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Chromosome instability, DNA repair deficiency and cancer: insights from Fanconi anemia

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Fanconi anemia (FA) is chromosome instability disorder characterized at the clinical level by malformations, progressive bone marrow failure and a high predisposition to leukemia and head and neck squamous cell carcinoma (HNSCC) and other tumors. FA cells show chromosome fragility and hypersensitivity to DNA interstrand cross-linking (ICL) mutagens due to deficiency in ICL repair. The only cure of the blood disease is hematopoietic stem cell transplantation and gene therapy appears on the horizon of new treatments thanks to successful clinical trials. Diagnosis and therapy are further complicated by the genetic complexity of the disease. There are at least 22 genes, from FANCA to FANCW, involved in this disease and their products interact in a complex genome stability and tumor suppression network: the FA/BRCA pathway. Notably, 5 out of 22 FA genes (FANCD1/BRCA2, FANCN/PALB2, FANCJ/BRIP1, FANCO/Rad51C and FANCM) are breast/ovarian cancer susceptibility genes in otherwise unaffected mutation carriers. FA HNSCCs are difficult to treat due to extreme toxicity of conventional chemotherapies. Extensive research is underway to genetically and functionally characterize FA tumors in search of therapeutic vulnerabilities. Therapeutic advances based on a deep understanding of the genetics of FA cancers will be shown, including the discovery and repurposing of drugs inducing cancer specific lethality.

Keywords:
Fanconi anemia; cancer; DNA repair; chromosome instability; mutation