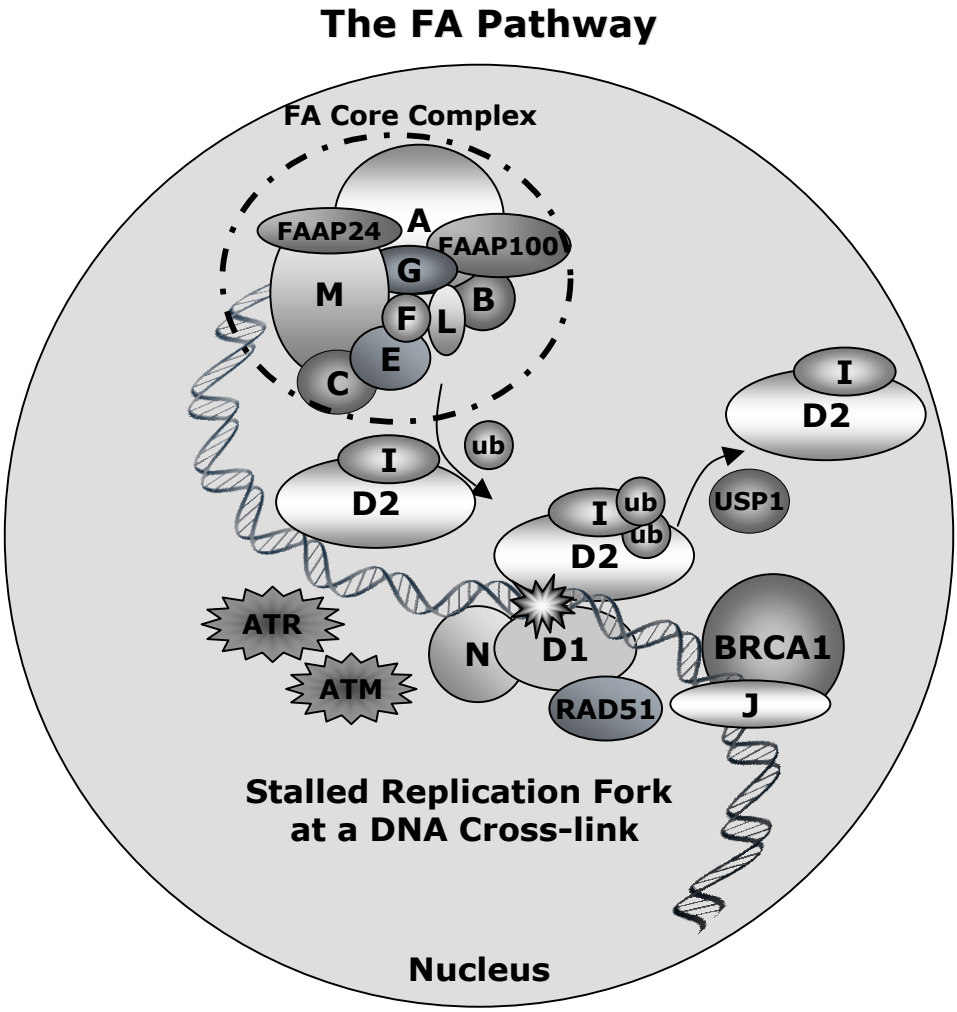

Fig 1. Model for the sequential assembly of the FA core complex proteins. In the nucleus, DNA cross-links or lesions that are caused by either endogenous or exogenous DNA-damaging agents are encountered by the advancing replication fork during S phase. The Fanconi Anemia (FA) nuclear core complex (consisting 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 FANCJ (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.