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Tissue Micro-channels Formed by Collagen Fibers and their Internal Components: Cellular Evidence of Proposed Meridian Conduits in Vertebrate Skin

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Abstract

In order to clarify fine structures of the hypothetical meridian conduits of Chinese traditional medicine (CTM) in the skin, the present study used light and transmission electron microscopy to examine fasciae in different vertebrate species. Collagen fiber bundles and layers were arranged in a crisscross pattern, which developed into a special tissue micro-channel (TMC) network, in a manner that was analogs to the proposed skin meridian conduits. It was further revealed that tissue fluid in lateral TMC branches drained into wide longitudinal channels, which were distinctly different from lymphatic capillary. Mast cells, macrophages, and extracellular vesicles such as ectosomes and exosomes were distributed around telocytes (TCs) and their long processes (Telopodes, Tps) within the TMC. Cell junctions between TCs developed, which could enable the communication between contiguous but distant Tps. On the other hand, winding free Tps without cell junctions were also uncovered inside the TMC. Tissue fluid, cell junctions of TCs, mast cells, macrophages, and extracellular vesicles within the TMC corresponded to the circulating "气血" ("Qi-Xue", i.e., information, message, and energy) of meridian conduits at the cytological level. These results could provide morphological evidence for the hypothesis that "meridians are the conduit for Qi-Xue circulation" in CTM.

Key words: Chinese traditional medicine, collagen fiber, meridian conduit, telocyte, tissue micro-channel

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Introduction

The serial anatomical continuity of different fasciae in the skin provides not only anatomical but also functional integration of all fascial structures in body (Kumka & Bonar, 2012; Jan, 2015). However, despite their crucial role, the fascial structures are relatively poorly investigated (Joanna et al., 2016). This might be a consequence of a general misconception that skin fasciae are non-specialized structures, whose only role is to passively assist muscle and bone activity (Schleip et al., 2005). From the histological point of view, the fascial structure constitutes loose and dense connective tissue, which is always referred as skin interstitium. While the anatomy and composition of the interstitial space between cells is increasingly understood, the existence, location, and structure of inter- and intra-tissue spaces in the fasciae are described only vaguely in the literature (Aukland, 1984; Benias et al., 2018).

Telocytes (TCs) are newly found special interstitial connecting cells all over the body (Popescu & Faussone-Pellegrini, 2010). A recent report showed that as one of the potential meridian cells of Chinese traditional medicine (CTM), TCs and their long protrusions (telopodes, Tps) develop a special network that may regulate and maintain body homeostasis by integrating different cells and structures in the interstitium of various organs including the skin (Shi et al., 2020). However, the morphological relationship between TCs and the proposed meridian conduits is not clarified.

Meridians are the theoretical basis for acupuncture treatment, disease diagnosis, and prescription herbal medicine in CTM. It was pointed out that 'meridians are the conduits for "Qi-Xue" (i.e., information, message, and energy) circulation' in *Huangdi Neijing* (*The Yellow Emperor's Classic of Medicine*) of the ancient Chinese medical book. Although Xie et al. (2007) suggested that meridians might be distributed in the tissue gap between two muscles, tendons, bones, joints, or depressions, the fine structures and compositions of the meridian conduit have not been scientifically expounded so far, which restricts the understanding of CTM by modern bio-medicine.

Morphological investigation is the first and most direct strategy for uncovering the structural characteristics of meridian conduits. The present study was designed to analyze the material essence of meridian conduits and their relationship with TCs and other interstitial cells in skin fasciae by light and transmission electron microscopy. It is hypothesized that this is compatible both traditional and modern medicine systems at the cellular level.

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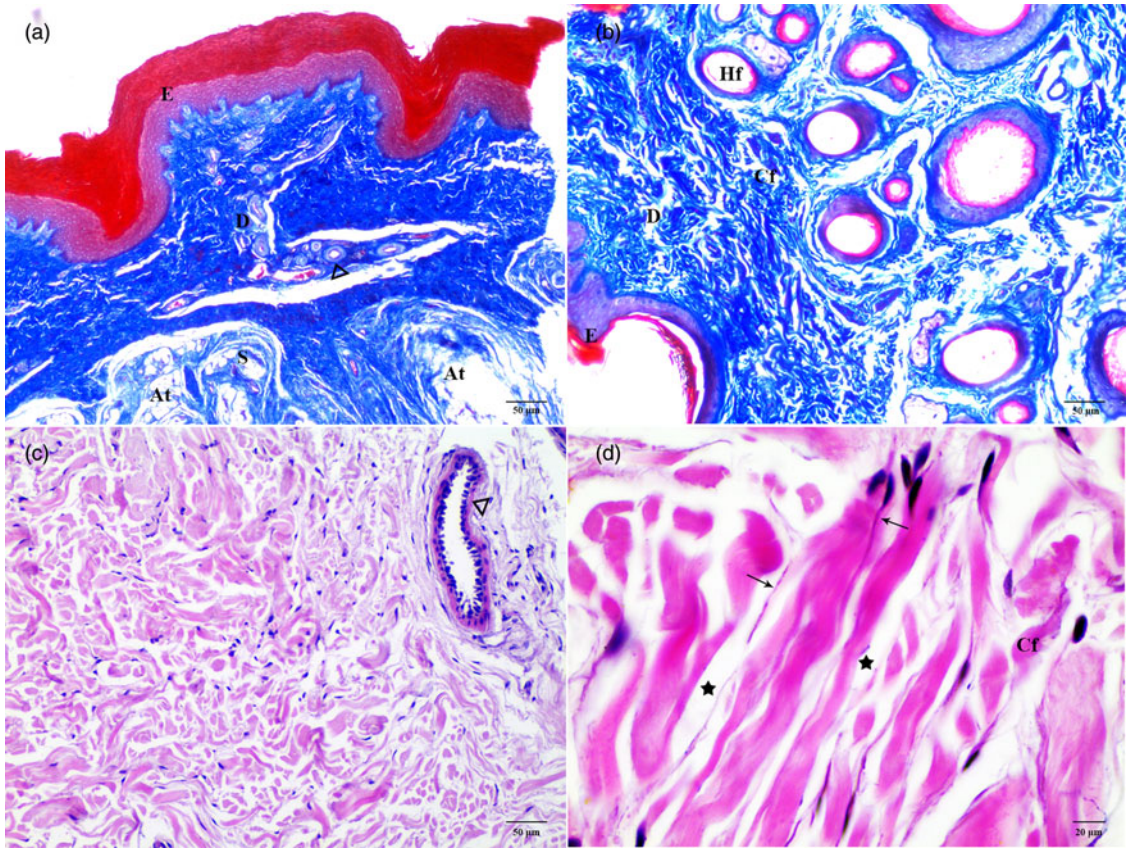

Fig. 1. Structures of collagen fibers in skin under light microscopy. **(a** and **b)** were stained by the Masson method, while **(c** and **d)** were stained by H–E. **(a)** was from chicken claw; **(b)** was from sheep forelimb; **(c** and **d)** were from midline part of sheep abdomen. An obvious narrow gap between collagen fibers in dermis, in which contains TCs. Epidermis (E), dermis (D), subcutis (S), hair follicle (Hf), collagen fibers (Cf), blood vessel (△), TMC (★), adipose tissue (At), and TCs (↑). Scale bars: **(a–c)** 50 μm; (**d**) 20 μm.

Materials and Methods

Adult frogs, Chinese soft-shelled turtles, chickens, and sheep were purchased from the breeding base of Nanjing, China and acclimatized in the laboratory for a week. Six healthy animals (three males and three females) of each species were used in this study. Animals were anesthetized by intraperitoneal injection of pentobarbital sodium (60 mg/kg) and euthanized by cervical dislocation, and tissue blocks of skin were collected and fixed immediately after slaughter. The skin tissues collected were from the head, back, abdomen, and limb of frog, chicken, and sheep. The skin of Chinese soft-shelled turtles was from the head and limb. The claw skin was also collected from the chicken. All animal-related protocols were approved by the Science and Technology Agency of Jiangsu Province (SYXK (SU) 2017-0007).

Hematoxylin and Eosin and Masson Staining

The skin tissue samples of different vertebrate species were fixed 48 h in 10% neutral-buffered formalin, embedded in paraffin wax, and cut into 6 μm thin sections. The paraffin sections were stained with hematoxylin and eosin staining (H–E) and Masson's staining, respectively, and analyzed on an OLYMPUS light microscope.

Immunohistochemistry

The above paraffin sections were deparaffinized and rehydrated with decreasing concentrations of ethyl alcohol. Endogenous peroxidase activity was blocked by 3% hydrogen peroxide, followed by incubation in the boiling water bath with sodium citrate buffer for 20 min. Sections were then blocked with 5% bovine serum albumin in room temperature for 30 min, followed by incubation with rabbit anti-CD34 (1:150 dilution; catalog no. BA3414; Boster, Wuhan, China) antibody at 4°C overnight. Negative control slides were performed by replacing the antibody with 0.01 M phosphate-buffered saline (PBS) (pH = 7.4) under the same conditions. After washing, the sections were incubated with biotinylated anti-rabbit IgG (Boster Bio-Technology, Wuhan, China) for 1 h at 37°C. They were then incubated with the avidin–biotinylated peroxidase complex. Peroxidase activity was determined by staining with 3,3′-diaminobenzidine (Boster Bio-Technology, Wuhan, China). The nuclei were stained with hematoxylin.

Transmission Electron Microscopy

The skin tissue blocks were cut into small pieces (1 mm^3) and fixed overnight in 2.5% glutaraldehyde in 0.1 M PBS (4°C, pH 7.4). After a rinse in PBS and incubation in buffered 1% osmium tetroxide for 1 h (37°C), the samples were dehydrated by ascending concentrations of ethyl alcohol (50, 70, 80, and 100%) after washing in the same PBS, permeabilized with a propylene oxide–Araldite mixture, and were embedded in Araldite. Ultra-thin sections (50 nm) were prepared and mounted on coated copper grids. The sections were stained with 1% uranyl acetate and Reynold's lead citrate for

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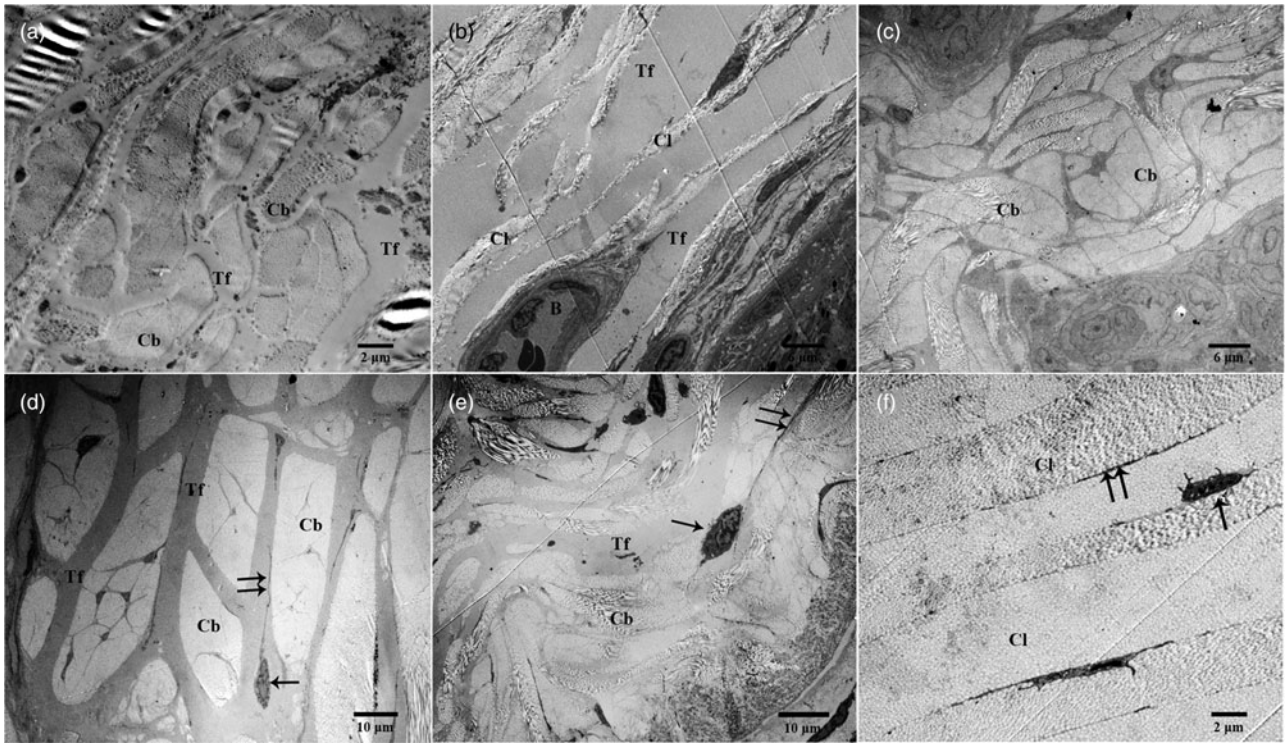

Fig. 2. TEM images of TMCs developed by collagen fiber bundles and layers in the skin of various vertebrates. **(a)** was from sheep forelimb and **(b)** was from the skin of sheep between spine and sacrum; **(c)** was from chicken claw; **(d)** was from soft-shelled turtle forelimb; **(e** and **f)** were from frog hind limb. **(a)** was a typical transmission section while **(b)** was a longitudinal section of the TMC. TCs were located on one side of collagen fiber bundles (Cb) and collagen fiber layers (Cl). Blood vessel (B), tissue fluid (Tf), TC (↑), and Tp (↑↑). Scale bars: **(a** and **f)** 2 μm; **(b** and **c)** 6 μm; **(d** and **e)** 10 μm.

20 min. The processed specimens were observed and analyzed in the transmission electron microscope (TEM; Hitachi H-7650, Japan).

Results

Collagen fibers were distributed throughout the dermis and subcutis, and they were arranged intensively in the dermis and sparsely in the subcutis, respectively (Fig. 1a). Collagen fiber bundles and collagen fiber layers were organized in a crisscross pattern (Figs. 1b, 1c). Tissue micro-channels (TMCs), also known as narrow gaps, were formed between them (Fig. 1d). TCs with thin and long processes extended inside TMC (Fig. 1d).

At transmission electron microscopy, a clear TMC network was formed between collagen fiber bundles or layers whether in transverse or longitudinal section (Figs. 2a–2e). The TMC presented in the skin of frogs, soft-shelled turtles, chickens, and sheep (Figs. 2a–2f) could be closed or undetectable sometimes because of the collagen fiber layers or bundles becoming tightly located (Figs. 2c, 2f). Some collagen fiber bundles and layers were thin (Fig. 1b), while some were thick (Fig. 1d). All TMCs were interlinked by offshoots, and tissue fluid in narrow lateral branches was drained into wide longitudinal channels (Fig. 2d). TCs and their Tps were observed within the TMC (Figs. 2d, 2e) or between collagen fiber layers (Fig. 2f).

TCs with very long Tps stood along the TMC (Fig. 3a), which sometimes lay on one side of collagen fiber layers (Figs. 3a, 3f). The TMC differed from the lymphatic capillaries that have continuous endothelium on both sides (Fig. 3b). TCs with winding and free Tp ends were sometimes seen inside the TMC (Figs. 3c, 3d). Straight Tps and cell junctions between their ends were observed at other times (Figs. 3e, 3f), which extended far away within the TMC. Developed mitochondria (Fig. 3c, 3d) and abundant dilated rough endoplasmic reticulum (Figs. 3c, 3d, 5d) stood within the TC cell body and the Tp podom.

CD34 is one of the most effective markers of TCs and their Tps. Within the TMC, TCs and Tps were identified by their CD34-positive reaction (Figs. 4a, 4b), compared with a negative control (Figs. 4c, 4d).

Mast cells (Figs. 5a, 5f) and macrophages (Fig. 5b) were distributed inside the TMC, attached to, or embedded in its collagen walls. Such extracellular vesicles as ectosomes (Fig. 5d) and exosomes (Figs. 5c, 5f) were observed on Tps, around mast cells or among collagen fibers. TCs with winding and free Tps ends were also observed inside the TMC (Fig. 5e).

Discussion

As the conduits of "Qi-Xue" circulation, meridians were distributed in the connective tissue of different organs including the skin fasciae throughout the body (Xie et al., 2009). Du et al. (2006) speculated that meridian conduits with minimum aperture were regular or irregular tracts in internal viscera and skin fasciae. However, there is no scientific evidence of detailed structures and compositions concerning the meridian conduits, which have to be uncovered by intuitive morphology. In the present study, a large number of collagen fiber bundles and layers in different orientations were observed by light and transmission electron microscopy, which developed an elaborate conduit network, named the TMC in the skin of various vertebrate species

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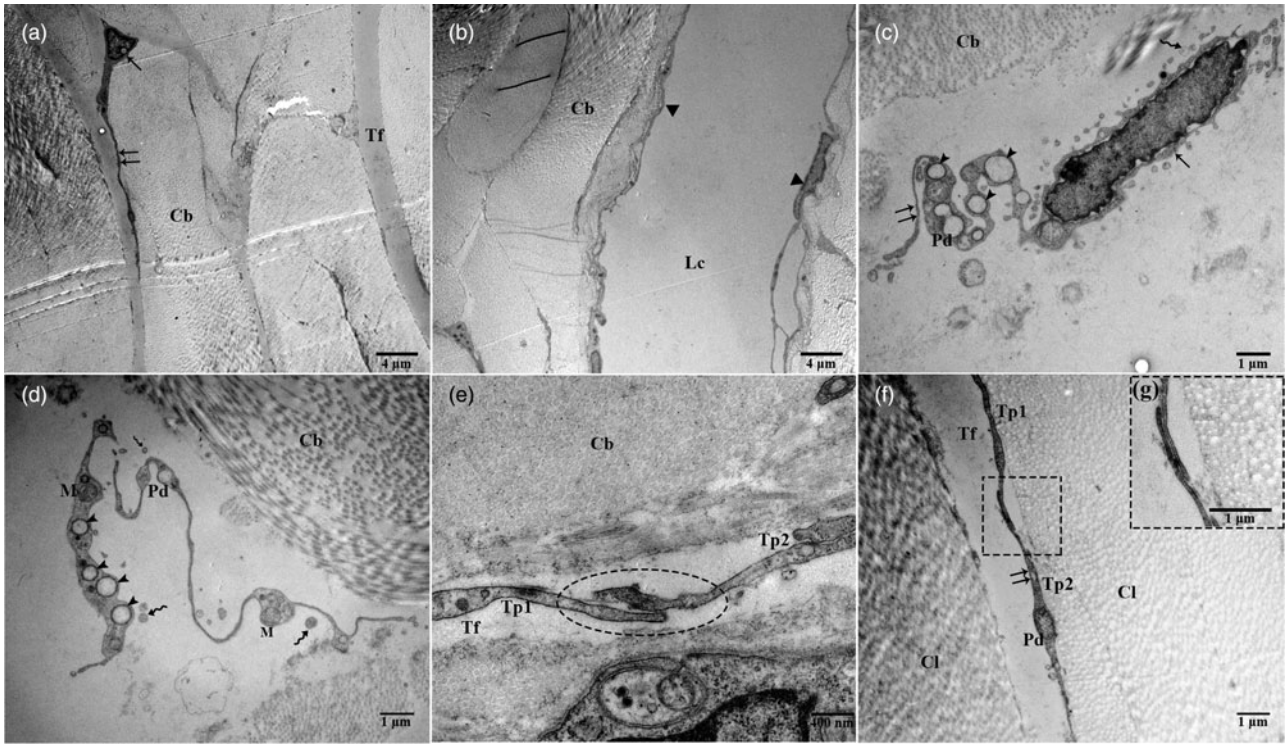

Fig. 3. TCs and Tps within the TMC. **(a**, **b, f,** and **g)** were from soft-shelled turtle forelimb skin; **(c**, **d,** and **e)** were from chicken claw skin. Tissue fluid (Tf), collagen fiber bundles (Cb), collagen fiber layers (Cl), TC (↑), exosomes (curved arrow) on Tp (↑↑), mitochondrion (M) inside the podom (Pd), dilated rough endoplasmic reticulum (arrowhead), lymphatic capillary (Lc), cell junctions (circle) between Tp1 and Tp2 within the TMC **(e**, **f** and **g)**. The upper right corner **(g)** was the magnified black box in photo **(f)**. Scale bars: **(a** and **b)** 4 μm; **(c**, **d**, **f**, and **g)** 1 μm; **(e)** 400 nm.

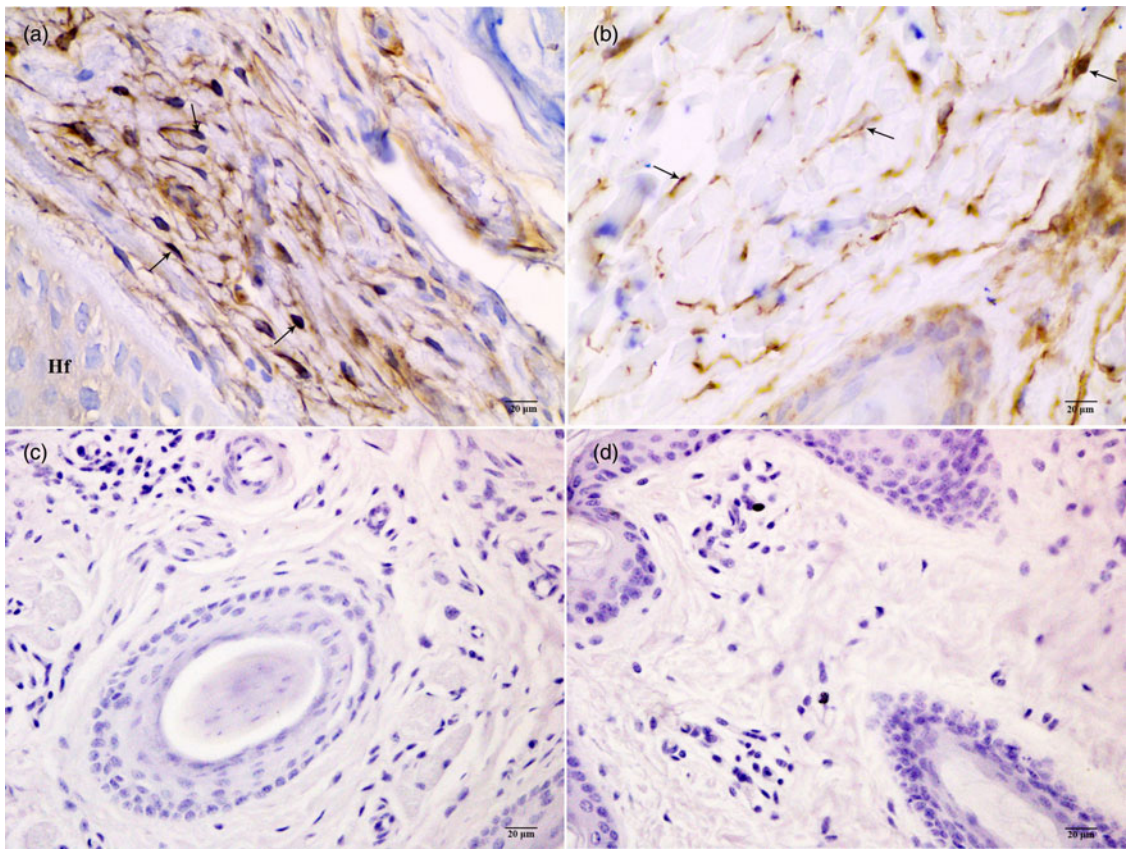

Fig. 4. CD34 immunohistochemistry in the skin of face **(a**, **c)** and abdomen **(b**, **d)** in sheep. CD34-positive TCs **(a** and **b)** were located in the connective tissue of the dermis. Negative control **(c** and **d)**. TC (↑), hair follicle (Hf). Scale bars: **(a–d)** 20 μm.

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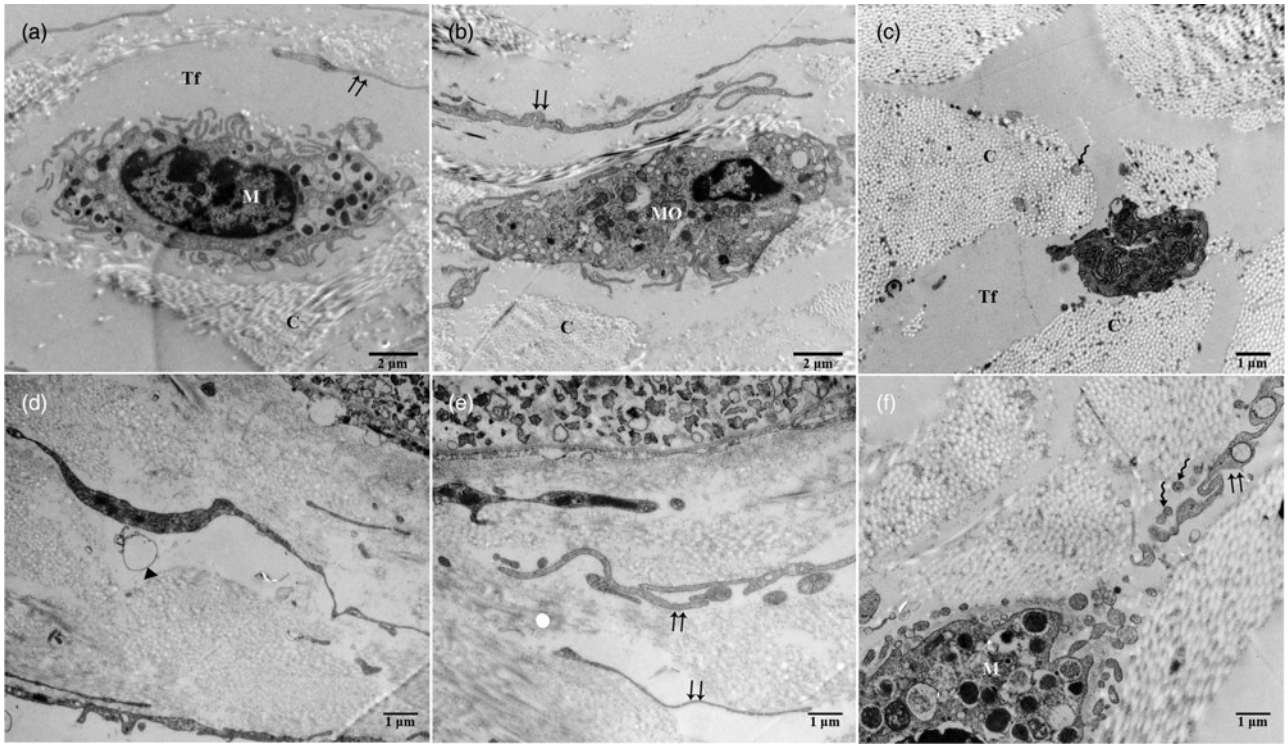

Fig. 5. Different cells, extracellular vesicles in TMC. **(a** and **b)** were from sheep abdomen skin; **(c)** was from sheep Erjian skin; **(d** and **e)** were from frog hind limb; **(f)** was from the skin of sheep between spine and sacrum. Mast cells and macrophages around the Tps of TCs in TMC. Moreover, exosomes and ectosomes also attached to Tps of TCs. Tissue fluid (Tf), collagen fibers (C), mast cell (M), macrophage (MØ), Tp (↑↑), exosome (curved arrow), ectosomes (▲). Scale bars: **(a** and **b)** 2 μm; **(c–f)** 1 μm.

investigated. TMCs could be "closed" when the collagen bundles and layers were overcrowded and their gaps disappeared (Figs. 2c, 2f). TMCs differed in diameter according to the thickness of the collagen bundles and layers but were always less than 10 μm, and their fine structures and compositions were markedly distinguishable from capillaries and lymphatic capillaries with the epithelium wall (Fig. 3b). It can be concluded that those micro-anatomical characteristics of the TMCs may be the similitude of meridian conduits in skin fascia at the histological level.

Decoding the scientific connotation of the "Qi-Xue" circulation in conduits is the key to academic research on CTM meridians. It has been suggested that meridians were conduits for water circulation (Jiang & Yao, 2019), while Zhang (2012) proposed that the meridian essence was the conduits of lower flow resistance liquid channel. Most of the previous reports considered that water or fluid circulated through the meridian conduits. By TEM, we observed that collagen TMCs were filled with tissue liquid of homogeneous low electron density (Figs. 2b, 2d, 3a, 3f, 5a, 5c), which corresponds to the extracellular fluid.

The meridian conduits or gaps were proposed to have the physical characteristics of cold shrinkage and heat expansion. The gap of meridian conduits expanded, and "Qi-Xue" was easy to circulate under higher temperature, while they shrank and "Qi-Xue" was difficult to circulate under lower temperature (Xie, 2002, 2003). It means that the diameter of the meridian conduits possessed some flexibility. Our results showed that according to the thickness of the collagen bundles, the TMCs were typical or atypical tracts, and some were open or closed. As a result, similar to meridian flexibility, TMCs were variable in diameter, which could develop a giant multi-level gap structure complex system—open and ordered dissipative structure, corresponding to "spongepores" for exchanging bioenergy and material (Xie et al., 2009).

Meridian phenomena can be regarded as a kind of life activity where cells are the basic units (Alberts, 2008). As the mechanical structures, collagen TMCs need cells to participate in their functions. It happens that there were special interstitial cells, TCs with long Tps distributed along the TMCs (Figs. 1d, 2d, 3a, 3e, 3f, 5a, 5b, 5d) or winding within the channels (Figs. 3c, 3d). Cell junctions arose between two ends of Tps (Figs. 3e, 3f), which enabled Tps extending long distance in the skin linking the meridian innovation to the viscera from skin acupoints. Developed mitochondria accommodated in the podom of the Tp (Fig. 3d) could provide adenosine triphosphate (ATP) for the transportation along TCs. Such extracellular vesicles as exosomes and ectosomes were distributed on or around Tps inside TMCs (Figs. 5d, 5f, 6b), which, as a third means of cell communication, could transport signaling substances like DNA, RNA, and proteins (Edelatein et al., 2016). By cytology, long TCs and their junctions developed mitochondria, and extracellular vesicles including exosomes happened to coincide with long distance, energy and stimulus signal of the meridian when acupuncture in CTM (Shi et al., 2020).

Within the collagen TMCs, mast cells, macrophages, and extracellular vesicles were often seen in this study. Those immunocytes can secret and release different cytokines (Zhang et al., 2020) into the TMCs and further circulate with tissue liquid, while the extracellular vesicles around TCs, as a membrane carrier (Zhuang et al., 2019), could transport various active factors controlling some metabolic functions. As a TC and Tp network has recently been identified as one of the potential meridian essence structures (Shi et al., 2020), TCs and their Tps within the

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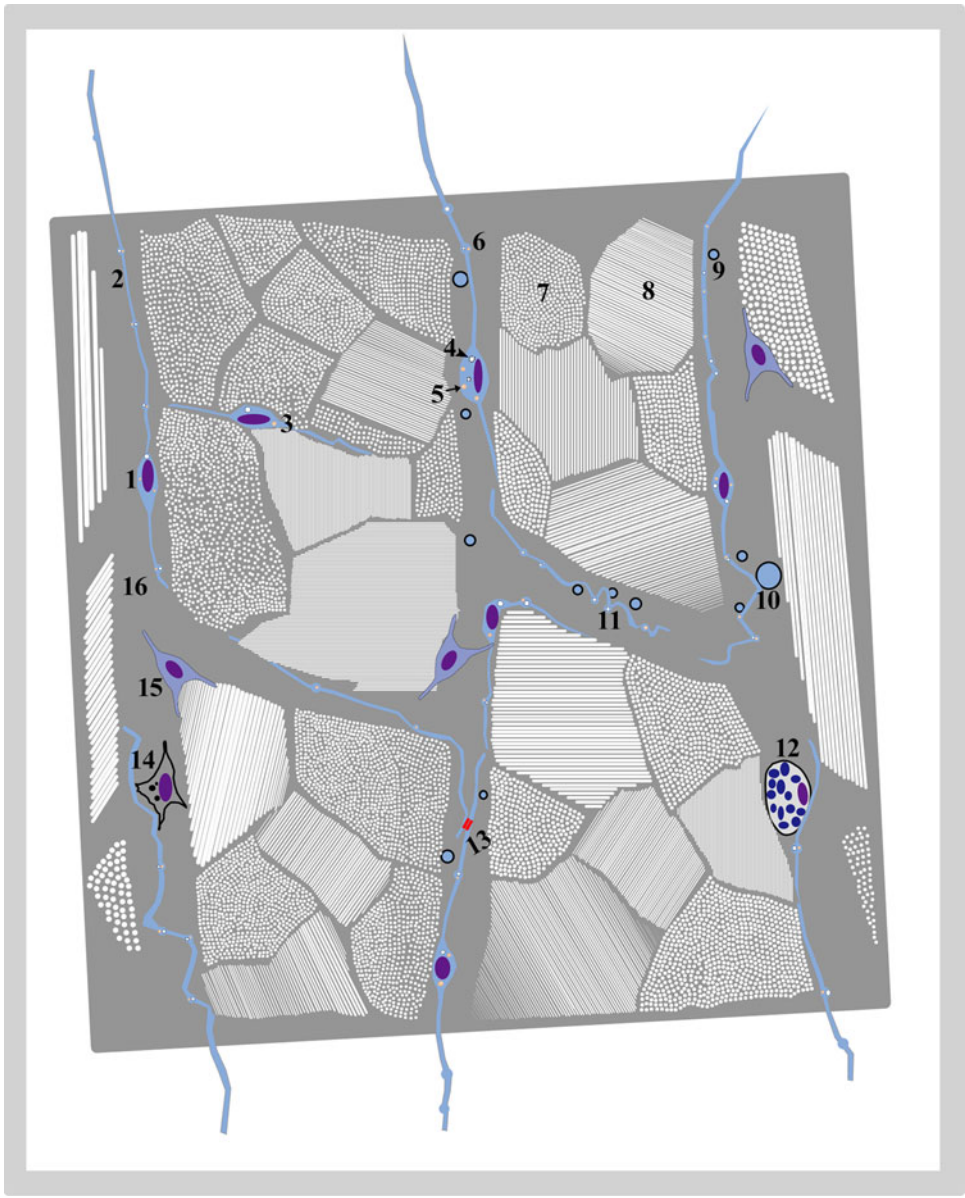

Fig. 6. Schematic diagram of the TMCs and their associated tissue fluid, cell junctions of TCs, mast cells, macrophages, and extracellular vesicles in skin. 1./3. TCs; 2. Telopode; 4. Rough endoplasmic reticulum; 5. Mitochondria; 6. Podom; 7. Cross section of collagen fibers; 8. Longitudinal section of collagen fibers; 9. Exosome; 10. Ectosome; 11. Telocyes with winding and free Telopodes; 12. Mast cell; 13. Cell junction; 14. Macrophage; 15. Fibroblasts; 16. Tissue fluid.

TMCs could be connected to the TC network in vertebrate skin. It can be suggested that TCs in the TMCs were ultrastructurally the connectors between the collagen channels and the meridian network in skin.

Related data try to tie the function of TCs into the broader field of volume transmission (VT) (Simons & Raposo, 2009; Cretoiu et al., 2012; Nedergaard, 2013; Fertig et al., 2014; Smythies & Edelstein, 2014). VT is a major mode of intercellular communication that occurs in the extracellular fluid (Bjelke et al., 1995; Agnati & Fuxe, 2014; Borroto-Escuela et al., 2015). Its signals are represented by almost any soluble signaling molecule such as transmitters, modulators, trophic factors, and ions. The signals move from source to target cells along energy gradients resulting in diffusion and flow (Fuxe et al., 2007). As contributors, unusually long, tenuous, and sinuous TCs can build up extracellular pathways for long distance VT (Zhuang et al., 2019). They can be both the sources and targets of VT signals and are known to be miniature communication devices, which utilize elaborate electrical, chemical, and epigenetic mechanisms, including the exchange of exosomes, to integrate many activities within and between nearly all types of cells in tissues and organs (Zhuang et al., 2019). All those discussed viewpoints need detailed cytological evidence. The present study showed that TCs and Tps were located along the TMC filled with tissue fluid, around which there were lots of exosomes and ectosomes. Cell junctions could be detected between the Tps. Those ultrastructural characteristics can support the viewpoints associated with the TC, TMC, and VT.

Conclusion

We present a structure model (Fig. 6) of the TMCs and their associated elements according to our data results. TMCs and their

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TCs, mast cells, macrophages, extracellular vesicles, and tissue fluid have always existed in different vertebrate, which were consistent with "meridians are the conduit for Qi-Xue circulation" in CTM.

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Conflict of interest. The authors have declared that no competing interests exist.

References

Agnati LF & Fuxe K (2014). Extracellular-vesicle type of volume transmission and tunnelling-nanotube type of wiring transmission add a new dimension to brain neuro-glial networks. *Philos Trans R Soc Lond B Biol Sci* **369**, 1652.

Alberts B (2008). *Molecular Biology of the Cell*, 5th ed. New York: Garland Publishing Inc. pp. 28–36.

Aukland K (1984). Distribution of body fluids: Local mechanisms guarding interstitial fluid volume. *J Physiol (Paris)* **79**, 395–400.

Benias PC, Wells RG, Sackey-Aboagye B, Klavan H, Reidy J, Buonocore D, Miranda M, Kornacki S, Wayne M, Carr-Locke D & Theise ND (2018). Structure and distribution of an unrecognized interstitium in human tissues. *Sci Rep* **8**, 4947.

Bjelke B, England R, Nicholson C, Rice ME, Lindberg J, Zoli M, Agnati LF & Fuxe K (1995). Long distance pathways of diffusion for dextran along fibre bundles in brain: Relevance for volume transmission. *Neuroreport* **6** (7), 1005–1009.

Borroto-Escuela DO, Agnati LF, Bechter K, Jansson A, Tarakanov AO & Fuxe K (2015). The role of transmitter diffusion and flow versus extracellular vesicles in volume transmission in the brain neural-glial networks. *Philos Trans R Soc Lond B Biol Sci* **370**, 1672.

Cretoiu D, Cretoiu SM, Simionescu AA & Popescu LM (2012). Telocytes, a distinct type of cell among the stromal cells present in the lamina propria of jejunum. *Histol Histopathol* **27**, 1067–1078.

Du QJ, Zhang HT, Li FS, Meng WH & Zheng LY (2006). Analysis of meridian essence and discussion of human life network. *Chinese Acupuncture and Moxibustion* **26**(Supplement 1), 106–108. [in Chinese].

Edelatein L, Fuxe K, Levin M, Popescu BO & Smythies J (2016). Telocytes in their context with other intercellular communication agents. *Semin Cell Dev Biol* **55**, 9–13.

Fertig ET, Gherghiceanu M & Popescu LM (2014). Extracellular vesicles release by cardiac telocytes: Electron microscopy and electron tomography. *J Cell Mol Med* **18**(10), 1938–1943.

Fuxe K, Dahlström A, Höistad M, Marcellino D, Jansson A, Rivera A, Diaz-Cabiale Z, Jacobsen K, Tinner-Staines B, Hagman B, Leo G, Staines W, Guidolin D, Kehr J, Genedani S, Natale B & Agnati L (2007). From the Golgi-Cajal mapping to the transmitter-based characterization of the neuronal networks leading to two modes of brain communication: Wiring and volume transmission. *Brain Res Rev* **55**, 17–54.

Jan D (2015). Functional atlas of the human fascial system. *J Bodyw Mov Ther* **19**(4), 679–680.

Jiang ZJ & Yao CP (2019). Cardiovascular disease electronic. *J Integr Tradit Chin West Med* **7**(24), 36–41. [in Chinese].

Joanna D, Natalia M, Sylwia S & Krzysztof M (2016). Chapter 26, Telocytes of fascial structures. In *Telocytes-connecting Cells. Advances in Experimental Medicine and Biology*, vol. **913**, Wang X & Cretoiu D (Eds.), pp. 403–424. Singapore: Springer Nature Press.

Kumka M & Bonar J (2012). Fascia: A morphological description and classification system based on a literature review. *J Can Chiropr Assoc* **56**(3), 179–191.

Nedergaard M (2013). Neuroscience. Garbage truck of the brain. *Science* **340** (6140), 1529–1530.

Popescu LM & Faussone-Pellegrini MS (2010). Telocytes—A case of serendipity: The winding way from interstitial cells of Cajal (ICC), via interstitial Cajal-like cells (ICLC) to telocytes. *J Cell Mol Med* **14**(4), 729–740.

Schleip R, Klingler W & Lehmann-Horn F (2005). Active fascial contractility: Fascia may be able to contract in a smooth muscle-like manner and thereby influence musculoskeletal dynamics. *Med Hypotheses* **65**(2), 273–277.

Shi YH, Wu RZ, Zhang Y, Bai XB, Imran T, Liang CH, Yang P & Chen QS (2020). Telocytes in different organs of vertebrates: Potential essence cells of the meridian in Chinese traditional medicine. *Microsc Microanal* **26**(3), 575–588.

Simons M & Raposo G (2009). Exosomes-vesicular carriers for intercellular communication. *Curr Opin Cell Biol* **21**(4), 575–581.

Smythies J & Edelstein L (2014). Telocytes, exosomes, gap junctions and the cytoskeleton: The makings of a primitive nervous system? *Front Cell Neurosci* **7**, 278.

Xie HR (2002). Study on Qi-passage of meridians and collaterals. *Chin Acupunct Moxibustion* **22**(9), 24–27. [in Chinese].

Xie HR (2003). Meridians and acupoints are composed of interstitial substances. *Chin Acupunct Moxibustion* **23**(8), 27–29. [in Chinese].

Xie HR, Li FC & Ma XS (2007). Discussion on the essence of meridian-collateral system. *Acupunct Res* **32**(3), 210–213. [in Chinese].

Xie HR, Li FC & Zhang WB (2009). Observation and analysis on the meridian-collateral running track-related anatomical structure in the human body. *Acupunct Res* **34**(3), 202–206. [in Chinese].

Zhang WB (2012). Meridian and health. *People's Health Press* **40–64**, 174–193. [in Chinese].

Zhang Y, Ma C, Wang Z, Zhou Q, Sun S, Ma P, *et al.* (2020). Large-sized graphene oxide synergistically enhances parenchymal hepatocyte IL-6 expression monitored by dynamic imaging. *Nanoscale* **12**(15), 8147–8158.

Zhuang M, Du D, Pu L, Song H, Deng M, Long Q, Yin XF, Wang YY & Rao L (2019). SPION—Decorated exosome delivered BAY55-9837 targeting the pancreas through magnetism to improve the blood GLC response. *Small* **15** (52), e1903135.

https://doi.org/10.1017/S1431927620024381