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Editorial

The 13th Fanconi anemia gene identified: *FANCI*

Importance of the 'Fanconi anemia pathway' for cellular oncology

After quite some scientific debate over the last decade, it has become evident that chromosomal instability is a major driving force in the pathogenesis of the vast majority of human cancers [1–3]. In addition, different patterns of chromosomal instability appear to have different clinical implications [4,5]. Yet, unlike for the less common form of genomic instability caused by failing DNA mismatch repair leading to microsatellite instability, the mechanisms leading to chromosomal instability are only beginning to be explored in appreciable detail. Chromosomal instability actually encompasses multiple biological types of chromosomal alterations giving rise to different biological and clinical phenotypes. In this respect, important lessons can be learned by studying genetic diseases characterized by chromosomal instability, like Fanconi anemia (FA). In the present issue of *Cellular Oncology*, a consortium lead by Dr. Joenje reports identification of the thirteenth FA gene, *FANCI*, a milestone in this field of research, accomplished by a group that has been critically involved in already 10 previous FA gene discoveries.

FA is a rare, recessively inherited disease featuring developmental defects, progressive bone marrow failure and an extremely high cancer risk [6]. Cells derived from FA patients exhibit spontaneous chromosomal breakage and are hypersensitive to the growth inhibitory effect of a class of chemotherapeutics known as polyfunctional alkylating or "cross-linking" agents, which include well-known compounds such as mitomycin C, cisplatin, melphalan, and cyclophosphamide. Research over the past 15 years has revealed a remarkable degree of genetic heterogeneity in FA. Many distinct disease genes have been identified, each of which – when inactivated by mutations – causes FA.

The proteins encoded by the FA genes appear to act in concert to support an integrated biochemical DNA maintenance process referred to as "the FA pathway" (Fig. 1). The function of this pathway is to protect the genome against accidental alterations that might push a cell onto the road to cancer. In addition, the FA pathway functions to protect a cell against killing by cross-linking agents.

How does the pathway work? Unfortunately, this is far from clear yet. Most of the proteins are 'orphans', as they do not appear to resemble any other protein in the database and therefore their precise molecular functions remain to be assessed.

Some proteins were already implicated in DNA repair processes before they were unmasked as participants in the FA pathway: BRCA2 (also known as FANCD1), BRIP1 (a BRCA1-binding DNA helicase, also called FANCJ) and the BRCA2-partner protein PALB2 (FANCN). Individuals who are heterozygous carriers of mutations in one of the 3 genes encoding these proteins appear to have a significantly increased risk of developing breast cancer, suggesting that FA pathway defects may play a role in the origin of cancer in the general population.

In fact, evidence is accumulating that a proportion of cancers in the general population is characterized by such defects [7,8]. The first publications reported the silencing of *FANCF* in a subset of ovarian cancer cell lines [9] and in one AML cell line [10]. Subsequently, different FA gene defects were demonstrated in a wide variety of additional cancers (summarized in [7]). These observations may have important implications for the choice of chemotherapeutic options that may be offered to cancer patients, since cancer cells that carry a FA pathway defect are predicted to be hyperresponsive to treatment with cross-linking agents. Even in cancer cells that still possess an intact FA pathway, deliberate interference with the pathway by small molecules (such as curcumin [11]) might be helpful to sensitize such cells for more effective treatment with cross-linkers. A similar approach is currently being explored to obtain more effective treatment of breast cancer by exploiting the *in-vitro* finding that FA-pathway-deficient cells are hypersensitive to poly(ADP-ribose) polymerase (PARP) inhibitors, which are relatively

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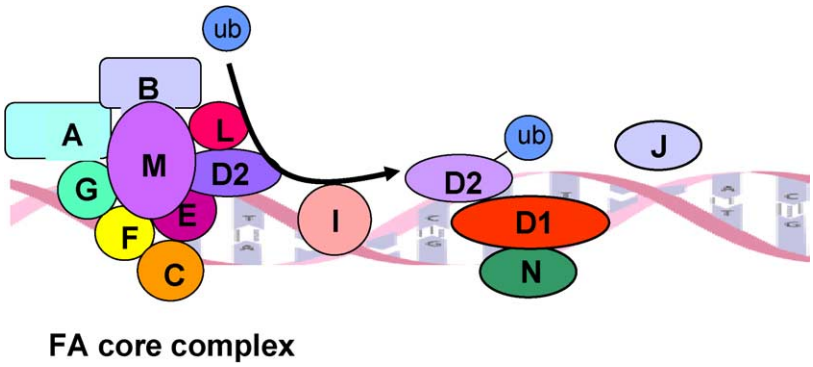

Fig. 1. Proteins participating in the FA pathway of genomic maintenance. The majority of FA proteins form the FA protein core complex, which is essential for the monoubiquitination of FANCD2 and referred to as the 'upstream' part of the pathway. The core complex consists of different subcomplexes (A/G, B/L, E/C/F) which assemble around the DNA translocase FANCM. The FANCE protein recruits FANCD2 to the core complex and allows the E3-ligase FANCL to monoubiquitinate FANCD2. FANCI is essential for the monoubiquitination step, but seems to act independently of the core complex, by tethering FANCD2 to the chromatin. FANCD1/BRCA2, FANCJ/BRIP1 and FANCN/PALB2 act downstream of the FA core complex, but co-localise with FANCD2 in DNA repair foci. All 13 proteins shown in this scheme cause, when defective, the syndrome Fanconi anemia.

non-toxic to cells that do not carry an FA pathway defect [12,13].

With the discovery of *FANCI* the cancer research field has obtained a novel tool to examine malignancies for possible FA pathway defects, which may turn out to be an important criterion for the diagnosis and treatment of cancer.

Gerrit A. Meijer
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References

[1] G. Meijer, Chromosomes and cancer, Boveri revisited, *Cell. Oncol.* **27** (2005), 273–275.

[2] P. Duesberg, R. Li, A. Fabarius and R. Hehlmann, The chromosomal basis of cancer, *Cell. Oncol.* **27** (2005), 293–318.

[3] W. Giaretti, Vanishing conflicts on cancer theories, *Cell. Oncol.* **28** (2006), 1–2.

[4] M. Grade, H. Becker, T. Liersch, T. Ried and B. Ghadimi, Molecular cytogenetics: genomic imbalances in colorectal cancer and their clinical impact, *Cell. Oncol.* **28** (2006), 71–84.

[5] T. Buffart, J. Coffa, M. Hermsen, B. Carvalho, J. van der Sijp, B. Ylstra, G. Pals, J. Schouten and G. Meijer, DNA copy number changes at 8q11-24 in metastasized colorectal cancer, *Cell. Oncol.* **27** (2005), 57–65.

[6] M. Levitus, H. Joenje and J. de Winter, The Fanconi anemia pathway of genomic maintenance, *Cell. Oncol.* **28** (2006), 3–29.

[7] C. Jacquemont and T. Taniguchi, Disruption of the Fanconi anemia pathway in human cancer, *Cancer Biol. Ther.* **5** (2006), 1637–1639.

[8] A. Lyakhovich and J. Surralles, Disruption of the Fanconi anemia/BRCA pathway in sporadic cancer, *Cancer Lett.* **232** (2006), 99–106.

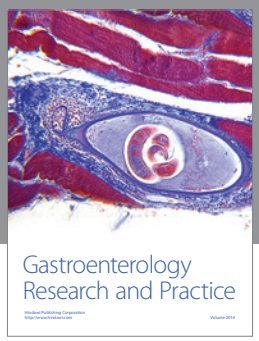
[9] T. Taniguchi, M. Tischkowitz, N. Ameziane, S.V. Hodgson, C.G. Mathew, H. Joenje, S.C. Mok and A.D. D'Andrea, Disruption of the Fanconi anemia-BRCA pathway in cisplatin-sensitive ovarian tumors, *Nat. Med.* **9** (2003), 568–574.

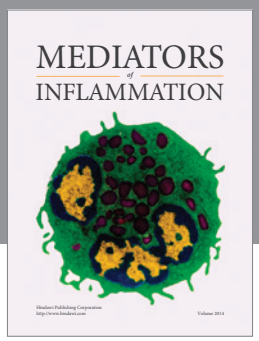
[10] M. Tischkowitz, N. Ameziane, Q. Waisfisz, J.P. de Winter, R. Harris, T. Taniguchi, A. D'Andrea, S.V. Hodgson, C.G. Mathew and H. Joenje, Bi-allelic silencing of the Fanconi anaemia gene *FANCF* in acute myeloid leukemia, *Br. J. Haematol.* **123** (2003), 469–471.

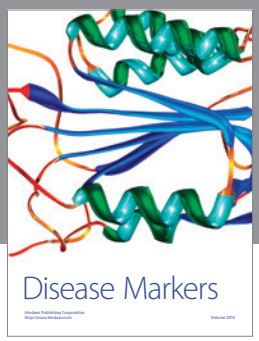
[11] D. Chrinomas, T. Taniguchi, M. de la Vega, A.P. Vaidya, M. Vasserman, A.R. Hartman, R. Kennedy, R. Foster, J. Mahoney, M.V. Seiden and A.D. D'Andrea, Chemosensitization to cisplatin by inhibitors of the Fanconi anemia/BRCA pathway, *Mol. Cancer Ther.* **5** (2006), 952–961.

[12] H.E. Bryant, N. Schultz, H.D. Thomas, K.M. Parker, D. Flower, E. Lopez, S. Kyle, M. Meuth, N.J. Curtin and T. Helleday, Specific killing of *BRCA2*-deficient tumours with inhibitors of poly(ADP-ribose) polymerase, *Nature* **434** (2005), 913–977.

[13] H. Farmer, N. McCabe, C.J. Lord, A.N. Tutt, D.A. Johnson, T.B. Richardson, M. Santarose, K.J. Dillon, I. Hickson, C. Knights, N.M. Martin, S.P. Jackson, G.C. Smith and A. Ashworth, Targeting the DNA repair defect in *BRCA* mutant cells as a therapeutic strategy, *Nature* **434** (2005), 917–921.







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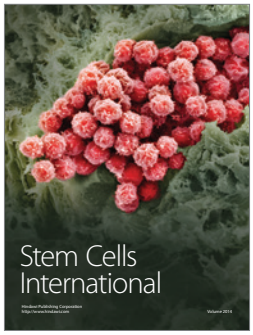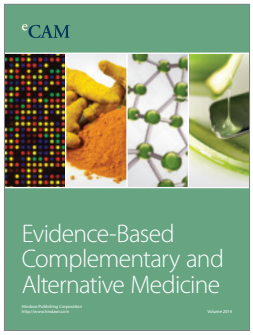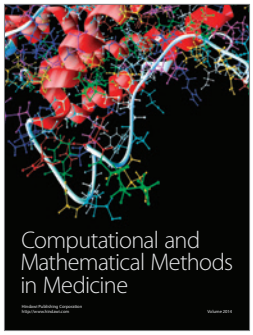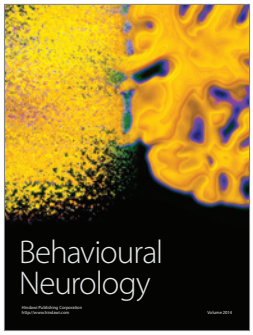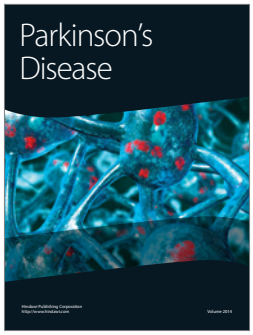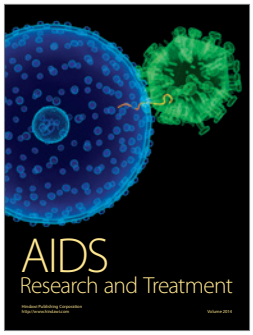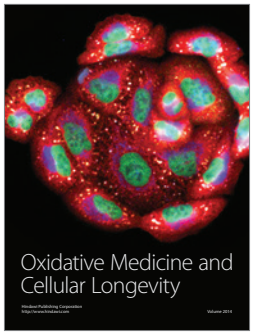
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