J Acupunct Meridian Stud 2019;12(1):25—28

Available online at www.sciencedirect.com

Journal of Acupuncture and Meridian Studies

journal homepage: www.jams-kpi.com

Perspective

The Primo Vascular System as a Possible Exosomal Route Across the Body: Implications for Tumor Proliferation and Metastasis

Chiara Ghiron*

The Yogi Cat, Yoga Studio, Siena, Italy
Available online 22 June 2018

Received: Apr 10, 2018
Revised: Jun 12, 2018
Accepted: Jun 18, 2018

KEYWORDS
cancer microenvironment;
exosomes;
hyaluronic acid;
primo vascular system;
tumor metastasis

Abstract
This literature study article will present the possibility of a correlation between the energy meridians of Traditional Chinese Medicine, which can be traced back to the recently described primo vessels (formerly known as Bong-Han ducts), their composition, and the ability of tumors to proliferate and metastasize. It is proposed that microvesicular bodies such as exosomes, known to be involved in cell-to-cell communication, immune response, and tumor proliferation, could be moving across the body via the primo vascular system. The ubiquity of the primo vascular system and its penetration through the blood—brain barrier could also explain the ability of some peripheral tumors (e.g., breast tumor) to metastasize in the brain.

1. Introduction

Considering the increasing interest of the scientific community for microvesicular cellular entities called exosomes [1], which are heavily involved in cell-to-cell communication, one might ask how such entities move around the body. The possibility that the primo vascular system may be involved in exosome movement has been tested in a study [2] involving synthetic exosomes. This is, to the author's knowledge, the only work exploring this hypothesis.

Information on long-distance communication between a tumor and its host organs is limited. It has been suggested that tumor cells exploit special delivery systems and that concerted activity between tumor-derived factors and exosomes may be required [3].

Exosome size makes these microvesicles suitable to enter and move along the primo vascular system, which is

* Strada Comunale di Salteano 1, 53041 Asciano, Siena, Italy.
E-mail: cghiron@gmail.com.

pISSN 2005-2901 eISSN 2093-8152
https://doi.org/10.1016/j.jams.2018.06.006

rich in hyaluronan, a medium of fundamental importance for both cancer cells and exosomes.

It is hypothesized by the author that exosomes move along primo vessels to reach target organs for tumor metastasis. Given that the primo vascular system is also present across the blood—brain barrier, exosome movement could explain the capacity of certain peripheral tumors, such as breast cancer, to metastasize in the brain.

Should this hypothesis prove correct, targeted chemotherapy could be an immediate practical consequence. Chemotherapy agents could be delivered through the primo vascular system from acupuncture points close to the tumor to the extracellular matrix of tumor cells.

2. Study method

The hypothesis proposed in this article is based on literature study, searching scientific publications through the Google Scholar engine for peer-reviewed articles in English language. Where available, reviews of existing literature have been referenced to provide a broad base of evidence.

3. The meridian theory and Bong-Han vascular system

Two main tenets in Oriental Medicine are herbal remedies and acupuncture. Acupuncture is based on a system of channels through which vital energy (Qi or Chi) flows. Imbalance of yin and yang forces in our bodies causes disease, and acupuncture therapy seeks to rebalance these forces by directing pressure to specific acupoints along energy channels (the meridians). There have been several attempts to anatomically define meridians and find a common ground between the meridian theory and Western medicine [4].

While the location of acupoints and meridians appears to be found over mixed nerve bundles containing motor units and sensory fibers that project to regions in the central nervous system regulating pain and blood pressure, a very interesting hypothesis was originated in the early 1960s by the Korean scientist Bong-Han Kim. According to this hypothesis, a novel, primordial circulatory system is present in all vertebrates and is analogous to the meridian system, with nodes (Bong-Han corpuscles, currently defined as primo nodes) corresponding to acupoints and ducts (Bong-Han ducts, currently defined as primo vessels) corresponding to meridians [5]. Limited evidence was provided in the original articles in support of this theory, but a number of Korean research groups dedicated resources to fully investigate and gained evidence of the correctness of Kim hypothesis with the aid of novel staining methods [6]. The Bong-Han circulatory system has more recently been renamed primo vascular system and appears to be comprised of several networks [7], located at various sites and depths inside the body. It is essentially a new anatomical system, which includes a superficial network located in the skin; an intravascular network that runs along the interior of the large veins, arteries, and lymphatic vessels and is afloat in the blood/lymph stream, not adhering to the vessel wall; an extravascular network that runs along the exterior of large blood vessels; an organ surface network that spreads on various internal organ surfaces; an intraorgan network located inside various internal organs; and a neural network that exists inside the brain and spinal cord and runs along the exterior of peripheral nerves. The vessels have definite dimensions with a diameter of ca 30 micron. These networks may well correspond to the meridian system, particularly in terms of the superficial network [8].

The recent publication of an article describing a new "organ" termed "interstitium" seems to have very strong overlaps with the primo vascular system [9] although similarities were not cited by the authors of the study.

It has also been postulated that the primo vascular system may be related to Qi (the vital energy implicated in acupuncture) production [10].

According to Kim, analysis of primo vessel (Bong-Han) liquid revealed the presence of neurotransmitter hormones such as adrenalin and noradrenalin, amino acids, free nucleotides, and, importantly, hyaluronic acid.

In their studies, Soh's group also evidenced the presence of adult stem cells in primo vessels (Bong-Han ducts) and mesenchymal stem cells markers. These are important findings as could not only point at the possibility that primo vessels may be a path for metastasis [11] but also open the opportunity for acupuncture as a means to modulate tumor tissue.

4. Microvesicular bodies

Microvesicles are circular membrane fragments released from the endosomal compartment. An increasing body of evidence indicates that they play a pivotal role in cell-to-cell communication [12]. For many years, microvesicles were thought to be inert cellular debris and the vesicles, frequently observed by electron microscopy in the interstitial space of tissues or in blood, were considered consequential to cell damage, or were thought to be the result of dynamic plasma membrane turnover. It has been suggested that circular plasma membrane fragments released from human cells may result from a specific process and that they may carry functional membrane enzymes in the same ratio as the membrane of the cells of origin. It is now recognized that microvesicles are integral to the intercellular microenvironment and may act as regulators of cell-to-cell communication. The release of microvesicles may be constitutive or consequent to cell activation by soluble agonists or physical or chemical stress such as oxidative stress and hypoxia.

Exosomes are a specific subtype of microvesicles with endosomal origin and constitute a relatively homogenous population with a size ranging from 30 to 120 nm. It is hypothesized that microvesicles could act as a signaling complex by direct stimulation of target cells and may transfer receptors, proteins, and genetic material between cells.

Tumor cells, on fusion with the plasma membrane, release abundant exosomes. Exosomes harbor, besides a common set of membrane and cytosolic molecules, cell

type—specific proteins that maintain functional activity. Exosomes also contain messenger RNA and microRNA which are transferred to target cells, where they can be translated or mediate RNA silencing. Exosomes function as a potent tool for intercellular communication and gene delivery also in metastasis [13]. Although exosomes are CD44 independent, they require a soluble matrix that is CD44 dependent [14].

The function of hyaluronidase in this soluble matrix and its impact on the length of hyaluronic acid may be one of the crucial factors at play in niche preparation, potentiating the efficacy of exosomes and their metastatic role.

5. Hyaluronic acid

Hyaluronic acid [15] (also termed hyaluronan) is an anionic, nonsulfated glycosaminoglycan distributed widely throughout connective, epithelial, and neural tissues. It is a major component of synovial fluids and one of its main lubricating components. Hyaluronic acid is also an important component of cartilage and skin and is involved in the movement and proliferation of cells, providing an open hydrated matrix that facilitates cell migration. It participates in a number of cellular interactions in the processes of wound healing, reepithelization, and inflammation, through some specific receptors (mainly CD44, RHAMM, and ICAM-1).

Interestingly, for this hypothesis, hyaluronic acid, together with its regulating enzymes hyaluronan synthases and hyaluronidases, plays an important role in tumor cells, participating, through interactions with its receptor CD44, in the cellular changes that allow tumor cells to infiltrate the vascular and lymphatic systems (and in this hypothesis, the meridian system constituted by primo vessels). Hyaluronan is a major component of the extracellular matrix and is enriched in many types of tumors. In cancer patients, hyaluronan concentrations are usually higher in malignant tumors than in corresponding benign or normal tissues, and levels of hyaluronan are predictive of malignancy in some tumor types [16]. Hyaluronan is often bound to CD44 isoforms that are ubiquitous, abundant, and functionally important cell surface receptors. Recently, it has been demonstrated that stem cell niches are rich in hyaluronan [17]. Settlement of metastasizing tumor cells is facilitated by the establishment of special niches in (pre)metastatic organs. Niche preparation involves stimulation of local fibroblasts by tumor-derived factors and chemokines that attract tumor cells and hematopoietic progenitors.

6. Conclusions and experimental studies needed to support the hypothesis

Analysis of existing literature seems to suggest the possibility for exosomes to move across the body using the primo vascular system, aided by its content in hyaluronan. The extension of the primo vascular system would allow long-range cell-to-cell communication and the spread of tumors from the original site to metastatic niches.

To prove this hypothesis, it would be necessary to isolate exosomes from primo vessels and nodes. These techniques are still very young, and exosome isolation from blood and plasma is relatively laborious. The experiment would nevertheless be feasible to somebody skilled in these practices, and the analytical techniques for the identification of exosomes are well known and do not require large quantity of material.

Delivery of chemotherapy agents through acupoints is a relatively novel idea, but proof of concept has been established [18], and microdevices and nanodevices for drug delivery are becoming reality [19, 20]. Of interest, hyaluronic acid conjugates show great promise in the development of anticancer and other drugs, giving further support to this hypothesis [21], and exosomes loaded with antitumor drugs are currently being tested [22].

Financial support declaration

No financial support was received for this study.

Disclosure statement

None declared.

References

[1] Corrado C, Raimondo S, Chiesi A, Ciccia F, De Leo G, Alessandro R. Exosomes as intercellular signalling organelles involved in health and disease: basic science and clinical applications. Int J Mol Sci 2013;14:5338—66.
[2] Website: Hall J, Interaction Between Synthetic Exosomes and the Primo Vascular System. 2017 Posters at the Capital, March 2, 2017. Available at: http://digitalcommons.murraystate.edu/postersatthecapitol/2017/UL/5/ [Date accessed: April 6, 2018].
[3] Dorayappan KDP, Wallbillich JJ, Cohn DE, Selvendiran K. The biological significance and clinical applications of exosomes in ovarian cancer. Gynecol Oncol 2016;142(1):199—205.
[4] Longhurst JC. Defining meridians: a modern basis of understanding. J Acupunct Meridian Stud 2010;3:67—74.
[5] Soh K-S, Kang KA, Ryu YH. 50 years of Bong-Han theory and 10 years of primo vascular system. Evidence-Based Compl Altern Med 2013:1—12. ID 587827.
[6] Soh K-S. Bonghan circulatory system as an extension of acupuncture meridians. J Acupunct Meridian Stud 2009;2:93—106.
[7] Lee B-C, Yoon JW, Park SH, Yoon SZ. Toward a theory of the primo vascular system: a hypothetical vascular system and the subcellular level. Evidence-Based Compl Altern Med 2013:1—5. ID 961957.
[8] Stefanov M, Potroz M, Kim J, Lim J, Cha R, Nam M-H. The primo vascular system as a new anatomical system. J Acupunct Meridian Stud 2013;6:331—8.
[9] Benias PC, Wells RG, Sackey-Aboagye B, Klavan H, Reidy J, Buonocore D, et al. Structure and distribution of an unrecognized Interstitium in human tissues. Nat Sci Rep 2018;8:4947.
[10] Avijgan M, Avijgan M. Can the primo vascular system (Bong Han Duct System) be a basic concept for Qi production? Int J Integr Med 2013;20:2013.
[11] Yoo JS, Kim HB, Ogay V, Lee B-C, Ahn S, Soh K-S. Bonghan ducts as possible pathways for cancer metastasis. J Acupunct Meridian Stud 2009;2:118—23.

[12] Camussi G, Deregibus MC, Bruno S, Cantaluppi V, Biancone L. Exosomes/microvesicles as a mechanism of cell-to-cell communication. Kidney Intern 2010;78:838—48.
[13] Bourguignon LYW. Hyaluronan-mediated CD44 activation of RhoGTPase signaling and cytoskeleton function promotes tumor progression. Semin Cancer Biol 2008;18:251—9.
[14] Jung T, Castellana D, Klingbeil P, Hernandez IC, Vitacolonna M, Orlicky DJ, et al. CD44v6 dependence of pre-metastatic niche preparation by exosomes. Neoplasia 2009; 11:1093—105.
[15] Fraser JRR, Laurent TC, Laurent UBG. Hyaluronan: its nature, distribution, functions and turnover. J Int Med 1997;242:27—33.
[16] Toole BP, Hascall VC. Hyaluronan and tumour growth. Am J Pathol 2002;161(3):745—7.
[17] Solis MA, Chen Y-H, Wong TY, Bittencourt VZ, Lin Y-C, Huang LLH. Hyaluronan regulates cell behavior: a potential niche matrix for stem cells. Biochem Res Int 2012:1—11. ID 346972.
[18] Han H-J, Sung B, Ogay V, Soh K-S. The flow path of alcian blue from the acupoint BL23 to the surface of abdominal organs. J Acupunct Meridian Stud 2009;2(3):182—9.
[19] Iverson BD, Garimella S. Recent advances in microscale pumping technologies: a review and evaluation. Microfluid Nanofluid 2008;5:145—74.
[20] Rosen Y, Gurman P, Elman N. Drug Delivery. An Integrated Clinical and Engineering Approach. 1st ed. Boca raton: CRC Press; 2017.
[21] Mero A, Grigoletto A, Martinez G, Pasut G. Recent developments in hyaluronic acid-based nanomedicine. Rec Adv Biotechnol 2016;3:102—29.
[22] Saari H, Lázaro-Ibáñez E, Viitala T, Vuorimaa-Laukkanen E, Siljander P, Yliperttula M. Microvesicle- and exosome-mediated drug delivery enhances the cytotoxicity of Paclitaxel in autologous prostate cancer cells. J Con Rel 2015;220: 727—37.