Fanconi Anemia

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KEYWORDS

• Fanconi anemia • Bone marrow failure • Genomic instability
• DNA damage and repair • Oxidative stress
• Monobiquitylation • Cytokines • BRCA1/2

Fanconi anemia (FA) is an autosomal and X-linked recessive disorder characterized by bone marrow failure, acute myelogenous leukemia (AML), solid tumors, and developmental abnormalities. At the molecular level, cells derived from FA patients display hypersensitivity to DNA cross-linking agents, resulting in increased numbers of chromosomal abnormalities including translocations and radial chromosomes. This hypersensitivity made treating FA patients a challenge in the past because traditional treatments of their symptoms resulted in more harm than good. Recent years have seen a dramatic improvement in FA patient treatment, however, resulting in a greater survival of children into adulthood. These improvements have been made despite the fact that a definitive cellular function for the proteins in the FA pathway has yet to be elucidated. Delineating the cellular functions of the FA pathway could help further improve the treatment options for FA patients and further reduce the probability of succumbing to the disease. This article reviews the current clinical aspects of FA including presentation, diagnosis, and treatment followed by a review of the molecular aspects of FA as they are currently understood (**Figs. 1** and **2**).

CLINICAL ASPECTS OF FANCONI ANEMIA

In earlier times, children with FA had the inevitable outcome of death, because most FA patients present with aplastic anemia and little in the way of supportive care was available. In the first part of the twentieth century, the advent of modern blood banking allowed the clinician to stem the immediacy of anemia and thrombocytopenia that resulted in death. As a result, the next major issue for these children became infection, even with the development of antibiotics. Neutropenic infections are generally not well tolerated and typically not curable with antibiotics alone, and many FA children succumbed to bacterial and fungal infections. Finally, even when a child could be

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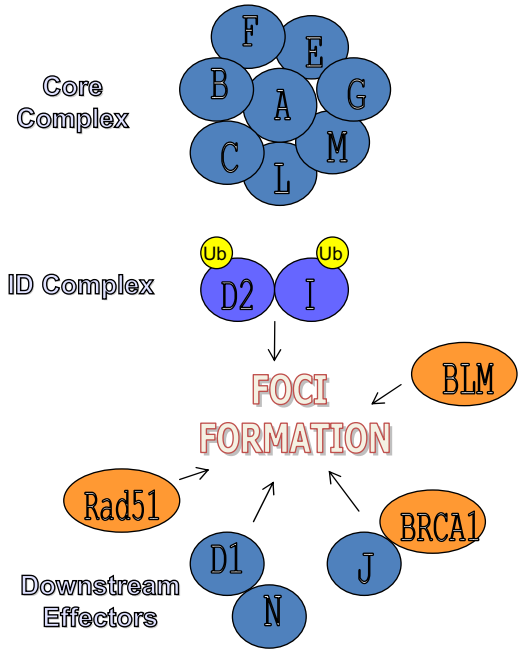

Fig. 1. The FA pathway proteins. The FA pathway is composed of at least 13 genes. Each of these genes, when biallelically mutated, causes FA. The encoded proteins can be subdivided within the FA pathway into three groups: (1) proteins that make up the core complex; (2) the FANCD2 and FANCI proteins, which compose the ID complex; (3) and three downstream effector proteins, FANCD1/BRCA2, FANCJ/BRIP1/BACH1, and FANCN/PALB2. Following treatment with DNA cross-linking agents or during S phase of the cell cycle, FANCD2 and FANCI become monoubiquitylated. An intact core complex is required for these modifications, which result in the translocation of the two proteins to chromatin within cells. Within chromatin, FANCD2 and FANCI colocalize with DNA repair proteins including the downstream effector FA proteins at sites of DNA damage in nuclear foci. FA proteins are in blue.

supported through the huge problem of aplastic anemia, the looming issue of AML nonetheless inevitably and inexorably presented itself. It was the exceptionally rare patient who survived to adulthood.[1–3]

Recent years have revolutionized the care of the FA patient. Although hematopoietic stem cell transplantation (SCT) has been performed on FA patients for almost 30 years, it is only in recent years that such approaches have been done more safely and successfully.[4] Even with the greater survival of children into adulthood as a result of SCT, the specter of potential of solid tumors, such as squamous cell carcinomas of the head, neck, and genitourinary track, remains a serious problem.[5–8]

PRESENTATION

Even though a classic set of features generally characterize these patients, FA children typically present in the first decade of life on recognition of aplastic anemia.[1–3] Nonetheless, classic features of FA consist of thumb and radial absence, malformation, or even less obvious features, such as a deeper cleft between the first two digits. In much the same way as the facial features of children affected by Down's syndrome allow