Vanishing conflicts on cancer theories

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A recent Editorial in Cellular Oncology titled “Chromosome and Cancer, Boveri revisited” [18] introduced critically the results of a conference on aneuploidy and cancer [1,20] and, in particular, a review article by Duesberg et al. titled “The chromosomal basis of cancer” [6].

After reading this stimulating review and considering that many new studies have been recently focussed on the mechanisms of chromosomal instability and aneuploidy, I would like to pose the question if the “aneuploidy theory” of cancer in relationship with the “mutation theory” still remains as controversial as in the near past [17,22,26]. Don’t we have now enough experimental evidence that cancer originates and progresses with the contribution of both gene mutations and aneuploidy?

Somatic gene mutations associated to the mitotic checkpoints were found (though at relatively low incidences so far) in samples from colon, lung, pancreatic, rectal, lymphoid, prostate, breast and bladder cancers [15,16]. Couldn’t we think that these findings already represent a proof of principle that gene mutation and aneuploidy are linked? Additional experimental evidences suggest similar conclusions. For example, changes in the expression levels of mitotic checkpoint proteins, as for MAD1 for example, were reported to be disrupted by TP53 gene mutations [15]. Similarly, mutations in RB1 and BRCA1 were shown to deregulate MAD2 expression [15].

KRAS and APC mutations in in vitro, in mouse systems and in the human colorectal adenoma–carcinoma sequence have been linked to an abnormal chromosomal segregation leading to aneuploidy [4,5,7,10,11,13,14]. Recently, it was shown that tetraploid but not diploid cultures, obtained by blocking cytokinesis in TP53-null mouse mammary epithelial cells, enabled the generation of malignant mammary epithelial cancers when transplanted subcutaneously into nude mice [8].

It is also worthwhile to mention two human models of preneoplastic disease, the Barrett’s oesophagus and ulcerative colitis, in which TP53 mutations, telomere shortening and aneuploidy were proven to be early events in cancer genesis and progression [19].

Recent studies that link genome-wide integrity analysis with gene expression profiles similarly provided powerful indications that gene mutations, chromosomal instability and aneuploidy massively deregulate the cellular transcriptome [2,3,9,12,21,23–25]. Specific recurrent genomic aberrations have been and are being discovered that encompass specific genes and come along with old and novel tumor associated gene mutations. The functional consequences of specific DNA gain/losses are, however, not only involving single specific gene dosage changes contributing to produce for example inactivation of a tumor suppressor gene by physical deletion or amplification of an oncogene by DNA gain. More subtle and complex mechanisms are present since many aberrations span large chromosomal regions including normal genes which coordinately and cooperatively may influence important cell functions as proliferation, differentiation, apoptosis and DNA repair. The principles that are being applied include stochastic occurrence of chromosomal aberrations and selection of cells bearing specific aberrations associated to specific changes in gene expression for clonal expansion.

It is likely that new studies directly comparing DNA copy number and gene expression will be performed in the near future on the role of aneuploidy in cancer, on what genetic events may induce chromosomal instability and on the validation of novel criteria for early diagnosis. It is predictable that these studies will vanish the conflicting views that either aneuploidy or gene
mutations are a unique cause of the origin and progression of cancer negating the role of the alternative mechanism. Today, these conflicting interpretations are increasingly being abandoned to let a more complex mixed paradigm take over from previous concepts. In brief, ideas stemming from the old Boveri theory and from the modern theories may soon be seen as cooperative and equally important to cancer.

References


[22] M. Sato, M.B. Vaughan, L. Girard et al., Multiple oncogenic changes (KRASV12, p53 knockdown, mutant EGFRs, p16 by-pass, telomerase) are not sufficient to confer a full malignant phenotype on human bronchial epithelial cells, Cancer Res. 66 (2006), 2116–2128.


