Gene Fusion due to Chromosome Misconnection May Seriously Affect Your Health

After observations of abnormal metaphases in sea urchin eggs, Theodor Boveri speculated that the occasional appearance of an abnormal nuclear division in normal tissue may provide a plausible explanation for the production of a malignant tumor or other abnormal phenotypes [Boveri, 1914]. In his view, malignant tumors may be driven to unrestrained proliferation as the result of certain abnormal chromosome constitutions. In this way, Boveri [1914] laid the groundwork for thorough cytogenetic investigations of both the germline and tumor cells. He admitted that ‘a hypothesis can be of value only if it leads to targeted new research and, above all, to new experimental investigations’. His work certainly did, and generated, among others, the ‘Cancer Genome Anatomy Project’ of the National Cancer Institute in Rockville, Md., USA. Analyzing the data in this resource, Mitelman et al. [2007] discovered that genome rearrangements in all forms of cancer had resulted in the formation of 358 gene fusions, which affected 337 genes. In the human germline, gene fusions were also found, albeit as extremely rare events resulting from copy number variations and complex chromosome rearrangements [Nothwang et al. 2001; Yue et al., 2005; Mansouri et al., 2006; Borsani et al., 2008; Backx et al., 2011; Eykelenboom et al., 2012; Holt et al., 2012; Di Gregorio et al., 2013; Malli et al., 2014; Rippey et al., 2013; van Heesch et al., 2014; Bertelsen et al., 2015]. Hence, one could argue that gene fusions, resulting from chromosome rearrangements and occurring in both somatic cells and in the germline, would be such a type of abnormal chromosome constitution as hypothesized by Boveri [1914].

Reanalyzing data from a previous study, van Heesch et al. [2014] discovered that in one patient a chromothripsis event had led to a genomic rearrangement in which 2

genes, *DYPD1* and *ETV1*, were juxtaposed [Kloosterman et al., 2012; van Heesch et al., 2014]. By RT-PCR, they showed that this produced a fusion transcript, which was expressed in peripheral blood lymphocytes. A second chromothripsis event caused a fusion of exon 1–11 of *FOXP1* with an unknown genomic element. The truncated N-terminal remnants of *ETV1* and of *FOXP1* showed reduced expression. Transfected into HEK293 cells, the *DYPD1-ETV1* fusion transcript did not produce a stable and functional protein. This suggests that the patient’s phenotypes were not caused by the fusion transcript, but possibly due to other gene disruptions or gene losses [Poot et al., 2011].

The *ETV1* gene is a frequent partner in gene fusions in prostate cancer [Gasi Tandefelt et al., 2014]. Therefore, the authors compared a set of 552 de novo germline chromosomal rearrangements, of which two-thirds resulted from chromothripsis, with a comprehensive set of 68,018 breakpoints from rearrangements in cancer cells [van Heesch et al., 2014]. Between the de novo germline events and the cancer breakpoints, they found an overlap of 13 breakpoints in 9 genes: *RUNX1* (3×), *FOXP1* (2×), *EBF1* (2×), and *GMPS*, *ETV1*, *FGFR1*, *NFIB*, *VTI1A*, *HMG2A2* (each once). This overlap prompted the authors to hypothesize that germline rearrangements may also predispose to malignant disease. For instance, patients with germline disruptions of *RUNX1* may develop hematological malignancies later in life [Buijs et al., 2012]. In this way, the ‘mutator hypothesis’ of cancer development is extended to also include genomic rearrangements [Fox et al., 2013]. In addition, these findings appear to substantiate the hypothesis Boveri [1914] has put forward a century ago.

Bleeker et al. [2014] identified 11 syndromes with more than 100 individuals involving microtia and 26 syndromes with hypospadias, in which tumors were found at the same body sites as the major and minor characteristics of the syndromes. This suggests that tumors in patients with malformation syndromes may be explained by abnormal functioning of the same gene that has caused the malformation syndrome. The autosomal recessive disorder Werner Syndrome (WRN), in which patients suffer from a defect in proliferative homeostasis of mesenchymal tissues leading to phenotypes of premature ageing and an increased risk of mesenchymal tumors, also fits the pattern observed by Bleeker et al. [2014] and Epstein et al. [1966]. In addition, this syndrome may provide a mechanistic link between germline and somatic genome rearrangements. Female WRN patients show reduced fertility, while males are completely azoospermic.

Somatic cells from WRN patients show a typical and diagnostic variegated chromosomal translocation mosaicism and spontaneous deletion formation [Salk et al., 1981; Fukuchi et al., 1989]. Absence of the WRN-encoded 3'-5' helicase-3'-5' exonuclease causes a reduction in recombinational repair, which results in hypersensitivity to DNA cross-linking and double-strand breaks provoking agents [Ogburn et al., 1997; Poot et al., 1999, 2001, 2002, 2004; Dhillon et al., 2007; Su et al., 2014]. In tumor cells, silencing WRN expression by RNA interference induces a mitotic catastrophe and eventually cell death, without affecting normal cells [Futami and Furuichi, 2015]. The studies of van Heesch et al. [2014], Bleeker et al. [2014] and Futami and Furuichi [2015] will certainly generate hypotheses that may lead to targeted new research, and above all, to novel approaches in cancer therapy.

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