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Editorial

Chromosomes and cancer, Boveri revisited

Already in the late 19th century, the link between chromosomal aberrations and the pathogenesis of cancer was described by von Hanssemann [9]. Moreover, as early as the first decade of the 20th century the German zoologist Theodor Boveri developed a genetic theory of cancer based on these chromosomal aberrations [3]. Until quite recently, these ideas have received only limited attention and focus in cancer genetics has been mainly on the role of individual oncogenes and tumor suppressor genes. Yet, there is striking contrast between the complex genomic alterations we find in most human cancers and the simplicity of model systems used to explain their biology. While in certain instances these models are informative, on multiple occasions this is not the case. Indeed multiple knock-out mice have been generated that don't have a disease phenotype.

The limited attention for chromosomal instability in cancer research nicely illustrates the influence of observer bias on science. Most of the time, you only find what you are looking for. In this case, the observer bias largely has a technical background. For a long time we have been devoid of tools to evaluate the biological complexity of cancer in high enough detail. In addition, we did not have convenient methods available to study chromosomal aberrations in large series of tumor samples. Banding techniques for karyotyping became available in nineteen seventy but this required cell culturing and cytogenetic skills [5]. Alternatively, fluorescence *in situ* hybridization, even today necessarily is restricted to a limited number of genomic probes [10,29]. One of the most popular methods for studying genomic alterations in cancer was LOH analysis, which only allowed to detected genomic losses. As a consequence, the scientific community for a substantial period of time was focused on explaining the biology of cancer mainly by the role of tumor suppressor genes. The publication of comparative genomic hybridization in the early nineteen nineties meant a large step forward and opened up new opportunities for studying chromosomal copy number changes in large tumor series [13]. Over the last decade indeed numerous studies in this field have demonstrated the presence of specific chromosomal aberrations in many different types of cancer, while in fact, not so long before that, such genomic alterations were easily regarded to be genomic noise, secondary to a cancer phenotype caused by the alteration of a few tumor suppressor genes and oncogenes [11]. Of the non-random cancer associated chromosomal alterations found, a large number actually turned out to be gains (e.g. trisomies) of larger parts of chromosomes rather than losses (which are consistent with Knudson's two hit model of tumor suppressor genes) or narrow high level amplifications, as known e.g. for Her2Neu. Introduction of the arrayCGH platform, especially in the last two years, has caused a tremendous number of studies on chromosomal instability in cancer [30]. In parallel, also microarray expression profiling studies have contributed to the appreciation that not only loss of function, but also increased expression of numerous genes plays a role in the pathogenesis of cancer. Moreover, the integration of microarray expression and arrayCGH analysis in cancer has demonstrated substantial correlation between DNA copy number alterations and expression of the genes involved, clearly demonstrating that these chromosomal alterations by no means are merely genomic noise, but have specific biological effects [31].

The concept that alterations involving building blocks (i.e. larger chromosomal areas with multiple genes) rather than bricks (i.e. the individual tumor suppressor genes or oncogenes) provide an efficient way for tumor cells to acquire a phenotype that yields a selection advantage, is an intriguing concept. Comparative genomics learns that the development of species is also associated with alterations of large blocks of of chromosomes [6]. When this mechanism is favorable for the evolution of species, it is quite plausible that this also holds for the evolution of tumors. As a consequence of chromosomal instability, the resulting tumor cells obtain an aneuploid genome. In a contribution to the present issue of *Cellular Oncology*, Peter

Duesberg argues that in fact this mechanism of aneuploidization would be the main explanation of cancer development [5]. Although the situation in real life will be more shaded and not as black and white as put in his paper, Duesberg certainly has a point that the importance of chromosomal instability or aneuploidy for a long time has been underestimated in the study of cancer biology. As argued, lack of methods for studying chromosomal instability in detail has played a role here, but also the fact that it in a reductionist approach it scientifically is more en vogue to study model systems in which only one or few variables have been modified, like in knock out mice, rather than to model the complexity of cancer that are facing in real life. However, times are changing, genomic instability is recognized as a major hallmark of cancer, and the mechanisms of genomic instability are a frequent subject of study [1,2,6,8,14,15,17,25,26,28,32]. Yet again, most study efforts have been put in a type of genomic instability that is not the most common, but for which the most convenient methodology was available, i.e. microsatellite instability. As a consequence, the mechanisms behind microsatellite instability have been resolved to a much larger extent than the mechanisms behind the most common type of genomic instability, i.e. chromosomal instability. But also here, mechanisms of chromosomal instability and aneuploidization more and more entering the focus of science [23,24]. One way of trying to resolve the mechanisms behind chromosomal instability is studying the biology of hereditary chromosomal breakage syndromes, like Fanconi anemia.

In perspective of this revival of aneuploidy as a major biological determinant of cancer, it is intriguing to see that in the clinical setting, the value of aneuploidy has been recognized for a long time and measurement of aneuploidy by means of DNA cytometry or FISH has been well established [12,16–22,27]. Joining forces in basic and clinical research on chromosomal instability holds great promise for making important advances in oncology with major implications for the diagnostics and therapy of cancer.

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