Abstract  The dissection of the molecular pathways participating in genetic instability disorders has rendered invaluable information about the mechanisms of cancer pathogenesis and progression, and is offering a unique opportunity to establish targeted anticancer therapies. Fanconi anaemia (FA) is a paradigm of cancer-prone inherited monogenic disorders. Moreover, accumulated evidence indicates that genetic and epigenetic alterations in FA genes can also play an important role in sporadic cancer in the general population. Here, we summarise current progress in the understanding of the molecular biology of FA and review the principal mechanisms accounting for a disrupted FA pathway in sporadic cancer. Additionally, we discuss the impact of these findings in the development of new anticancer therapies, particularly with DNA interstrand cross-linkers and with new inhibitors of the FA and/or alternative DNA repair pathways.

Keywords  Fanconi anaemia · Sporadic cancer · Cross-linkers · PARP inhibitors · Chronic myeloid leukemia · Acute myeloid leukemia · Synthetic lethality

Introduction

Fanconi anaemia (FA) is an autosomal recessive disease (except for FANCB, which is X-linked) characterised by congenital abnormalities, progressive bone marrow failure and cancer susceptibility, mainly acute myeloid leukaemia (AML) and squamous cell carcinoma (SCC) [1]. At the cellular level, FA cells are highly sensitive to DNA inter-strand cross-linking (ICL) agents and also to oxidative stress [2].

Because of the current evidence showing the role of the FA pathway in DNA repair and cancer suppression, increasing attention is being paid to understanding the physiological consequences of mutations in FA genes with three main purposes: (1) to elucidate the role of FA genes in inherited and sporadic cancer, (2) to conduct prognostic studies of cancer progression and (3) to predict the response of cancer cells with a disrupted FA pathway to anticancer agents.

The Fanconi anaemia pathway

To date 13 different complementation groups have been characterised in FA, each of them associated with mutations in the corresponding FA gene (FANCA, -B, -C, -D1/BRCA2, -D2, -E, -F, -G, -I, -J/BRIP1, -L, -M and N/PALB2). A FA-like disorder has been recently reported in patients from the same family with biallelic mutations in RAD51C (potentially FANCO) [3].

As shown in Fig. 1, the FA/BRCA pathway can be organised into three different molecular complexes in the cell nucleus: (1) the FA core complex (FACC); (2) the complex formed by FANCI and FANCD2 proteins (ID complex) and (3) proteins located downstream from the ID complex.

The FA pathway can be activated both by DNA damage and DNA replication (see review in [4]). Initially, eight FA proteins (FANCA, -B, -C, -E, -F, -G, -L and -M) together with other FA-associated proteins (FAAP24, FAAP100),
MHF1 and MHF2 are assembled, forming a large nuclear ubiquitin E3 ligase complex in Fig. 1. Only two proteins of this core have a recognised catalytic activity: FANCL, with an E3 ubiquitin ligase domain [5], and FANCM, with ATP-dependent translocase activity [6]. After the generation of an ICL, the FANCM/FAAP24/MHF1-2 proteins recognise it in the stalled replication fork and recruit the FACC by direct interaction between FANCM and FANCF (see review in [4]). In a second step, the FACC facilitates the monoubiquitination of the tandem FANCD2/FANCI proteins [7, 8]. The activated ID complex is then loaded onto chromatin and binds the Fanconi-associated nuclease 1 (FAN1), which provides the nuclease activity during ICL repair in DNA-damaged sites and colocalises with downstream proteins [9–12]. These proteins include FA proteins such as FANCD1/BRCA2, FANCE/PALB2 and FANCJ/BRIP1, as well as other proteins, such as RAD51C (putative FANCO), BRCA1 and RAD51, associated with homologous recombination (HR) [13]. Also other nucleases and translesion synthesis polymerases are probably recruited by the ID complex for the processing of the ICLs (see review in [4]). Finally, the FA pathway is inactivated by the tandem USP1/UAF1 enzyme complex, which deubiquitinates FANCD2 and FANCI, resolving the ICL damage [14].

The main upstream regulator of the FA pathway is ATR. This kinase phosphorylates directly or via its effector kinase Chk1, multiple proteins of the FA pathway and other FA-associated proteins, including FANCA, FANCE, FANCI, FANCD2 and BRCA1. These kinases coordinate the cell response to DNA damage in the S-phase. Additional molecular interactions have been reported with proteins including BLM, NBS and H2AX among others (review in [15]).

As can be deduced from the nomenclature given to proteins participating in the FA pathway, not all of them are identified as FA proteins. This is explained either because there are no FA patients whose disease can be accounted for by mutations in these genes (i.e., FAAP24, FAAP100, MHF1, MHF2), or because their mutations are associated with phenotypes that only partially overlap with the phenotype of FA patients (i.e., ATR, BLM, NBS1, whose mutations account for Seckel [16], Bloom [17] and Nijmegen [18] breakage syndromes, respectively).

The Fanconi anaemia pathway and sporadic cancer

The prevalence of cancer in carriers of FA mutations has been reviewed in detail by García and Benítez in this journal [19]. Defects in the FA/BRCA pathway are, however, not exclusive to inherited cancer. In this respect, different studies have already shown the relevance of FA pathway inactivation in malignancies from individuals without a family history of cancer (see review in [20]).

As shown in Table 1, the principal mechanisms that account for a disrupted FA pathway in sporadic cancer can be summarised as follows: (1) epigenetic silencing of FA genes, (2) somatic mutations leading to loss of function of FA...