PROGRESS IN NEUROSCIENCE PINS

Seminar Series of the
Brain & Mind Research Institute
Weill Cornell Medical College (WCMC)
&
The Graduate Program in Neuroscience of
WCMC and Sloan Kettering Institute

Thursday, 9/26/13, 4 PM, coffee at 3:45 PM
Weill Auditorium

An Oppositional Relationship Between Stemness and p53 in Malignant Glioma

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Abstract:

High-grade gliomas are notoriously insensitive to radiation and genotoxic drugs. Paradoxically, the p53 gene is structurally intact in the majority of these tumors. Resistance to genotoxic modalities in p53-intact gliomas has been attributed to attenuation of p53 functions by other mutations within a p53 signaling axis that includes CDKN2A($p14^{Arf}$), MDM2 and ATM. However, my colleagues and I have generated an alternative and potentially actionable resolution to the p53 paradox. Our data resonate with recent studies that document an intrinsic oppositional relationship between "stemness" and p53 function. Put briefly we show: (1) The bHLH transcription factor OLIG2 opposes p53 responses to genotoxic damage in both normal and malignant neural progenitors (2) that that the p53-supressive function of OLIG2 requires phosphorylation of an amino terminal triple serine motif and (3) that this triple serine motif of OLIG2 is phosphorylated in high-grade human gliomas. Transcription factors per se are notoriously difficult targets for drug development because their interactions with DNA and with co-regulator proteins involve large and complex surface area contacts. However, protein kinases lend themselves readily to the development of relatively specific small molecule antagonists. Accordingly, in the fullness of time, small molecule inhibitors of the OLIG2 protein kinase(s) could serve as targeted therapeutics for high-grade gliomas – either as stand alone modalities or (more likely) as adjuvants to radiotherapy and genotoxic drugs.

Recent relevant publications:

Ligon, K. L., E. Huillard, S. Mehta, S. Kesari, H. Liu, J. A. Alberta, R. M. Bachoo, M. Kane, D. N. Louis, R. A. Depinho, D. J. Anderson, C. D. Stiles, and D. H. Rowitch. 2007. Olig2-regulated lineage-restricted pathway controls replication competence in neural stem cells and malignant glioma. *Neuron* **53:**503-17.

Mehta, S., E. Huillard, S. Kesari, C. L. Maire, D. Golebiowski, E. P. Harrington, J. A. Alberta, M. F. Kane, M. Theisen, K. L. Ligon, D. H. Rowitch, and C. D. Stiles. 2011. The central nervous system-restricted transcription factor Olig2 opposes p53 responses to genotoxic damage in neural progenitors and malignant glioma. *Cancer Cell* **19:**359-71.

Sun, Y., D. H. Meijer, J. A. Alberta, S. Mehta, M. F. Kane, A. C. Tien, H. Fu, M. A. Petryniak, G. B. Potter, Z. Liu, J. F. Powers, I. S. Runquist, D. H. Rowitch, and C. D. Stiles. 2011. Phosphorylation state of Olig2 regulates proliferation of neural progenitors. *Neuron* **69:**906-17.

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