Cell Cycle 14:5, 689–690; March 1, 2015; © 2015 Taylor & Francis Group, LLC

GHSR hypermethylation: a promising pan-cancer marker

Pouria Jandaghi[1,2], Jörg D Hoheisel[3], and Yasser Riazalhosseini[1,2,*]

[1]Department of Human Genetics; McGill University; Montreal, QC Canada; [2]McGill University and Genome Quebec Innovation Centre; Montreal, QC Canada; [3]Functional Genome Analysis; Deutsches Krebsforschungszentrum (DKFZ); Heidelberg, Germany

The advent of high-throughput technologies such as microarrays, global gene knockout, and next generation sequencing (NGS) has revolutionized the field of molecular oncology. Large-scale endeavors of the kind represented by the *International Cancer Genome Consortium* (ICGC) and *The Cancer Genome Atlas* (TCGA) are generating comprehensive portraits of human cancers at different molecular levels spanning over genome, epigenome and transcriptome landscapes. These data have made substantial contributions to our knowledge of the molecular biology of cancer, and have highlighted novel factors which had not been acknowledged previously. For example, emerging data indicate that the mutational makeup of tumors can significantly vary based on geographical variations among patients,[1] pointing to the contribution of potentially different mechanisms (e.g. environmental) to tumorigenesis in different populations. On the other hand, cancer profiling data have also provided catalogues of cancer-associated molecular variations, which can serve as reliable biomarkers for cancer prevention or personalized management of patients. Successful examples include the refined diagnosis of disease subtype in breast cancer using gene expression signatures and protein markers, and stratifying patients affected by colorectal cancer for anti-EGFR therapy based on *KRAS* mutations.

In recent years, much attention has been focused on epigenetic marks, in particular on the development of DNA methylation-based markers. Abnormal DNA methylation patterns are uniquely attractive for marker development: (i) they are abundant in tumors; (ii) they happen at early stages of tumorigenesis; and (iii) as covalently bound modifications to DNA molecules, they are stable in different body fluids. These characteristics point to the notion that monitoring the presence and abundance of methylated DNA in "liquid biopsy" samples from cancer patients or people who are at high risk for cancer can facilitate non-invasive cancer prognosis and early diagnosis. Indeed, recent studies have reported successful examples of assaying cancer-associated DNA methylation marks in body fluids in order to monitor response to treatment[2] or tumor recurrence[3] in different cancers. Likewise, new data have shown that DNA methylation markers perform as well as routine clinical procedure (e.g. cytology examination) in the prioritization of patients for clinical management.[4] These reports together with several other recent studies have demonstrated that tools and technologies for reliable screening of abnormal DNA methylation patterns in non-invasive manners have become available.

An essential step in this respect, however, is the identification of truly informative markers that are to be interrogated in screening procedures. Accordingly, it is of paramount importance to factor for changes in epigenetic patterns that happen naturally during life-time when looking for sensible cancer markers.[5] In an earlier study, we had found DNA hypermethylation in the promoter of the growth hormone secretagouge receptor (*GHSR)* gene as an epigenetic marker of highest accuracy for detection of breast cancer.[6] This finding was supported by analyzing tumors as well as an extensive list of control samples including normal-appearing tissue samples from cancer patients and healthy individuals, as well as benign lesions. The gene promoter was significantly hypermethylated in both invasive and non-invasive *in situ* ductal breast cancer as compared to other samples. Moreover, we noted that *GHSR* hypermethylation may be involved in an epigenetic field defect in breast cancer, as the level of methylation was higher in normal-appearing tissue samples of cancer patients compared to those from healthy individuals after adjustment for age. These findings showed that while *GHSR* hypermethylation is a cancer specific pattern, it is detectable in early stage tumors.

Motivated by the high accuracy of *GHSR* hypermethylation for detection of breast cancer (with a sensitivity and specificity of 89.3 and 100%, respectively), we expanded our study to other cancers elucidating if this pattern could represent a pan-cancer marker. We observed that *GHSR* hypermethylation is able to discriminate cancers of lung, breast, prostate, pancreas, colorectum as well as B-cell chronic lymphocytic leukemia from tissue-matched control samples.[7] Similar to the abovementioned cancers, the locus was also hypermethylated in glioblastoma samples. By including tumors of different stages, where available, we showed that *GHSR* hypermethylation is detected

*Correspondence to: Yasser Riazalhosseini; Email: Yasser.riazalhosseini@mcgill.ca
Submitted: 12/08/2014; Accepted: 01/05/2015
http://dx.doi.org/10.1080/15384101.2015.1006051
Moskalev EA, Jandaghi P, Fallah M, Manoochehri M, Botla SK, Kolychev OV, Nikitin EA, Bubnov VV, von Knebel Doeberitz M, Strobel O, et al. GHSR DNA hypermethylation is a common epigenetic alteration of high diagnostic value in a broad spectrum of cancers. Oncotarget 2015. In press.

already in early-stage tumors. That is, while all tumors were significantly hypermethylated compared to non-tumoral samples, no significant differences existed for this marker between tumors of lower and higher stages. Collectively, these data indicate that *GHSR* hypermethylation is a pan-cancer marker regardless of the tissue from which the tumor originates. Therefore, interrogating *GHSR* methylation may provide a supplemental approach to routine clinical examination for cancer diagnosis.

Analyzing this marker in plasma samples and other body fluid from cancer patients will be the next step in verifying its usefulness in non-invasive screening procedures. Mechanistically, it is plausible to assume that *GHSR* hypermethylation may have a functional role in tumorigenesis in different cancers or there is an inherent susceptibility of the locus to DNA methylation, which is acquired by accelerated cell proliferation. Future studies should address these possibilities.

References

1. Scelo G, et al. Nat Commun 2014; 5:5135; PMID: 25351205; http://dx.doi.org/10.1038/ncomms6135
2. Fackler MJ, et al. Cancer Res 2014; 74(8):2160-70; PMID: 24737128; http://dx.doi.org/10.1158/0008-5472.CAN-13-3392
3. Su SF, et al. Clin Cancer Res 2014; 20(7):1978-89; PMID: 24691641; http://dx.doi.org/10.1158/1078-0432.CCR-13-2637
4. Verhoef VM, et al. Lancet Oncol 2014; 15(3):315-22: PMID: 24529697; http://dx.doi.org/10.1016/S1470-2045(14)70019-1
5. Riazalhosseini Y, and Hoheisel JD. Genome Biol 2008; 9(11):405; PMID: 19040775; http://dx.doi.org/10.1186/gb-2008-9-11-405
6. Botla SK, et al. Breast Cancer Res Treat 2012; 135 (3):705-13; PMID: 22899222; http://dx.doi.org/10.1007/s10549-012-2197-z
7. Moskalev EA, et al. Oncotarget 2015; PMID:25557172.