

The diagram illustrates the FA Core Complex and its involvement in the DNA damage response. The FA Core Complex is shown as a cluster of proteins: FAAP24, A, FAAP100, M, G, B, F, L, E, and C. This complex is associated with a DNA double helix. A stalled replication fork is depicted at a DNA cross-link, with a starburst indicating the site of damage. Key proteins involved in the response include ATR, ATM, N, D1, RAD51, BRCA1, J, I, D2, and USP1. Ubiquitin (ub) is shown as a small circle. The entire process occurs within the Nucleus.

Fig 1. Model for the sequential assembly of the FA core complex proteins. In the nucleus, DNA cross-links or lesions that are caused by either endogenous or exogenous DNA-damaging agents are encountered by the advancing replication fork during S phase. The Fanconi Anemia (FA) nuclear core complex (consisting of: FANCA, -B, -C, -E, -F, -G, -L, -M, FAAP24, and FAAP100) responds to the DNA damage and becomes an active ubiquitin ligase (E3) which, in turn, leads to the monoubiquitylation of the FANCD2 and FANCI proteins which exist in a complex. Following monoubiquitylation, the FANCD2/FANCI complex is targeted to chromatin where it interacts with FANCD1 (BRCA2) and its binding partner FANCN (PALB2) and possibly FANCF (BRIP1/BACH1), to help coordinate the repair processes to overcome DNA cross-links or other lesions. The deubiquitylating enzyme USP1 is a negative regulator of the FA pathway, through the removal of ubiquitin from FANCD2 and FANCI.