Neurosurgical forum
Letters to the editor

Neurosurgery in obsessive-compulsive disorder

To the Editor: We read with interest the recent publication by Sheehan et al. (Sheehan JP, Patterson G, Schlesinger D, et al: Gamma Knife surgery anterior capsulotomy for severe and refractory obsessive-compulsive disorder. Clinical article. J Neurosurg 119:1112–1118, November 2013). The authors suggested performing Gamma Knife surgery (GKS) for severe obsessive-compulsive disorder (OCD). Four (80%) of 5 patients demonstrated remarkable improvement, with more than a 50% reduction in the Yale-Brown Obsessive Compulsive Scale (YBOCS) score at a median 24-month follow-up. We are conducting an ongoing study of deep brain stimulation (DBS) for OCD in Asia, which makes us interested in Dr. Sheehan’s report.

As he mentioned, growing evidence shows that GKS could provide OCD patients unwilling to undergo DBS or radiofrequency ablation with a safer approach and reasonable improvement. Although the precise correlation between radiosurgical technique and patient outcome will be confirmed in future larger trials, a placebo effect cannot be eliminated in such a non-blinded treatment and device study.

In 2009, the United States FDA approved DBS for OCD under the humanitarian device exemption program. While the targets of DBS are variable and a dreadful surgical morbidity risk does exist (such as intracerebral hemorrhage), DBS affords adjustable strategies for OCD with different characteristics and severities. Stimulation side effects are transient and sometimes provide a prognostic factor as well. Furthermore, precise localization of active contacts and their effects also make refinement of DBS electrode positions possible.

Recently, Dr. Sheth and colleagues described their thermoelectric ablation techniques for treatment-refractory OCD. At a mean 63.8-month follow-up, nearly one-half of the patients (47%) revealed ≥ 35% reductions in YBOCS scores. This study reminds us that such conventional stereotactic lesioning could also provide results comparable to those of DBS or GKS. In addition, neurophysiological characterization during surgery provides not only scientific underpinning of clinical improvement, but also evidence on how human behavioral adaptation reacts with external stimuli.

Accurate target nuclei localization and the presumed territory of influence from treatments are prerequisite to a successful outcome for stereotactic neurosurgery. Given that more neurosurgeons adopt various stereotactic techniques for neuropsychiatric patients, a comparative study in the future could provide more insight into how we weigh pros and cons. We can anticipate that this evidence could provide our neuropsychiatric patients with more clear information without bias, which would make them more willing to accept such treatments.

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Disclosure
The authors report no conflict of interest.

References

Response: We appreciate the interest that Dr. Tsai and colleagues have in our recent publication. There has been a recent resurgence of interest in the use of GKS for the treatment of functional disorders including severe and refractory OCD.1-3 Our group and others have also begun to explore the application of focused ultrasound (FUS) for functional disorders such as trigeminal neuralgia and OCD.4,5

Beyond the selection of a neurosurgical tool (for example, Gamma Knife, DBS, radiofrequency ablation, or FUS) and a target (for example, anterior internal capsule, nucleus accumbens, and so forth), neurosurgeons need to shed more light on both the fundamental pathophysiology that occurs in OCD patients and the beneficial changes that an intervention facilitates. To that end, Figee et al. recently showed that DBS targeted at the nucleus accumbens (NAc) normalized its activity and reduced excessive connections between the NAc and the prefrontal cortex.6

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Ceconi et al. showed that GKS-produced ventral capsulotomy induced a significant regional increase in gray matter volume in the right inferior frontal gyrus (Brodmann area 47).2

We look forward to the results of Dr. Tsai and colleagues’ study of DBS for OCD. As they indicated, higher levels of evidence are preferred for neurosurgical studies. However, randomization or double-blinded techniques for studies involving patients with young-onset Parkinson’s disease, much less psychiatric ones, raise challenges in terms of design, financing, statistical power, and clinical equipoise. In such instances, we will have to glean as much as possible from studies even if they are imperfect. It seems clear that neurosurgery is poised for a new era of meaningful therapeutic intervention for patients with severe, medically intractable OCD.

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References

In this article, the authors present a case of schwannoma (4.4 cm × 4.2 cm) extrinsic to the sciatic nerve at the sciatic notch that was resected (piecemeal) through an infragluteal approach. Only a few cases of schwannoma at this location have been reported, and therefore this case is an important addition to the literature.

Although the case is interesting, we do not agree with the authors that the infragluteal approach should be favored in sciatic notch schwannoma, because, as they mention, neurosurgeons routinely operate through small windows.

As the authors probably know best, multiple roads lead to Rome. Likewise multiple approaches may be used for the surgical treatment of schwannomas at the sciatic notch. In the Discussion the authors mention the other approaches (the translumbar approach,1 and the combined 1-stage transabdominal-transgluteal approach3), but they state that the transabdominal approach may be complicated by nerve, vessel, and visceral injuries (sacral plexus, sciatic nerve, sigmoid colon and upper rectum, ureter, and iliac and gonadal vessels) and the translumbar approach (as least we assume that they mean “transgluteal” instead of “infragluteal” on p. 754) by nerve and vessel injuries (posterior femoral cutaneous and sciatic nerve, gluteal nerves, and gluteal veins and arteries). They also added a drawing to illustrate that the cases by Spinner et al.5 and Consales et al.1 could have been performed through the infragluteal approach.

We advocate that when deciding on the approach for a sciatic notch schwannoma several factors should be considered, including the size of the tumor, its relation to neurovascular structures (for example, the lumbar-sacral plexus), whether it is extrinsic or intrinsic to the sciatic nerve, its proximal and distal extensions, patient-related factors (for example, previous abdominal or hip surgery), and the experience of the surgeon.

We recently operated on 2 schwannomas at the sciatic notch through the translumbar approach. These lesions were located anterior to the sciatic nerve, which was located anterior to the piriformis muscle (Fig. 1). The tendinous portion of the piriformis muscle was temporarily detached from the greater femoral trochanter and was retracted medially to expose the sciatic nerve and the underlying schwannomas (Fig. 2). The schwannomas were separated from the sciatic nerve, and the proximal and distal branches were identified. There was no muscle

Fig. 1. Coronal (left) and transverse (right) T2-weighted MR images demonstrating 2 schwannomas in the left sciatic notch region, anterior to the piriformis muscle. The arrows indicate the lesions. There is scattering on the right site from previous hip prosthesis surgery. GM = gluteus maximus muscle; Pi = piriformis muscle.
contraction after stimulation; therefore the schwannomas were resected en bloc. The piriformis tendon was reconstructed by direct refixation at the original insertion point in the piriform fossa. The surgery took 2 hours. There was 100 ml of blood loss. The patient was discharged the next day without neurological deficit.

We do acknowledge that in our case the lesions were small (1.5 × 1.5 cm) and extrinsic to the sciatic nerve. For larger schwannomas, as in the cases presented by Spinner et al.3 and Consales et al.1 we would prefer to use the transabdominal approach, because of the potential close relationship with the lumbosacral plexus and iliac vein and artery lying anteriorly (see Fig 5A in the article by Spinner et al.3) and because of difficulty in identifying the proximal and distal branches with the sciatic nerve lying posteriorly. Even so, we would prefer an anterior approach (retroperitoneal) for more proximal lesions, thereby minimizing the risk for damage to intraabdominal organs. We did not choose the infragluteal approach in our case because of the longer working distance compared with the transgluteal approach, which would make it more difficult to separate the small branches from the sciatic nerve. Although we agree with the authors that piecemeal resection is generally preferable in the resection of schwannoma, we agree with Consales et al.1 that in the case of sciatic notch schwannomas extrinsic to the sciatic nerve, en bloc extracapsular resection has the advantages that it can be performed more rapidly with minimal bleeding, and resection is radical. As pointed out by Spinner et al., schwannomas at the sciatic notch often arise from small branches rather than the main sciatic nerve branch.3 As illustrated by our case, sacrificing these small branches does not necessarily lead to neurological deficit.

The reasons why neurosurgeons generally prefer the infragluteal approach could be because of historic evolution,2 but also because this approach in the reconstruction of sciatic nerve lesions has the advantage that the sciatic nerve can be followed more distally to the posterior thigh, which is especially useful in grafting procedures.2 In the case of a sciatic notch schwannoma without distal extension, however, this exposure is not per se indicated, and therefore the transgluteal approach in our opinion is preferred because of the reasons mentioned above. This approach is routinely used by orthopedic surgeons to access the acetabulum and femoral head. Although we do acknowledge that this procedure might lead to the complications mentioned by Montano et al., the risk for vascular and neural complications is small with careful blunt dissection of the gluteus maximus in line with the muscle fibers.

With this letter we wanted to point the reader of the Journal of Neurosurgery to the transgluteal approach as an alternative to the infragluteal approach presented by Montano et al. As mentioned before, various factors should be considered when deciding on the approach, and preferably the decision is made in a multidisciplinary setting.

Disclosure

The authors report no conflict of interest.

References


RESPONSE: We thank de Ruiter and colleagues for their interest in our article. They reported on a case in which 2 small schwannomas at the sciatic notch located anterior to the sciatic nerve were removed through a transgluteal approach. After detaching the tendinous portion of the piriformis muscle from the greater femoral trochanter and identifying the lesions under the sciatic nerve, they isolated the proximal and distal branches of the tumors and removed them en bloc. Moreover, they stated that in their case the infragluteal approach was not chosen because of the longer working distance compared with that in the transgluteal approach, which would make it more difficult to separate the small branches from the sciatic nerve. They also added that in our case, as well as the cases of Spinner et al.2 and Consales et al.1 they would prefer to use the transabdominal approach because of the potential close relationship with the lumbosacral plexus and iliac vein and artery lying anteriorly and the difficulty in identifying the proximal and distal branches with the sciatic nerve lying posteriorly. As we reported in our article, no general agreement exists regarding the best management of these rare tumors. The transabdominal approach alone or combined with a gluteal approach has been extensively reported. Clearly, more factors can play a role in deciding how to...
approach these tumors, including the experience of the surgeon with the selected approach.

We think that the key point of the discussion is the attempt of an en bloc removal of the tumor. This factor probably directs most surgeons to choose the transabdominal approach, which permits a wider exposure of the neurovascular structures. However, in schwannomas that are extrinsic to the sciatic nerve an en bloc removal can be difficult to achieve. In fact, identifying the proximal and distal branches and the tumor capsule and separating it from the sciatic nerve can be difficult, especially with large lesions. Based on these considerations, for large tumors we prefer to perform piecemeal removal, which facilitates the subsequent identification of the capsule and originating branches of the tumor. Thus, we chose the infragluteal approach, which, in our opinion, is less invasive than the transabdominal approach and offers a wider and more comfortable exposure of the deep-seated intrapelvic mass across the small window of the sciatic notch than the transgluteal approach. However, we did not intend to absolutely exclude the use of the transgluteal approach, which is an alternative to the infragluteal one. In the case of de Ruiter and colleagues, because of the very small tumor sizes, despite the narrower exposure of the sciatic notch, the transgluteal approach allowed for an en bloc removal of the lesions.

References


Stem cells and the origin of different glioma subtypes

To The Editor: The findings recently reported by Tamura et al.10 (Tamura K, Aoyagi M, Ando N, et al: Expansion of CD133-positive glioma cells in recurrent de novo glioblastomas after radiotherapy and chemotherapy. Laboratory investigation. J Neurosurg 119:1145–1155, November 2013) reveal several interesting aspects related to the role of putative cancer stem cells (CD133-positive cells) in glioma. The authors found significant expression of CD133 in glioblastoma (GBM) cells from tumor samples, but not in lower-grade gliomas. In addition, the percentage of CD133-positive cells in GBM was significantly higher in recurrent tumors after radiotherapy and chemotherapy than in tumors obtained from primary surgery. Furthermore, the frequency of CD133 expression was very low in secondary GBM (originating from lower-grade gliomas) even after malignant progression following radiation and chemotherapy.

An aspect of these findings that can be discussed in further detail is that they are strongly consistent with the view that different glioma subtypes may originate from distinct cells of origin. The identification of the cellular origin of gliomas remains a challenge for increasing our understanding of the disease as well as for the development of targeted therapies. Gliomas could be derived from neural stem cells (NSCs), progenitor cells, or fully differentiated cells. The aggressiveness of primary GBM, and its higher expression of CD133, particularly in recurrent tumors (as reported by Tamura et al.10), suggests a role for cancer stem cells in this particular glioma type. Glioblastoma-derived cancer stem cells share many features of NSCs, including the activation of signaling pathways related to cell proliferation and survival, the expression of several stem cell markers (for example, CD133 and nestin), and the ability to differentiate into more mature cells expressing neuronal and glial markers.1,3,6,7,13 In fact, a number of findings support NSCs as the possible cells of origin in glioma. For example, cultured NSCs derived from human glioma tissues showed high genomic instability, formation of CD133-positive neurospheres, and the ability to initiate intracranial tumors in mice.9 In a mouse model, p53 deficiency in the brain led first to an accumulation of mutations primarily in NSCs in the subventricular zone. However, glioma formation in this model was initiated by the expansion of transit-amplifying progenitor-like cells rather than directly by NSCs.12 Strong support for a glioma-initiating role of progenitor cells that may derive from NSCs, in particular oligodendrocyte precursor cells (OPCs), has also been provided by other elegant mouse models. Thus, when mosaic analysis with double markers (MADM) was used to induce concurrent p53/Nf1 mutations in NSCs, aberrant growth was evident only in OPCs, but not in other NSC-derived cell types, and the same mutations produced gliomagenesis when introduced directly in OPCs.5 In addition, transferring platelet-derived growth factor B to OPCs in mice resulted in the formation of gliomas resembling human Grade II oligodendroglioma.4 Finally, it is possible that gliomas can also arise from the dedifferentiation of fully mature glial cells. Exposing astrocytes to transforming growth factor led to their sequential conversion to neural progenitor cells and then NSCs.8

In relating this evidence to the findings reported by Tamura et al.,10 one could hypothesize, for instance, that CD133-positive glioma stem-like cells originating directly from NSCs might be primarily involved in primary GBM and its recurrence after radiation or chemotherapy, whereas OPCs or dedifferentiated astrocytes could preferentially originate lower-grade gliomas that can progress to secondary GBMs. However, one major caveat for the interpretation of these findings from a “cell of origin” perspective is that CD133 is not a specific marker for NSCs and glioma stem cells and may not allow for separation of NSCs from OPCs. Recent findings have indicated that CD133 can enrich for oligodendrocyte potential, and a subpopulation of CD133-positive cells that also express CD140a consists of OPCs capable of oligodendrocyte differentiation.11 Additional studies that include the use of multiple markers,
genetic alterations, and functional assays when analyzing glioma samples from patients will be required to help elucidate the origin of different glioma types.

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References


RESPONSE: We would like to thank Dr. Roesler for his interest in our paper and his thoughtful commentary. Glioblastoma can derive either de novo with no prior evidence of a lower-grade glioma or through malignant progression from lower-grade gliomas (that is, secondary GBM). Growing evidence indicate these two GBM subtypes constitute distinct disease entities that evolve through different genetic pathways and derive from different cellular origin. The recent identification of R132 mutations in isocitrate dehydrogenase 1 (IDH1R132H) in the majority of low-grade gliomas and secondary GBMs, with relative exclusion from primary GBMs, implicates IDH1R132H as a defining marker and key oncogenic event for GBMs that evolve from lower-grade glioma. In our study, CD133 expression was mostly confined to de novo GBMs and was not observed in lower-grade gliomas, including anaplastic oligodendrogliomas. Secondary GBMs rarely expressed CD133 antigen after malignant progression. Our findings are consistent with those reported previously by Beier et al and may lead to the proposed hypothesis by Dr. Roesler that CD133-positive glioma stem-like cells observed in primary GBM originate directly from NSCs, whereas OPCs or dedifferentiated astrocytes could originate lower-grade gliomas that can progress to secondary GBMs. This hypothesis is quite attractive but needs further elucidation. Evidence to date indicates that the cells of origin for GBM may be either NSCs or their more differentiated progeny, such as astrocytes or OPCs. Recent evidence points to OPCs as the candidate cell of origin for proneural gliomas. In the MADM analysis introducing P53/NF1 mutations in NSCs, malignant transformation generating gliomas occurred only in OPCs. Neural stem cell is the cell of mutation (nontransforming) while OPC serves as the cell of origin (transforming). Although recent data indicate the distinct cellular origin of secondary GBM, few data in relation to the cellular origin have been provided for primary GBM. Oligodendrocyte precursor cells can revert to multipotent neural stem cells, which can self-renew and give rise to neurons and astrocytes, as well as to oligodendrocytes. CD133/CD140a dual-positive OPCs derived from fetal human brain dissociates reported by Wang et al may represent early committed OPCs that could be reprogrammed and give rise to primary GBM. Further studies are needed to clarify whether a distinct cell of origin could give rise to a different glioblastoma subtype or distinct genetic mutations might transform the same cell of origin into different pathological manifestations.

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**CD133-positive stem cells**

To The Editor: Recently, we read with interest the article by Tamura et al.8 (Tamura K, Aoyagi M, Ando N, et al: Expansion of CD133-positive glioma cells in recurrent de novo glioblastomas after radiotherapy and chemotherapy. Laboratory investigation. *J Neurosurg 119:*1145–1155, November 2013). In this article, Tamura et al.8 reported that the mean percentage of CD133-positive glioma cells in sections from glioblastomas (GBMs) recurring after radiotherapy and chemotherapy was 12.2% ± 10.3%, which was significantly higher than that obtained at the primary surgery (1.08% ± 1.78%). In addition, the mean Ki 67 index of CD133-positive glioma cells in recurrent tumors (14.5% ± 6.67%, n = 20) was significantly higher than that in primary tumors (2.16% ± 2.60%, n = 14, p < 0.000001, unpaired t-test). On the basis of these results, the authors concluded that CD133-positive glioma cells could survive, change to a proliferative cancer stem cell phenotype, and lead to recurrence of GBM.

The glycosylated CD133 epitope has been identified as a reliable tumor marker for the purification of a subpopulation of GBM cells demonstrating cancer stem cell phenotypes.2 CD133-positive glioma cells display significant resistance to conventional radiation and chemotherapy. A previous study has shown that CD133-positive glioma cells persist in greater fractions after treatment with ionizing radiation through preferentially activating Chk1 and Chk2 checkpoint kinases, and this radioresistance is lost following Chk1 and Chk2 inhibition.1 In addition, CD133-positive glioma cells are associated with resistance to chemotherapy. This resistance is probably related to higher expression of BCRP1 and MGMT, as well as the antiapoptosis protein and inhibitors of apoptosis protein families in CD133-positive glioma cells. CD133 expression was significantly higher in recurrent GBM tissue obtained from 5 patients as compared to their respective newly diagnosed tumors.3 Most importantly, there was marked accumulation of CD133-positive glioma cells in sections obtained after Gamma Knife surgery (GKS) plus external beam radiation therapy (EBRT), whereas CD133-positive cells appeared very infrequently in primary sections prior to adjuvant treatment. In addition, high MIB-1 indices but reduced numbers of tumor blood vessels were observed in recurrent GBM after GKS and EBRT.7 These findings suggest that accumulation of CD133-positive glioma cells contributes to radiochemoresistance and is related to an adverse prognosis.

A recent study from Pallini et al.5 showed that in recurrent GBM, CD133-positive cells were significantly increased compared with the percentage in primary GBMs, but, unexpectedly, the increase in CD133 expression was significantly associated with longer survival after tumor recurrence. Interestingly, the CD133-positive cell compartment of recurrent GBM was composed of both cancer stem cells and nontumor neural stem cells (NSCs). Nontumor CD133-positive cells are thought to migrate from surrounding brain toward the tumor, which is linked significantly to a better outcome. This is consistent with the finding that in a mouse model, the GBM-induced attraction of endogenous neural precursor cells was associated with improved survival because of antiproliferative and proapoptotic actions of the neural precursors in GBM cells.3 These results suggest that tumor and nontumor CD133-positive cells may play completely different roles in recurrent GBM.

In summary, although many investigators agree that accumulation of CD133-positive cells in recurrent GBM after radiochemotherapy is correlated with a worse prognosis, subsequent scenarios seem to lead to opposite outcomes. The role of CD133-positive cells in recurrent GBM seems to be controversial. To ascertain the exact mechanisms of action of CD133-positive cells in recurrent GBM, both more animal studies and additional human studies with larger patient populations will be needed. Unraveling the role of tumor and nontumor CD133-positive cells in recurrent GBM may then allow for the identification of relevant targets for therapeutic intervention.

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**References**


**Response**: We would like to thank Bian and colleagues for their interest in our work.

The infiltration of nontumor cells is frequently observed in GBM tissues. In a murine experimental GBM model, endogenous neural precursors might migrate toward the tumor and suppress tumor growth by antiproliferative and proapoptotic actions. In the recent report by Pallini et al. (mentioned by Bian et al.), recurrent GBMs showed an increase in CD133-positive cells composed of both cancer stem cells and nontumor cells. The authors used elegant but somewhat complex methods to show that recurrent GBM tissues contain nontumor CD133-positive cells. The nontumor CD133-positive cells may represent NSCs that could exert an antiglioma effect causing a better prognosis for tumors with a high frequency of CD133 expression on recurrence. In our series, increased in the frequency of CD133-positive cells was greater in specimens from recurrent GBMs obtained after high-dose radiation with EBRT and GKS than in those subjected to EBRT alone. The survival of the patients with GBMs treated with high-dose radiation therapy appeared to be longer (no significant difference) than that of patients treated with EBRT alone. We thought that the better prognosis was caused primarily by high-dose irradiation. However, the survival of patients with GBMs may be influenced by many factors, including tumor biological behavior, tumor location, methods of treatment, and patient selection bias.

In the article by Pallini et al., no direct evidence was provided for the antitumor effects of nontumor CD133-positive cells on recurrent GBM. The cellular origin of nontumor CD133-positive cells was not known. The role of nontumor CD133-positive cells in recurrent GBMs after radiochemotherapy awaits further validation.

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**Glioma immunoenvironment**

To The Editor: We read with great interest the article by Yang et al. (Yang I, Han SJ, Sughrue ME, et al: Immune cell infiltrate differences in pilocytic astrocytoma and glioblastoma: evidence of distinct immunological microenvironments that reflect tumor biology. Laboratory investigation. *J Neurosurg* **115**:505–511, September 2011).

Glioblastoma is associated with a poor outcome despite aggressive resection, concomitant with radiotherapy and oral temozolomide therapies. There is an urgent need for better understanding of the underlying mechanisms to investigate novel therapies and improve survival. Recent advances in the study of tumor stem-like cells have proved that glioma stem-like cells contribute to immunosuppression. Yang et al. investigated immunohistochemical staining of CD8+ cytotoxic T cells, CD56+ natural killer (NK) cells, and CD68+ macrophages from brain tumor specimens obtained in 91 patients with glioblastoma or pilocytic astrocytoma. They found that glioblastomas had a significantly higher proportion of perivascular CD8+ cytotoxic T cells than pilocytic astrocytoma (62% vs 29%, p = 0.0005). The CD56+ NK cells and the CD68+ macrophages were more prevalent in the perivascular and intratumoral space in glioblastoma. In both the intratumoral space and the perivascular space, CD68+ macrophages were significantly more common in glioblastoma than in pilocytic astrocytoma.

The finding of increased numbers of CD8+ T cells and CD56+ NK cells in glioblastoma suggests that immune tolerance is more prevalent in glioblastoma than in pilocytic astrocytoma. Because regulatory T cells mediate immune tolerance, the authors’ results prompt further inquiry about the results of immunohistochemical staining in CD4+CD25+Foxp3+ regulatory T cells. Moreover, it is not yet clear whether the immune modulation is directly mediated by tumor cells or concomitant with brain-resident cells, such as astrocytes, neurons, and oligodendrocytes. Furthermore, the study results also stimulate readers to ask what kind of immunosuppressive proteins are regulating the CD8+ cytotoxic T cells and preventing them from attacking or eradicate the glioma cells. The under-
lying immunological modulations between glioblastoma and immune cells are particularly important.

The authors’ contributions have provided solid evidence of immune cell infiltrate within human glioblastoma and pilocytic astrocytoma. Future cell-based investigation through co-culture of tumor cells with immune cells will clarify the underlying cell biologic roles and immune modulations.

**Disclosure**

The authors report no conflict of interest.

**References**


**Response**: No response was received from the authors of the original article.