (2). The EGF family membership includes many membrane or signal pathway proteins such as epidermal growth factor (EGF), transforming growth factor alpha (TGF- α), heparin-binding epidermal growth factor-like factor (HB-EGF), amphiregulin (AR), keratinocyte autocrine factor or colorectal-cell derived growth factors, epiregulin (EPR), betacellulin (BTC), and neuregulins (NRGs) (4). Matrilin-1 is strictly a cartilage matrix protein. In mice lacking the matrilin-1 gene, skeletal development is normal and only type II collagen fibrillogenesis and fibril organization have ultrastructural alterations (5,6). Why does 'redundant' matrilin-1 have so many relatives in its protein society?

SP-A, as multiple family membership of matrilin-1, is a member of the collectin family, and also possesses memberships in the collagen and lectin family. The collectins are a group of C-type lectins containing collagen-like regions (7). The family consists of SP-A, SP-D, mannose binding protein (MBP), conglutinin, collectin 43 (CL 43), and collectin liver 1 (CL-L1). SP-A and SP-D are pulmonary collectins, MBP, conglutinin and CL 43 are serum collectins. CL-L1 is a new member of the collectin family, which was cloned from the human liver (8), and is mainly expressed in the liver and stomach, muscle, testes, intestines, and embryos (9). The collagen family includes several large transcripts, usually exceeding 1000 amino-acid residues per single chain (10). They are the major macromolecules of most connective tissue and the most abundant proteins in the body. As a group, they make up 1/3 of all the protein in the body and are responsible for modeling the framework of connective tissue (11). The other six containing collagenous region proteins are serum complement C1q, α - and β -ficolin, hibernation protein, macrophage scavenger receptor, and membrane acetylcholinesterase (12). SP-A also has many relatives in the lectin family, even though SP-A gene knockout mice are normal (13).

Matrilin-1 forms collagen-independent and collagen-dependent filamentous networks in certain cartilage matrices (14). It may interact with aggrecan, hyaluronic acid and the collagen fibril (15). SP-A is implicated in innate host defense (16). Matrilin-1 and SP-A are different functional proteins with absolutely different expressional patterns. Within vWFA and collagen family memberships, they have the same relatives of vWFA collagens that contain 57 of the 134 vWFA domains to date (2) (Fig. 1). In general, matrilin-1 and SP-A interact with their surroundings and consist of a highly ordered, subtly-supramolecular arrangement that plays a structure-related function in its community. In their communities, matrilin-1 and SP-A cooperate together with many other family membership proteins, enacting molecular structure-related roles that depend on microenvironment interaction (17), or binding orientation in the community (18). These services in the local community and cooperation with other community members are their regular jobs despite the fact that they have many other family memberships in the body protein society.

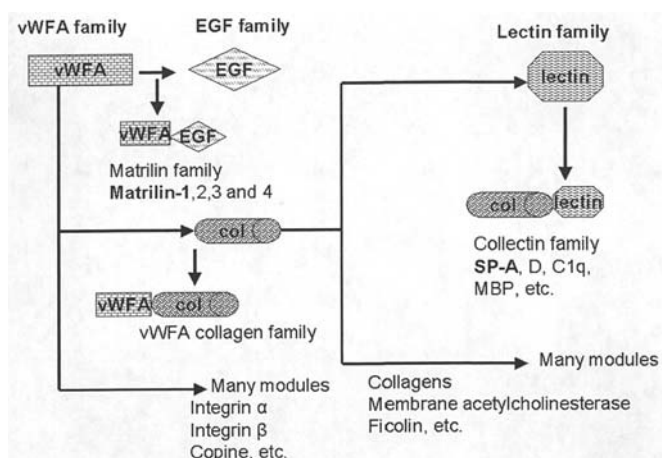


Figure 1. Family memberships and their relatives of matrilin-1 and pulmonary surfactant protein A (SP-A). Matrilin-1 and SP-A are absolutely different in expressional pattern and functional proteins, only focusing on the vWFA and collagen family memberships, they have similar relatives - vWFA collagens.

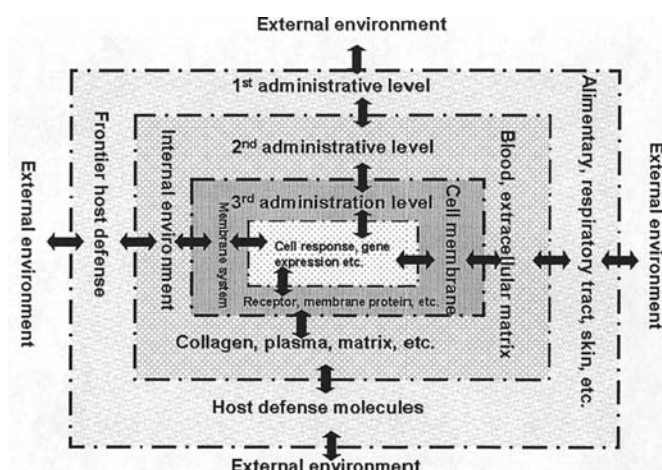


Figure 2. A model for three administrative levels of open body system machinery and external environmental challenges. There is a reciprocal co-operation among vWFA and collagen family members in the three administrative levels. The alteration of mRNA and protein levels of cell response is a detectable molecular communication event.

3. Regularity of distribution of family proteins

To organize the regulation and distribution of the family members, body functions that face the external environmental challenge have three administrative levels (Fig. 2). The first level is the skin, and surface mucosa in the respiratory, alimentary, or reproductive tracts. The second level is the plasma or extracellular matrix. The third level is the cell membrane system and intracellular matrix (1). Increasing evidence indicates that there is reciprocal cooperation among those three administrative levels by signal conduction pathways which depend on the neuroendocrine immune network (1,19). All cell activities depend on the cooperation of these three administrative levels (1). Of the vWFA and collagen families, SP-A and SP-D reside in the surface of the respiratory tract, and may also reside in the alimentary and reproductive tracts as the frontier host defense molecules of the first administrative

level. On the second administrative level, complement B2, C, C1q, MBP, conglutin, CL-43, and von Willebrand factor are circulated members; matrilin-1, -2 and -4 and a variety of collagens are network forming members of the extracellular matrix; matrilin-3, trypsin inhibitors, hemicentins, polydom, cochlin, vitrin, hibernation protein, α - and β -ficolin are extracellular matrix proteins. The second level administrative resident members may form networks, or combine with themselves or other members which have the potential molecular structure for multiprotein complexes in the extracellular matrix. They may also bridge first and third administrative levels. Integrins, anthrax toxin receptor family, calcium channel $\alpha 2\delta$ family, CLCA family of putative chloride channel subunits, macrophage scavenger receptor, and membrane acetylcholinesterase reside in the cell membrane system. Rpn10-26S proteasome regulatory subunit, TFIH44, Ku70/80 DNA helicase family, ATPases associated with diverse cellular activities (AAA)-vWFA proteins, Sec-23, copines and CL-L1 are intracellular matrix members on the third administrative level. The members at the third level are involved in functions such as gene transcription, DNA repair, ribosomal and membrane transport, and the proteasome (2).

For tissue and organ distribution, matrilin-1, matrilin-3, type II, and type X collagen are limited to cartilage; SP-A, SP-D and CL-L1 are organ specific, SP-A and SP-D are lung specific, and CL-L1 is liver specific (9). Some of these are specific to one tissue; for example, complement B, C2, C1q, von Willebrand factor and MBP are plasma specific; membrane acetylcholinesterase is neuro-muscular specific; and macrophage scavenger receptor is macrophage specific. Others are widely distributed; for example, type IV is basement membrane specific; matrilin-2, matrilin-4, type I and type III collagen are connective tissue specific; integrins, anthrax toxin receptor family, calcium channel $\alpha 2\delta$ family, and CLCA family of putative chloride channel subunits are cell membrane specific.

In terms of function, matrilins and collagens form collagen or non-collagen filamentous networks; many other extracellular proteins combine collagen or non-collagen filamentous networks as signal transduction, cell adhesion, receptor, and frontier or plasma innate defense molecules (Fig. 3). Although the majority of members of the vWFA and collagen families are located in the extracellular matrix in different tissues or serum, the members in the cell membrane, cytoplasm, or nucleus play dominant roles in development, immune response, cell movement, gene expression, homeostasis, carcinogenesis, autoimmunity, and many human diseases (1,2). In accordance with those roles mentioned above, stimulation or injury would always be accompanied by laboratory detectable structural and functional alteration of proteins, mRNA, and enzyme activity.

4. Accumulated evidence from clinical investigation

Family members and their relatives are almost ubiquitous, and distribution is regulated at all three administrative levels, to form an interacting multiprotein complex (2). The key question is whether there is potential communication or response among the family members. Unfortunately, less attention has been paid to this subject, since multidomain organization and elusive allosteric functional conformation were invisible to the microscope and conventional tools and,

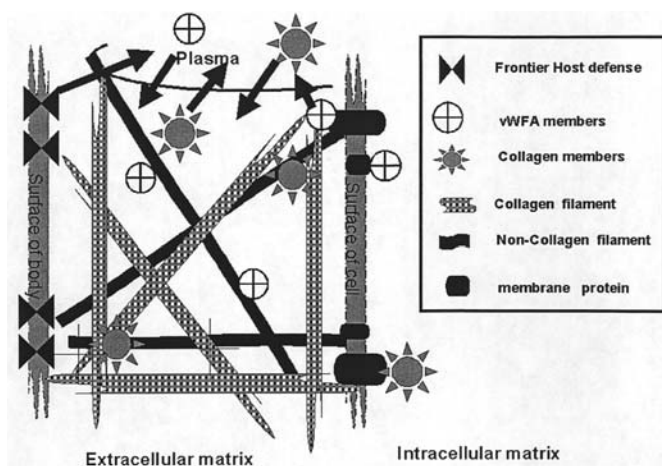


Figure 3. A model for the multiprotein complex of vWFA and collagen family members. The collagen and non-collagen filamentous members form a network; other members in the extracellular matrix combine themselves, collagen and non-collagen filamentous members. In physiological and pathological conditions, the circulated members may enter the extracellular matrix and, in turn, the extracellular matrix members and frontier host defense members may enter into circulated plasma.

thus, no laboratory evidence was available. Fortunately, the potential communication or response among the family members is always accompanied by clinically observable systemic differentiation, overexpression, hyperplasia, carcinogenesis, allergies and autoimmunity. In view of this, multiple sclerosis (20), scleroderma (21), amyloidosis (22), many idiopathic diseases (23), autoimmunity (1,24), allergies (25), and multiple carcinogenesis (26) may relate to pathological communication or responses within the protein society. Otherwise balanced systems between the external environment and open body system are broken by this pathologically missing link of communication or response. In spite of the fact that the fibroblast, lymphocyte, mast cell, endometrium, macrophage, polymorphocyte, neuroendocrine, chondrocyte, or stem cell are located in various organs or in circulating blood, there may be a potential common union, and messages may conduct from some site to others by unknown mechanisms. It is likely that there are many molecules involved in this event. A lot of similar molecules contribute to the pathogenesis of multiple organ involvements. Systemic, ectopic lesions or response is the observable evidence of a pathologically missing link of communication or response within the protein society.

5. Proposed mechanisms

Although there is some clinical evidence, capturing detectable laboratory evidence with current scientific equipment to show potential communication or response among family members remains a distant objective. An individual protein must cooperate with its partners in its microenvironmental community, and a repeatable laboratory model of only one individual protein or group of proteins responding to even the extremely fine acupuncture needle is impossible to set up. Meanwhile, an individual protein itself is not a linear amino-acid molecule, it may be modified by glycosylation, hydroxylation or phospholysation, and may form an elusively folded and

allosteric secondary and tertiary structure. The communication of the protein society should therefore be subtly regulated and always play a dominant role in keeping balance between the external and internal environment.

6. 'Qi' may be the best concept for the communication among family members

Large quantities of epidemiologic investigations and case reports have showed that occupational exposure (27), allergens (28), non-specific infection (29), smoking (30), inhalation injury (1,31), trauma (32), depression and stress (33) are high risk factors in autoimmune diseases, allergies and carcinogenesis for multiple organ involvement. The above non-specific factors may trigger many molecular events and lead local injury from the primary site to distal sites. In turn, multiple organ involvements are clinically observable molecular events. What is the mechanism? Current knowledge remains insufficient for understanding why these factors lead to multiple organ involvement of autoimmunity, allergy and carcinogenesis under pathological conditions; local stimulation leads to distal sites and even to whole body response by acupuncture, qigong and massage under physiological conditions. Traditional Chinese medicine scholars believe that the whole body is an open system which cooperates with the external environment. 'Qi' as a core concept of Chinese traditional medicine is a means of communication between the body and the external environment, and among organs or systems. Scholars of traditional Chinese medicine have been using this theory for explaining etiology, pathogenesis, treatment of disease and healthy life. It has been helping Chinese people for several thousands of years and, today, an increasing number of Western people are accepting this strange concept of therapy and obtaining 'miraculous' curative effects. What is the miraculous 'Qi'? Thus far it has remained a black box (34,35). Our recent report suggested that SP-A may be a candidate of the 'Qi' molecule and its distribution of immunoreactivity is compatible with the primary injury sites of some autoimmune diseases (1). The protein family, community, and society are so subtly designed that all society members may be candidate 'Qi' molecules.

The protein society is so regulated and sophisticatedly designed that communication among the members should be precisely controlled. The communications among the members play dominant roles in the balance of the external environment and the open system of the body. In the clinic, many cases of multiple organ involvement in auto-immune diseases (36), allergy (37) and carcinogenesis (38,39) are associated with a particular genetic background from genomic and epidemiologic investigation. Many investigators agree that these disorders are protein communication-related diseases. The mutant gene of some of these diseases has been found. For example, R602W point mutation in a protein tyrosine phosphates gene has been associated with a high risk of rheumatoid arthritis in a British population (36). Unfortunately, little attention has been paid to mutant protein-associated protein communication. Why does this missing link in communication contribute to the pathogenesis of multiple site involvements? What is the mechanism? To investigate the mutant molecular structure, its community and society, it would be necessary to capture

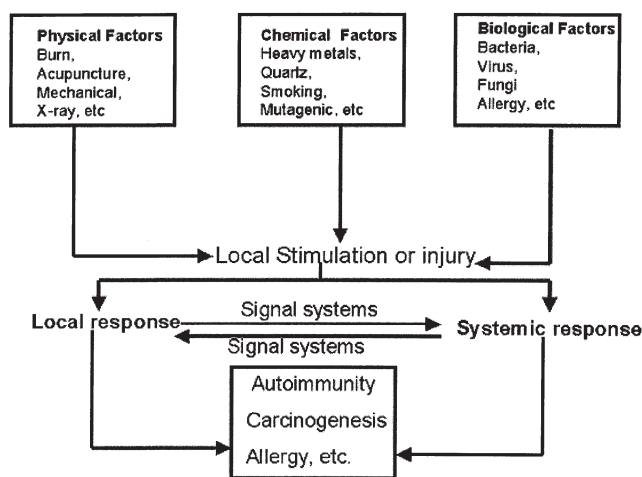


Figure 4. A model for the relationship between the external environment, local and systemic response. External environmental factors lead local and systemic responses. Those responses are clinically detectable involvements of autoimmunity, carcinogenesis, and allergies.

detectable laboratory evidence of the pathologically missing links of communication or response among family members.

7. Cell communication and protein communication

The open body system is constantly exposed to environmental factors and the body properly reacts to maintain homeostasis of body machinery (1). For the body, organs are a highly ordered cell city. The lung is a highly ordered cell city of >40 different types of cells. In that precisely designed cell city, type I and type II cells are lung specific. Fibrocytes, lymphocytes, chondrocytes, mast cells, neuroendocrine cells, and macrophages are also found in extrapulmonary tissue. Whether lung specific or not, each of them is an important participant in pulmonary function and the commonwealth union in physiological and pathological conditions. Any physical, chemical or biological stimulation or injury to the lung is not limited to the lung but also elicits other organ responses or disorders (24). For example, inhalation injury is often accompanied by whole body disorders, especially in the alimentary tract (40); and pulmonary hemorrhage is associated with many renal diseases, including Goodpasture syndrome (41). There are many cell and molecular events involved in 'purely' pulmonary stimulation or injury and in conduction to extrapulmonary sites. Immune system communication has been well studied. Although there is limited information on signal conduction from primary to secondary sites in physiological and pathological conditions, cell activation, mRNA, protein overexpression, injury, hyperplasia and carcinogenesis are all detectable. According to Hayday and Viney's opinion of the ins and outs of body surface in local and systemic immunological response, local and systemic immune responses are probably connected via an 'informational relay' (42). The bidirectional 'informational relay' of lymphocytes conducts the local mucosal surface in immunological tolerance, suppression, immunization response and systemic response. In view of this, local and systemic lymphocytes are the potential commonwealth union. In the pathological conditions, cells in

different organs may respond to some factors. Clinically, the etiologies, mechanisms and pathogenesis of endometriosis (43), inflammatory response (44), allergies (25), multiple involvements of the endocrine neoplasia (26), mastocytosis (45), multiple sclerosis (20), and Proteus syndrome (46) remain unknown. There is, however, visible evidence of morphological resemblance in cell pathology, which may be the missing link of communication from organ to organ. Based on this evidence, the systemic response of resembling cells is not limited to lymphocytes but is also in endometrium, macrophages, polymorphocytes, mast cells, neuroendocrines, chondrocytes, and fibroblasts. In spite of the fact that they are in circulating blood and in all organs, there is a commonwealth union via some unknown mechanism. Do they have a bidirectional 'informational relay' conducting the morphological resemblance of macrophages, mast cells, endometrium, chondrocytes, neuroendocrines, polymorphocytes, and fibroblasts from one site to others? The bidirectional 'informational relay' is a precise molecular event controlled by cell junctions, plasma, and the extracellular matrix of microenvironment interaction. The mechanism of the bidirectional 'informational relay' remains unknown. Protein societies are more complicated than the cell world. Many proteins are multi-domain complexes and combine with others consisting of highly ordered supramolecular arrangements. The functional activities are accurately controlled by pH, ionic strength, temperature, polysaccharide, lipid, hormone, and other proteins involved in microenvironmental interactions. Does the protein society have a bidirectional 'informational relay', conducting the structural resemblance of molecules from one site to another? From clinical observation, systemic fibrosis, amyloidosis, autoimmune response, etc., are very common. There is an unknown pathologically missing link of communication in the structural resemblance molecules such as collagen, immunoglobulins, and fibrillary proteins from one site to the other sites. Does a bidirectional 'informational relay' conducting the resemblance molecules from one site to the others exist? The exact arrangement and communication of vWFA and collagen families' members remain to be elucidated. According to visible cell world data, the structural resemblance molecular communication from organ to organ may relate to the distribution pattern, supramolecular arrangement formation, circulation of family members and trace amounts of molecules (Fig. 3).

8. Does the filamentous protein network crosslink with family members?

In the visible cell world, fibrocytes, neurons and muscle cells form networks in the body. Cell network communication is dependent on cell junctions and connective tissue of the extracellular matrix. In the protein society, collagen and some non-collagen elements assemble filamentous networks in the extracellular matrix. Those filamentous networks are a bridge of matrix-matrix and matrix-cell interactions. Although an increasing number of signaling pathways among the matrix network elements and other extra- and intracellular matrix and cell membrane proteins have been discovered, the molecular 'junctions', elusive allosteric functional conformation, and activation and inactivation among the signal participants are

still to be uncovered. The exact assembly of the members of the vWFA and collagen families remains to be elucidated. Double immunolabeling and electron microscopic observation reveals that complexes of matrilin-1 and biglycan or decorin connect collagen VI microfibrils to both collagen II and aggrecan (15). The formation of this network was recently shown to depend on vWFA domain in vWFA collagen such as collagen VI (47,48). vWFA collagens are an important component of collagen filamentous networks and matrilins form one of the non-collagen filamentous networks of the vWFA family. Accumulating evidence indicates that the members of the vWFA family interact with collagen and non-collagen networks and could potentially form multiprotein complex crosslinks with other family members (Fig. 3). Matrilin-1 displays a periodicity of 59.3 nm (5), enhances cell adhesion and spreads via integrin $\alpha 1 \beta 1$ (49). Mice lacking matrilin-1 have normal skeletal development but have alterations in type II collagen fibrillogenesis and fibril organization (5). Ligand-binding assays, co-labeling immunohistochemistry and transmission electron microscopy elucidate that matrilin-2 binds itself, collagen-1, fibrillin-2, fibronectin, laminin-1-nidogen-1 complexes, and ligands in the dermal-epidermal basement membrane into the dermis and dermal extracellular matrix, indicating that there is a physiological relevance in the interactions and assembly of supramolecular extracellular matrix structures (50). vWFA collagens contain 57 of the 134 vWFA domains found in the human proteome. The 16 vWFA collagens include collagen 6 $\alpha 1$, $\alpha 2$, $\alpha 3$, collagen 7 $\alpha 1$, collagen 12 $\alpha 1$, collagen 14 $\alpha 1$, collagen 20, collagen 21 $\alpha 1$, collagens A, B, C, D, E, F, G and vWFAEGF. The functions of these molecules may be protein-protein interactions with other matrix proteins and possibly with cells (2).

Based on molecular structural evidence, collagen and non-collagen filamentous proteins form an extracellular network. vWFA, collagen and other family proteins are directly or indirectly combined by collagen and non-collagen filamentous networks. Although this complicated multiprotein complex is invisible to current scientific tools, accumulating data indicates that collagen and non-collagen filamentous networks are a molecular 'joint' in frontier host defense molecules at the first administrative level, other extracellular matrices of the second administrative level, and membrane systems and intracellular matrices of the third administrative level (Fig. 3). The function of this collagen and non-collagen filamentous network is not only to maintain tissue structural integrity but also to keep molecular communicational integrity. This network is a bridge of matrix-matrix and matrix-cell interactions.

9. Are circulated members moving communication?

The metabolism of organs and cells depends on an intact circulation system for the continuous delivery of oxygen, nutrients, hormones, electrolytes, and water as well as for the removal of metabolic waste and carbon dioxide. Homeostasis of an open system of the body depends on circulated cells and molecules for cooperation in local and systemic response. The circulated polymorphocytes, lymphocytes, and macrophages move to recognize and clean pathogens in the blood and infected or injured sites, and to provide very important communication in systemic response. In malignant tumors

and some benign chronic diseases, non-circulating cells are also detectable in the peripheral blood and outside organs. For example, bronchoepithelial cell markers, such as SP-A mRNA, can be detected in some cases of idiopathic pulmonary fibrosis. The author suggests that there are some circulating bronchoepithelial cells expressing mRNA for SP-A in the peripheral blood of patients with idiopathic pulmonary fibrosis, which may also be associated with the pathogenesis of collagen vascular disorders (51). There is no further observation regarding functions of the peripheral blood and non-circulating bronchoepithelial cells, or whether they may enter and grow outside the lung. There have been no exact molecular explanations for malignant and benign chronic invasion and metastasis, except for in endometriosis. Endometriosis is an easily observable case of non-circulating endometrium-like glands and stroma entering and growing outside of the uterus (43). Many cases of endometriosis were believed to be chronic, invasive and metastasizing disease (43). In endometriosis, endometrium glands and stroma outside and inside the uterus respond to menstruation. In the vWFA and collagen families, there are some members found in plasma like polymorphocytes, lymphocytes, and macrophages of the cell world: complement factor B and C2, von Willebrand factor, and von Willebrand factor also found in the extracellular matrix, in the vWFA family; and complement factor C1q, MBP, conglutinin, collectin 43 are circulated members in the collagen family. MBP, complement C1q and C2 are involved in the classical complement activation pathway, and complement B is involved in the alternative pathway. Those soluble components present in serum participate in innate immunity through a variety of mechanisms, such as activating immune cells, promoting inflammation at the site of infection, opsonizing pathogens, and directly lysing susceptible microorganisms (52). There is a moving innate immunity that responds in the serum and in the injury site. The directly molecular event between the serum members and non-serum members has been found *in vivo*. *In vitro* experiments indicate that complement factors bind filamentous network members of collagen and matrilins, and can also bind SP-A, SP-D, and other members (52). When the body is exposed to physical, chemical and biological factors in autoimmunity, carcinogenesis, and allergy response, the serum concentration of non-serum members significantly increases. For example, serum levels of SP-A and SP-D are useful biomarkers for interstitial lung disease in patients with progressive systemic sclerosis (21). In fact, an increasing amount of data suggests that trace amounts of non-serum members are detectable in circulated blood and extracellular matrices using advanced techniques. It is unknown whether the circulated non-serum members enter the extracellular matrix under the physiological condition, but it is known that the Ag-Ab complex enters the basement membrane of the glomerulus and other extracellular matrix under pathological conditions. When the circulated Ag-Ab complex enters the extracellular matrix, it may activate many signaling pathways which play dominant roles in tissue response to autoimmune injury sites. Therefore, the circulated non-serum proteins may not be only a useful clinical biomarker for diagnostic merits but may also enter the extracellular matrix and play an unknown molecular communication role in the protein society.

10. Does the transmembrane protein crosslink members of the extra- and intracellular matrices?

The cell membrane system is a selective barrier that surrounds not only the cell surface but also every intracellular organelle that requires an internal milieu different from that of the cytosol. The cell is a membrane separated functional unit, the cell organelles such as the nucleus, mitochondria, endoplasmic reticulum, Golgi apparatus, and lysosome are also membrane separated functional units. It is known that the cell surface and intracellular organelle's functional commonwealth is determined by many molecular events. Proteins and lipids are two major components of the cell membrane system. Many membrane proteins extend across the lipid bilayer. All of the activities of the cell are dependant upon membrane proteins of the cell membrane system. Membrane proteins are the bridge between the cell and matrix, and other cells, and also form a bridge between intracellular organelles. The hormone receptor is a well-studied membrane protein. The bidirectional loops within the endocrine system and neuroendocrine-immune interactions would then be anticipated to involve feedback and feedforward loops that maintain homeostasis (53). Integrins are well studied within the membrane receptor proteins of the vWFA family, making transmembrane connections to collagen and non-collagen filamentous network proteins and to other extracellular matrix proteins as well as cytoskeleton intermediate filamentous network proteins and other intracellular matrix proteins (54). Shedding of integrins into the extracellular matrix is consistent with cell growth (55) and is an important ion channel and signal receptor. The vWFA family members in the cell membrane, cytoplasm or nucleus are involved in functions such as gene transcription, DNA repair, ribosomal and membrane transport, and the proteasome. It is a core and detectable response of protein societies.

11. Conclusion

Family proteins in the body consist of a subtly designed society. Increasing information about the molecular structure, conformational structure, structure-related activation, and signal communication of individual proteins is being discovered, but it is still insufficient for understanding the communication between local tissue, distal tissue and the whole body. There are many idiopathic diseases and there is 'non-scientific evidence' for the effectiveness of acupuncture, qigong and other Chinese medicines, in addition to the fact that these techniques have been used for thousands of years for therapy, anesthesia and maintaining a healthy life.

In the body, functional units of individual proteins combine with themselves or other proteins to form homo- and hetero-oligomers, working routinely with other proteins. Meanwhile, the members of a family may be involved in important molecular events of local response to systemic response. These molecular involvement events may be related to the social property of proteins. Under certain pathological conditions, the member of a family's communication from local to systemic may be detectable as an alteration of mRNA and proteins. Under normal conditions, the communication of family members from local to systemic may not always be accompanied by scientific tool detectable alteration of mRNA

and protein; it may only be accompanied by non-scientific tool detectable bidirectional and elusive allosteric signaling of a molecule. A plausible hypothesis is that proteins form a society, as do human beings. The protein society may consist of many family commonwealth unions which live in the same body world and face the same external environmental challenge. Individual proteins, as members of a society, follow the same rule. They should work cooperatively with their 'co-workers', with a regular job for local 'service'. The individual job may be a small but integral part of this society. Meanwhile, multidomain individuals have several memberships. In this precisely designed society, the potential systemic response is accurately controlled by pH, ionic strength, temperature, polysaccharide, lipid, hormone, other proteins, and emotion. Evidence of communication among family members would greatly provide insight into the mechanisms of traditional Chinese medicine and multiple involvements of clinic manifestations. It would facilitate the study of the molecular events of typical local injuries inducing many secondary site disorders. The communication among family members may be molecular evidence of traditional Chinese medicine scholars' 'Qi' and its communication. The pattern of distribution of family members may be related to social roles in the open body system.

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