Perspective

CINSARC: a new look into an old concept gives hope for new treatments for synovial sarcomas

Bertha A. Brodin

Department of Oncology and Pathology, Karolinska Institutet, Stockholm 171 76, Sweden

Correspondence to: Bertha A. Brodin. Cancer Centrum Karolinska CCK R8:00, Stockholm 171 76, Sweden. Email: Bertha.Brodin@ki.se.

Submitted Mar 25, 2013. Accepted for publication Apr 19, 2013.
doi: 10.3978/j.issn.2224-4336.2013.04.04
View this article at: http://www.thetp.org/article/view/1847/2595

Genomic instability is a characteristic of all human cancers with its frequency, causes and consequences having been extensively studied and reviewed (1-8). Genomic Instability can be manifested as: whole chromosome aneuploidy that later gives rise to chromosome instability (CIN), gene copy number alterations, structural chromosomal abnormalities like translocations, telomere dysfunction, and gene mutations (9). Genomic instability not only can be a factor for tumor initiation but also favours the evolution of cancer cells with capabilities of proliferation, survival and dissemination, therefore genomic instability is considered as an enabling hallmark of cancer (10). The frequency of cytogenetic abnormalities in cancer has been systematically documented in the Mitelman database which contains karyotype data from nearly 66,000 cancer types. Most recently, with the development of genome-wide molecular techniques, the genomic landscape of many tumor types have been mapped and gene signatures of chromosomal instability that predict clinical outcomes in cancer have been defined (11). In a cancer cell, an average of 17% of the genome is amplified and 16% deleted either affecting almost the length of a chromosome arm or whole chromosomes and the gain or loss of specific chromosomes is cancer lineage specific, implying a selective process (12).

Soft tissue sarcoma (STS) is a heterogeneous tumor group consisting of more than 50 entities with distinct morphology and cytogenetic features. While the majority of STS have complex genotypes, about 30% carry specific chromosomal translocations and consequently express fusion genes that not only are diagnostic markers but also have a strong impact on the phenotype and biology of the specific sarcoma subtype.

Several groups have performed genomic and gene expression profiling of soft tissue sarcomas and have identified diagnostic and prognostic signatures that characterize specific sarcoma subgroups [for review see (13)]. A general observation derived from these studies is that there is a correlation between cell pleomorphism and genomic complexity. For example the most common adult sarcomas have complex karyotypes and pleomorphic histology, while sarcomas with chromosomal translocations often display a non-pleomorphic histology.

Frédéric Chibon and colleagues identified and validated a 67 gene signature of chromosome instability that predicts metastasis in individuals with no-translocation related soft-tissue sarcomas including undifferentiated sarcomas, leiomyosarcomas and dedifferentiated liposarcomas (14). This signature named CINSARC (for genome Complexity INdex in SARComas) showed to be a "best in test" predictor of metastasis free survival (MFS) in these tumors. Many of the genes identified encode for proteins involved in mitosis, cytokinesis, mitotic check point, the cell cycle, and DNA repair.

In a recently published paper (15), the same group, further explored whether the CINSARC signature could predict a clinical outcome in synovial sarcomas. Two series of a total of 100 untreated synovial sarcomas were analyzed by CGH and/or gene expression profiling and the results were correlated with metastasis free survival (MFS) of affected patients.

The CINSARC signature divided synovial sarcomas into two groups with different metastasis outcomes. The tumors that develop metastasis frequently harboured chromosomes with segmental alterations while non metastatic tumors rarely had chromosome losses or gains.

Of 67 genes from the CINSARC signature, two genes,

CDCA2 (cell division cycle A2) and *KIF14* (kinesin family member 14) were ranked-top as differentially expressed genes in metastatic synovial sarcomas. When their expression was correlated with patient survival, both CDCA2 or KLF14 could independently predict the metastasis outcome in patients similar or nearly better than CINSARC (*CDCA2* MFS $P=1.13\times10^{-5}$ and *KIF14* MFS $P=5.93\times10^{-6}$).

Genomic instability determined by the CINSARC signature identifies synovial sarcoma patients at high risk of metastasis and could impact treatment decisions. For example in the use of paclitaxel, there it exists a correlation between response to taxanes and genomic instability (16). The correlation between CINSARC scores and response to chemotherapy in STS remains to be investigated. Information on clinical response to chemotherapy in patients with synovial sarcomas could however be limited since patients are seldom treated with chemotherapy as the majority of STS, including synovial sarcoma, have a poor clinical response to pre or post-operative chemotherapy.

The CINSARC genes include several regulators of mitosis entry, check-point and exit such as polo-like kinase 4 (Plk4) and aurora kinases A and B, members of the kinesin family such as KLF4, Eg5 and CENP-E, of which several small molecule inhibitors have been developed and are in preclinical testing for sarcomas (17-20), giving new hopes for treatments.

The contributions of genomic instability to the metastatic phenotype and evolution of the synovial sarcoma cell is not yet defined. Interestingly chromosomal instability is associated with higher expression of genes implicated in epithelial-mesenchymal transition, cancer invasiveness, and metastasis (21). Synovial sarcomas have a relatively normal karyotype (13,22), with the translocation t(X:18) (SS18/SSX) as the main cytogenetic event. A role for SS18/SSX on genomic instability remains to be investigated.

Acknowledgements

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

1. Kendal WS, Frost P. Genomic instability, tumor heterogeneity and progression. Adv Exp Med Biol 1988;233:1-4.
2. Hill RP. Tumor progression: potential role of unstable genomic changes. Cancer Metastasis Rev 1990;9:137-47.
3. Usmani BA. Genomic instability and metastatic progression. Pathobiology 1993;61:109-16.
4. Sen S. Aneuploidy and cancer. Curr Opin Oncol 2000;12:82-8.
5. Duensing S, Münger K. Centrosome abnormalities, genomic instability and carcinogenic progression. Biochim Biophys Acta 2001;1471:M81-8.
6. Krämer A, Neben K, Ho AD. Centrosome replication, genomic instability and cancer. Leukemia 2002;16:767-75.
7. Kops GJ, Weaver BA, Cleveland DW. On the road to cancer: aneuploidy and the mitotic checkpoint. Nat Rev Cancer 2005;5:773-85.
8. Colnaghi R, Carpenter G, Volker M, et al. The consequences of structural genomic alterations in humans: genomic disorders, genomic instability and cancer. Semin Cell Dev Biol 2011;22:875-85.
9. Gordon DJ, Resio B, Pellman D. Causes and consequences of aneuploidy in cancer. Nat Rev Genet 2012;13:189-203.
10. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646-74.
11. Carter SL, Eklund AC, Kohane IS, et al. A signature of chromosomal instability inferred from gene expression profiles predicts clinical outcome in multiple human cancers. Nat Genet 2006;38:1043-8.
12. Beroukhim R, Mermel CH, Porter D, et al. The landscape of somatic copy-number alteration across human cancers. Nature 2010;463:899-905.
13. Nielsen TO, West RB. Translating gene expression into clinical care: sarcomas as a paradigm. J Clin Oncol 2010;28:1796-805.
14. Chibon F, Lagarde P, Salas S, et al. Validated prediction of clinical outcome in sarcomas and multiple types of cancer on the basis of a gene expression signature related to genome complexity. Nat Med 2010;16:781-7.
15. Lagarde P, Przybyl J, Brulard C, et al. Chromosome instability accounts for reverse metastatic outcomes of pediatric and adult synovial sarcomas. J Clin Oncol 2013;31:608-15.
16. Swanton C, Nicke B, Schuett M, et al. Chromosomal instability determines taxane response. Proc Natl Acad Sci U S A 2009;106:8671-6.
17. Arai R, Tsuda M, Watanabe T, et al. Simultaneous inhibition of Src and Aurora kinases by SU6656 induces therapeutic synergy in human synovial sarcoma

growth, invasion and angiogenesis in vivo. Eur J Cancer 2012;48:2417-30.
18. Winter GE, Rix U, Lissat A, et al. An integrated chemical biology approach identifies specific vulnerability of Ewing's sarcoma to combined inhibition of Aurora kinases A and B. Mol Cancer Ther 2011;10:1846-56.
19. Shan W, Akinfenwa PY, Savannah KB, et al. A small-molecule inhibitor targeting the mitotic spindle checkpoint impairs the growth of uterine leiomyosarcoma. Clin Cancer Res 2012;18:3352-65.
20. Brewer Savannah KJ, Demicco EG, Lusby K, et al. Dual targeting of mTOR and aurora-A kinase for the treatment of uterine Leiomyosarcoma. Clin Cancer Res 2012;18:4633-45.
21. Roschke AV, Glebov OK, Lababidi S, et al. Chromosomal instability is associated with higher expression of genes implicated in epithelial-mesenchymal transition, cancer invasiveness, and metastasis and with lower expression of genes involved in cell cycle checkpoints, DNA repair, and chromatin maintenance. Neoplasia 2008;10:1222-30.
22. Barretina J, Taylor BS, Banerji S, et al. Subtype-specific genomic alterations define new targets for soft-tissue sarcoma therapy. Nat Genet 2010;42:715-21.

Cite this article as: Brodin BA. CINSARC: a new look into an old concept gives hope for new treatments for synovial sarcomas. Transl Pediatr 2013;2(2):70-72. doi: 10.3978/j.issn.2224-4336.2013.04.04