TO THE EDITOR: We read with interest the recent article by Siegal et al.4 (Siegal T, Charbit H, Paldor I, et al: Dynamics of circulating hypoxia-mediated miRNAs and tumor response in patients with high-grade glioma treated with bevacizumab. J Neurosurg [epub ahead of print January 22, 2016. DOI: 10.3171/2015.8.JNS15437]). The authors found that serum levels of hypoxia-associated microRNAs (miRNAs) miR-10b and miR-21 were elevated in patients with glioblastoma (GBM) during therapy with the monoclonal antibody bevacizumab, which targets vascular endothelial growth factor (VEGF). They concluded that the circulating levels of both miRNAs might reflect the angiogenic effect of therapy. However, the role of increased miR-10b and miR-21 in patients undergoing treatment with bevacizumab remains unclear.

When discussing their findings, Siegal et al.4 did not address some aspects of the interactions between miR-21 and VEGF, and the possible role of miR-21 in angiogenesis, which may be relevant for interpreting the data and raising hypotheses. For example, miR-21 co-localizes with VEGF in astrocytomas.1 In bladder cancer, increased miR-21 mRNA expression is accompanied by higher VEGF-C content, and overexpression of both miR-21 and VEGF-C is associated with a poorer prognosis.2 In human umbilical vein endothelial cells, VEGF upregulates miR-21 levels, and overexpression of miR-21 supports VEGF-mediated angiogenesis, whereas miR-21 inhibition contributes to impairing angiogenesis.2 Experiments using transformed human bronchial epithelial cells have shown that miR-21 from exosomes increases VEGF levels through STAT3 activation, leading to increased angiogenesis, whereas knockdown of STAT3 reduced miR-21 levels and inhibited angiogenesis.3 Finally, in VEGFR2-luc transgenic mice implanted with breast cancer cells, miR-21 knockdown impaired angiogenesis through suppression of the HIF-1α/VEGF/VEGFR2 pathway.4

This evidence indicates that, beyond being a hypoxia marker upregulated in GBM, miR-21 expression is closely related to VEGF levels, and, most importantly, miR-21 displays a crucial functional interaction with VEGF in mediating angiogenesis. This further supports the possibility raised by Siegal et al.4 that the increase in miR-21 levels during treatment with bevacizumab observed in their study may be a compensatory response to overcome therapy-induced inhibition of VEGF-mediated angiogenesis. If that hypothesis is confirmed by further research, combining anti-VEGF therapy with miR-21 inhibitors may represent a novel opportunity to increase the efficacy of antiangiogenic therapy in patients with brain tumors.

Rafael Roesler, PhD
Institute for Basic Health Sciences, Cancer and Neurobiology Laboratory, Experimental Research Center, Clinical Hospital (CPE-HCPA), Federal University of Rio Grande do Sul, Porto Alegre, Brazil

Gustavo R. Isolan, MD, PhD
Clinical Hospital (CPE-HCPA), Federal University of Rio Grande do Sul, Advanced Center of Neurology and Neurosurgery (CEANNE)–Brazil, Porto Alegre, Brazil

References

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Response

No response was received from the authors of the original article.

Should osseointegration be a target to achieve during cranioplasty?

TO THE EDITOR: We read with great interest the paper by Schwarz et al.3 (Schwarz F, Dünisch P, Walter J, et al: Cranioplasty after decompressive craniectomy: is there a rationale for an initial artificial bone-substitute implant? A single-center experience after 631 procedures. J Neurosurg 124:710–715, March 2016). Based on a retrospective series of patients who underwent cranioplasty after decompressive craniotomy, the authors suggest that patients younger than 30 years of age and older patients with a fragmented bone flap may be candidates for an initial artificial bone substitute, rather than an autograft, because of the high incidence of bone flap necrosis. We believe that the authors missed the important concept of achieving osseointegration between the bone flap and the skull.

The term osseointegration was used for the first time by Albrektsson et al. in 19861 for the first time by Albrektsson et al. in 19861 (with a low capacity for resistance to mechanical forces). The biological steps start from the formation of lamellar bone that is transversely oriented. This process is favored by the positioning within the gap of osteoconductive material, such as bone dust, and promoted by the presence of blood. The insertion of hemostatic material in the gap is not encouraged because it supports the formation of fibrous tissue.

Indirect healing takes place when adequate rigidity and stability exist between the craniolacunia and the bone flap. For this reason, the body implements mechanisms that lead from a biomechanical point of view to the progressive reduction of movement between bone and implants (Perren’s theory).2 The biological steps start from the formation of a hematoma in the soft tissues that surround the gap between the skull and bone flap, followed by replacement by granulation tissue and bone reabsorption of margins as a result of the action of osteoclasts. The granulation tissue remodels the connective tissue, whose cells have the highest capacity for proliferation within a moving environment. The connective tissue remodels fibrocartilage tissue that can partially calcify as a consequence of the osteoblasts to obtain osteofibrointegration (with a low capacity for resistance to mechanical forces). In case of abnormal osteoclast activity, bone reabsorption is established.

In conclusion, to obtain osseointegration, the bone flap and the margins of the craniolacunia must be viable without interposed fibrous tissue,2 and appropriate biological and mechanical factors are required. We encourage neurosurgeons to obtain osseointegration with autologous bone both during cranioplasty procedures and in the surgical closing phase after craniotomy. The bone flaps have to be placed to sustain and assist extensive cell colonization and anchorage to the existing bone, ultimately leading to osseointegration, which also allows biomechanical competence to be gained. Osteoconductivity ensures physical and mechanical integration with the surrounding bone, which prevents micromovements, bone flap necrosis, and bone reabsorption.
Roberto Stefini, MD
Ospedale Civile di Legnano, Milan, Italy

Umberto Zanetti, MD
University of Brescia, Spedali Civili di Brescia, Brescia, Italy

References

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Response
We thank Drs. Stefini and Zanetti for their careful analysis of our paper. The authors have stated that we have not gone into detail about osteointegration. They state that different mechanical and biological factors (e.g., a mixture of bone dust and blood) seem to be responsible for bone healing and the consolidation of the bone flap with the skull. Also they discuss their belief that the reduction of macro- and micromovement of the bone flap should result in an improvement of bone healing. They have mainly referenced Perren’s 1979 study.2

Evidence in the current literature differs from Drs. Stefini and Zanetti’s opinion regarding the role of micromovement. Kassis et al. and Yamaji et al. have shown that micromovement does improve bone healing.1,3 These authors used long bones as study objects. To the best of our knowledge, there are no comparable studies in which the skull is used as a study object. In relation to macromovement, in the section “Operation Procedures” we did state that every bone had been fixed with rigid titanium plates.

Regarding biological factors, the use of bone dust was not possible in our operations, because all cranioplasties done with an autograft were operations that were performed after cryoconservation of the bone flap. Cryoconservation of bone dust was not done. To compare the different surgical techniques, a prospective randomized study would be beneficial.

Falko Schwarz, MD
Pedro Dünisch, MD
Jan Walter, MD
Yasser Sakr, PhD, MD
Rolf Kalff, MD
Christian Ewald, MD

Jena University Hospital–Friedrich Schiller University, Jena, Germany

References

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