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Sarrrruay Shuangshoti

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Cellular origin of meningioma*

Samruay Shuangshoti**

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The term 'meningioma' means tumor of the meninges without specifying the cellular origin of the lesion. This designation has resulted in diverse opinion regarding the tumor origin especially when it occurs at the site of great distance from the neuraxis such as in the lung and finger. Meningocyte, fibroblast, and Schwann cell have been proposed as the origin of meningioma. Review of the related literature as well as the author's experience reveals the fact that meningocyte, fibroblast, and Schwann cell are mesenchymal type cells. Meningioma, hence, may arise from any one or a combination of these cells as well as may arise directly from mesenchymal cells. This mesenchymal concept clarifies the origin of meningiomas wherever they are as well as their diverse tissue components such as inclusion of bone, cartilage, adipose tissue or even striated muscle in some meningiomas. The pluripotential mesenchymal cells or mesenchymal type cells may differentiate into various mesenchymal tissue components under appropriate circumstances. The concept, furthermore, helps to understand why meningioma and nerve sheath tumors are easily confused histopathologically because of their overlapping cellular origin.

Reprint request : Shuangshoti S, Department of Pathology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

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** Department of Pathology, Faculty of Medicine, Chulalongkorn University.

สารวย ช่วงโชติ. เซลล์ต้นกำเนิดของเม็นจีโอมา. จุฬาลงกรณ์เวชสาร 2533 กันยายน ; 34 (9): 661-666

ตามรูปศัพท์ "เม็นจีโอมา" หมายถึงเนื้องอกของเยื่อหุ้มระบบประสาทส่วนกลาง โดยไม่บ่งบอกถึงเซลล์ต้นกำเนิด ก่อให้เกิดความคิดต่าง ๆ นานาเกี่ยวกับเซลล์ต้นกำเนิดของเนื้องอกนี้ โดยเฉพาะอย่างยิ่งเมื่อพบเม็นจีโอมาเกิดห่างไกลจากระบบประสาทส่วนกลาง เช่นที่ปอดและนิ้ว เป็นต้น เม็นจีโอซัยท์ ไฟโบร بلاสท์ และเซลล์ของชวานน์ ส่วนแล้วแต่มีผู้แนะนำว่าอาจเป็นเซลล์ต้นกำเนิดของเม็นจีโอมาได้ทั้งนั้น ผู้เขียนได้ทบทวนวารสารที่เกี่ยวข้อง กับ ทั้งได้ใช้ประสบการณ์ของตนเองเข้าคลี่คลายปัญหานี้ พบว่าเม็นจีโอซัยท์ ไฟโบร بلاสท์ และเซลล์ของชวานน์ ล้วนเป็นเซลล์ประเภทเมเซนคัยม์ เม็นจีโอมาอาจเกิดได้จากเซลล์ชนิดใดชนิดหนึ่งดังกล่าวนี้ หรือมากกว่าหนึ่งชนิดปนกัน หรือเกิดจากเมเซนคัยม์เซลล์โดยตรง มโนคติ (concept) นี้ช่วยให้เข้าใจการเกิดของเม็นจีโอมาไม่ว่า ณ ที่ใด กับ ทั้งช่วยให้เข้าใจได้ง่ายว่าอาจมีเนื้อเยื่อประเภทเมเซนคัยม์ เช่น กระดูก กระดูกอ่อน เนื้อเยื่อไขมัน หรือแม้แต่กล้ามเนื้อ ปะปนอยู่ในเม็นจีโอมาได้ เมเซนคัยม์และเซลล์ประเภทเมเซนคัยม์นั้น มีศักยภาพในการแตกตัวไปเป็นเนื้อเยื่อดังกล่าวได้ มโนคตินี้ยังช่วยให้เข้าใจ ได้ดียิ่งขึ้นว่าทำไมบางที่เม็นจีโอมาจึงมีรูปลักษณะที่คล้ายคลึงกับเนื้องอกของปลอกประสาท จนยากที่จะแยกจากกัน หรืออาจเกิดปนในก้อนเดียวกันก็ได้ ทั้งนี้เป็นเพราะมีเซลล์ต้นกำเนิดเหลื่อมล้ำกันนั่นเอง

The term "meningioma" was proposed by Cushing and Eisenhardt⁽¹⁾ to designate the tumor that primarily arise in the meninges without specifying the cellular origin. The meninges cover the neuraxis (central nervous system). The latter, hence, is the usual site of occurrence of meningiomas. Occasional meningiomas occur outside the neuraxis by direct extension or metastasis of primary neuraxial meningiomas. Rarely primary meningiomas arise outside the neuraxis as ectopic primary extraneuraxial meningiomas and raise questions about the cellular origin of both primary neuraxial and extraneuraxial meningiomas.

Meningiocytes are generally considered to be the cells of origin of primary neuraxial meningiomas, based on the similarity between the cells comprising some meningiomas and the arachnoid cells capping the Pacchionion granulations (arachnoid villi).^(1,2) Courville and Abbott⁽²⁾ clearly demonstrated the transition between the meningocytic cluster of a Pacchionion granulation and a symptomless prefrontal meningioma found incidentally in postmortem examination. Meningiocytes are also widely disseminated throughout the arachnoid and have been additionally called meningotheial, arachnoid, mesotheial, endothelial cells as well as meningoblasts.⁽¹⁾ Meningioma was also previously named endothelioma.⁽¹⁾

When primary extraneuraxial meningiomas are encountered they are often considered to be associated with meningocytic cellular rests⁽³⁻⁵⁾ and Schwann cells.⁽⁶⁾ The theory of meningocytic cellular rests proposed that meningocytes may be included within the peripheral nerve sheaths where nerves pass through the foramens of the skull or intervertebral foramens or they may be embedded within the sac of meningoceles as a developmental error. The occurrence of primary extraneuraxial meningiomas around the cranium and along the vertebral column supports this theory. Indeed many primary extraneuraxial meningiomas, especially the intraorbital meningiomas, are attached to portion of the nerves that are close to the site of their exits from the cranial and intervertebral foramens.^(3,5,7,8) A few intraspinal meningiomas, moreover, arose from the spinal nerve roots.^(9,10) Craig and Gogela⁽³⁾ demonstrated meningocytic cellular rests within the sheath of the optic nerve.

The theory of meningocytic cellular rests, however, fails to explain the occurrence of many primary extraneuraxial meningiomas unrelated to the cranial foramens and sutures as well as to the intervertebral foramens. These tumors were encountered as primary intraorbital meningiomas that lay outside the cone of the ocular muscles without connection to the optic nerve,^(3,11) in the brachial neural plexus,⁽¹²⁾ deltoid region,⁽¹³⁾ finger,⁽¹⁴⁾ lung,⁽¹⁵⁾ and adrenal gland.⁽¹⁶⁾ Meningocytes,

furthermore, are not the only type of cells found in meningiomas. Many meningiomas are composed of fibroblasts or mixed meningocytes and fibroblasts or combined mesenchymal cells, meningocytes, and fibroblasts.^(5,8) The alternative suggestion, therefore, was made that meningocytic meningioma is a tumor of meningocytes; fibroblastic meningioma arises from fibroblasts.^(17,18) Indeed meningioma has also been called meningeal fibroblastoma.⁽⁸⁾

Bain and Shanika⁽⁶⁾ in their study of a cutaneous meningioma, on the other hand, called attention to the similarity between cells of meningocytic meningioma and nevus cells. They suggested that Schwann cells regarded by Masson⁽¹⁹⁾ as the origin of nevus cells may produce meningocytes because they have a common "neuroectodermal" origin. They believed that under appropriate circumstances Schwann cells may differentiate into meningocytes and transform into an ectopic meningioma.⁽⁶⁾ Some meningiomas indeed contain melanin⁽²⁰⁾ as frequently seen in dermal nevi. Intradermal nevus with formation of psammoma bodies, furthermore, has been documented.⁽²¹⁾

The behavior of meningiomas, however, differs considerably from that of any genuine neuroectodermal neoplasm. The presence of reticulin fibers in most meningiomas and of bone,^(1,5,16,20,22) cartilage,^(1,5,20) adipose tissue,^(16,20,23) and even striated muscle⁽¹⁶⁾ in some meningiomas indicates that they are mesenchymal type neoplasm^(5,7,8) which is further supported immuno-histochemically by positivity to vimentin in many meningiomas.⁽¹⁶⁾ It is, therefore, necessary to evaluate the association among meningocytes, fibroblasts, Schwann cells, and mesenchymal cells.

Shuangshoti and Netsky,⁽²⁴⁾ in their study of the histogenesis of the choroid plexus in man, suggested a mesenchymal origin of meningocytes. They observed that at the early stage of development the matrix (stroma) of the choroidal primordium is entirely composed of mesenchymal cells. At later stages, the mesenchymal cells gradually decrease in number and are replaced by such mesenchymal type elements as the primitive endothelial cells that form blood vessels, fibroblasts, meningocytes, and fibers of the connective tissue. These findings suggest differentiation of mesenchymal cells into various described mesenchymal type cells including meningocytes. Schwann cells produce reticulin fibers,⁽²⁵⁾ a feature not seen in neurons and neuroglia which are generally accepted as genuine neuroectodermal type cells. The neural crest has been considered to be the origin of Schwann cells. It is, therefore, necessary also to determine the origin and nature of the neural crest. Developmentally, the neural crest is derived from the mingling of mesenchymal cells

and developing cells of the neural folds. The neural crest, thus, is ectomesenchymal in nature as previously commented.^(22,26) It can differentiate along neuroectodermal and mesenchymal lines. For example, cells from the cranial part of the neural crest migrate to the upper portion of the face and form the cranial and some spinal sensory ganglions, autonomic ganglions, sheath cells including Schwann cells, pigmented cells (melanocytes), leptomeninges, membrane bone of the skull, and subcutaneous tissue cells including fibroblasts.⁽²⁷⁾ Yntema,⁽²⁸⁾ nevertheless, demonstrated that sheath cells including Schwann cells could develop from a source other than the neural crest. In embryos of *Amblystoma punctatum*, bilateral removal of spinal portion of the neural crest produced deficiency of sheath cells about the proximal part of the spinal nerve. The sheath cells, however, were present distally. With advancing age, they became more numerous and occurred also on the nerve nearer the spinal cord.⁽²⁸⁾ Yntema's experimental findings suggest that sheath cells can be derived from sources other than the ectomesenchyme of the neural crest. It is reasonable to assume that after ablation of the neural crest, the sheath cells including Schwann cells develop from the mesenchyme around the spinal nerve. Yntema's findings, moreover, indirectly suggest that even in the presence of the neural crest, the sheath cells would originate from the mesenchymal portion rather than from the neuroectodermal part of the crest. Formation of bone, cartilage, and adipose tissue in Schwannomas has as well been described.⁽²⁹⁾ Based on these various findings, it is reasonable to recognize Schwann cells as mesenchymal type cells as are fibroblasts and meningocytes.

The "mesenchyme" is defined as primitive connective tissue consisting of stellate-shaped cell embedded in gelatinous matrix in which there are reticulin fibers.⁽⁵⁾ Mesenchymal cells and their derivatives are pluripotential; under appropriate circumstance, they may differentiate into fibrous, osseous, chondrous, adipose, hematopoietic, muscular, meningeal, vascular, and

reticuloendothelial tissues.⁽⁵⁾ Most of these tissues have been identified in meningiomas.^(1,5,16,20,22,23)

The presence of mesenchymal cells in some meningiomas^(5,8) is of great interest. It is suggested that meningiomas arise directly from mesenchymal cells as well as from meningocytes, fibroblasts, and Schwann cells, or from a combination of these cells. It is appropriate to designate meningioma as a mesenchymal neoplasm.^(5,7,8) This mesenchymal concept clarifies the diverse morphologic features and histogenesis of meningiomas wherever they are located. The concept, moreover, helps to understand as to why meningioma sometimes is easily confused with nerve sheath tumors (neurilemmoma and neurofibroma) or even occurs in combination with nerve sheath tumors because of the overlapping cellular origin among them.

The finding of positivity to glial fibrillary acidic protein (GFAP) in a few papillary meningiomas^(16,30) should not invite categorizing meningioma as neuroectodermal type tumor because this finding has been observed as well in some mesenchymal type cells such as in normal osteocytes and chondrocytes, neoplastic chondrocytes, and chordoma cells.^(31,32) A suggestion relating to transformation of the neuroectodermal type cells into mesenchymal type cells, such as neoplastic astrocytes into chondrocytes based on GFAP positivity in astrocytes and chondrocytes in some gliomas containing cartilage,⁽³³⁾ is not convincing as already commented.^(31,32)

Several neoplasms are now known to arise from multiple types of cells, either in the same or different lines. Combined mesenchymal tumor,^(26,34) mixed gliomas,^(35,36) and neoplasm of mixed mesenchymal and neuroectodermal (neuroepithelial) origin (ectomesenchymoma)^(22,37,38) are illustrative examples. Their histogenesis is in accord with the results of various experiments on tumor production. A single dose of carcinogen, either chemical⁽³⁵⁾ or viral^(39,40) may induce a neoplasm of mixed cellular population as well as pure form.

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