Our panel of experts highlight the most important research articles across the spectrum of topics relevant to the field of CNS oncology

Expert panel: Larry Junck, University of Michigan Health System, MI, USA; Maura Massimino, Fondazione Istituto di Ricovero & Cura a Carattere Scientifico Istituto Nazionale dei Tumori, Milan, Italy

Zhang L, Chen LH, Wan H *et al.* Exome sequencing identifies somatic gain-of-function *PPM1D* mutations in brainstem gliomas. *Nat. Genet.* 46(7), 726–730 (2014).

The authors sequenced whole genomes of 14 brainstem gliomas (BSGs) and 12 thalamic gliomas, and they carried out targeted sequencing of additional tumors [1]. Genetic subtypes common among BSGs were *TP53-H3F3A* co-mutation (9/33), *TP53-IDH1* co-mutation (8/33), and *PPM1D-H3F3A* co-mutation (6/33). Of these subtypes, only *TP53-H3F3A* co-mutation was found in thalamic gliomas (10/17). *PPM1D* is a known oncogene that is amplified in breast and other cancers. *PPM1D* encodes wild-type p53-induced protein phosphatase 1D (WIP1). *PPM1D* mutations were truncating mutations in exon 6 that enhanced the ability of *PPM1D* to suppress activation of the DNA damage response checkpoint protein CHK2. Further results indicate that mutant *PPM1D* contributes to cell growth and to p53 and CHK2 dephosphorylation after radiation treatment. *PPM1D* mutations were mutually exclusive with *TP53* mutations; the presence of either mutation in 25/33 BSGs implicates abnormal function of the *TP53* pathway in oncogenesis of BSGs. *PPM1D* is a potential therapeutic target in the subset of BSGs with mutations.

– Written by Larry Junck

Suvà ML, Rheinbay E, Gillespie SM *et al.* Reconstructing and reprogramming the tumor-

propagating potential of glioblastoma stem-like cells. *Cell* 157(3), 580–594 (2014).

The authors studied matched pairs of glioblastoma cultures from three human tumors as stem-like tumor-propagating cells (TPCs) grown in serum-free spherogenic culture expressing CD133 or as differentiated glioblastoma cells (DGCs) grown as adherent monolayers in serum [2]. By mapping histone H3 lysine 27 acetylation (H3K27ac), they identified 19 transcription factors (TFs) with higher expression in TPCs than in DGCs. They found a subset of four of these TFs, POU3F2, SOX2, SALL2, and OLIG2, that coordinately bind and activate TPC-specific regulatory elements. These four TFs were demonstrated to be able to reprogram differentiated glioblastoma cells, inducing cells to recapitulate the epigenetic characteristics of TPCs, to express CD133, and to be tumorigenic in mice. The authors found that ~2–7% of primary human glioblastoma cells express all four TFs, and CD133 expression is almost completely limited to this subset. This study is informative about the epigenetic basis of differing cell lineages in glioblastoma, provides detailed insight into underlying gene regulatory programs, and suggests potential treatment strategies.

– Written by Larry Junck

Deprez S, Vandenbulcke M, Peeters R *et al.* Longitudinal assessment of chemotherapy-induced alterations in brain activation during multitasking

and its relation with cognitive complaints.
***J. Clin. Oncol.* 32(19), 2031–2038 (2014).**

To explore cognitive symptoms after chemotherapy, the authors studied brain activation using functional MRI and compared the results with task performance and cognitive symptoms [3]. Subjects included 18 patients with breast cancer studied before and 4–6 months after chemotherapy, compared with 16 women with breast cancer not treated with chemotherapy and 17 healthy controls. Although task performance was similar in the three groups and did not decline at the later timepoint in any group, task-related activation declined in the group treated with chemotherapy in two areas activated by multitasking. These regions were the left anterior cingulate gyrus, known to be important in directing attention, and the left intraparietal sulcus, important in visual attention relevant to this task. The change in activation in these two areas was related to self-reported cognitive symptom severity ($r = -0.58$ and -0.60 , respectively; $p < 0.05$ after correction for multiple comparisons). This study provides a possible neurobiological substrate for cognitive symptoms after chemotherapy.

– Written by Larry Junck

Al-Mahfoudh R, Zakaria R, Irvine E, Pizer B, Mallucci CL. The management of bifocal intracranial germinoma in children. *Childs Nerv. Syst.* 30(4), 625–630 (2014).

This paper reports on a very small series of bifocal (i.e., pituitary and pineal) germinomas admitted at a single institution and all treated with craniospinal irradiation [4]. The interest of this paper is not strictly correlated to this series that is quite small, with a short median follow-up – since germinomas can relapse very late – and with two criticisms that can be raised both to the type of diagnostic approach that was chosen – biopsy in three of four – and to the following treatment that was craniospinal irradiation. The authors in fact report also a literature review and they have to be praised for this effort showing a very deep heterogeneity. Bifocal germinomas present most commonly with diabetes insipidus, but can also present with hydrocephalus, pituitary dysfunction, or visual symptoms. While it is mandatory checking markers (i.e., α -fetoprotein and β -coriogonadotropin) both

in serum and cerebrospinal fluid, to exclude any non-germinomatous cell component that deserve a more intensive treatment, the MRI is pathognomonic if combined with the clinical signs, and biopsy is not required. The therapeutic approach, considering that the bifocality is more the synchronous occurrence of a germinoma in the pineal and pituitary region rather than a metastatic manifestation of the disease, can follow the current SIOP II protocol (i.e., chemotherapy followed by whole ventricle irradiation). This approach can save from craniospinal irradiation whose activity has already been demonstrated in many series but whose toxicity is also very well known.

– Written by Maura Massimino

Cosman R, Brown CSB, DeBraganca KC, Krashaw M. Patterns of care in adult medulloblastoma: results of an international online survey. *J. Neurooncol.* 120(1), 125–129 (2014).

The authors present the results of a survey among different specialists dealing with adult medulloblastoma [5]. What is really astonishing is that only 54 patients aged over 17 years old with medulloblastoma and PNET over 17 years old were treated by the 45 clinicians answering to the online survey. To a pediatric oncologist that sees more than ten medulloblastoma patients each year, thinking about such a spread of patients is quite unusual. The quite predictable results of this analysis are the inhomogeneity of all the data collected both for the use of radiotherapy and chemotherapy, as well as changes in choice of treatment over time. The authors say that the annual incidence of medulloblastoma in Europe is 1.1 per million in men and 0.8 per million in women that is nearly one tenth of childhood incidence. As the authors correctly say the population given is very small and has been treated along a wide time span during which not only neurosurgical skills have changed, but also radiotherapy tools and biology knowledge. All these facts must persuade all physicians dealing with adult medulloblastoma to refer patients to biggest units where the amount of cases can help the knowledge and better treatment, maybe beginning with pediatric neurooncology centers that have interest also in treating adults patients.

– Written by Maura Massimino

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- 3 Deprez S, Vandenbulcke M, Peeters R *et al.* Longitudinal assessment of chemotherapy-induced alterations in brain activation during multitasking and its relation with cognitive complaints. *J. Clin. Oncol.* 32(19), 2031–2038 (2014).
- 4 Al-Mahfoudh R, Zakaria R, Irvine E, Pizer B, Mallucci CL. The management of bifocal intracranial germinoma in children. *Childs Nerv. Syst.* 30(4), 625–630 (2014).
- 5 Cosman R, Brown CSB, DeBraganca KC, Krashaw M. Patterns of care in adult medulloblastoma: results of an international online survey. *J. Neurooncol.* 120(1), 125–129 (2014).