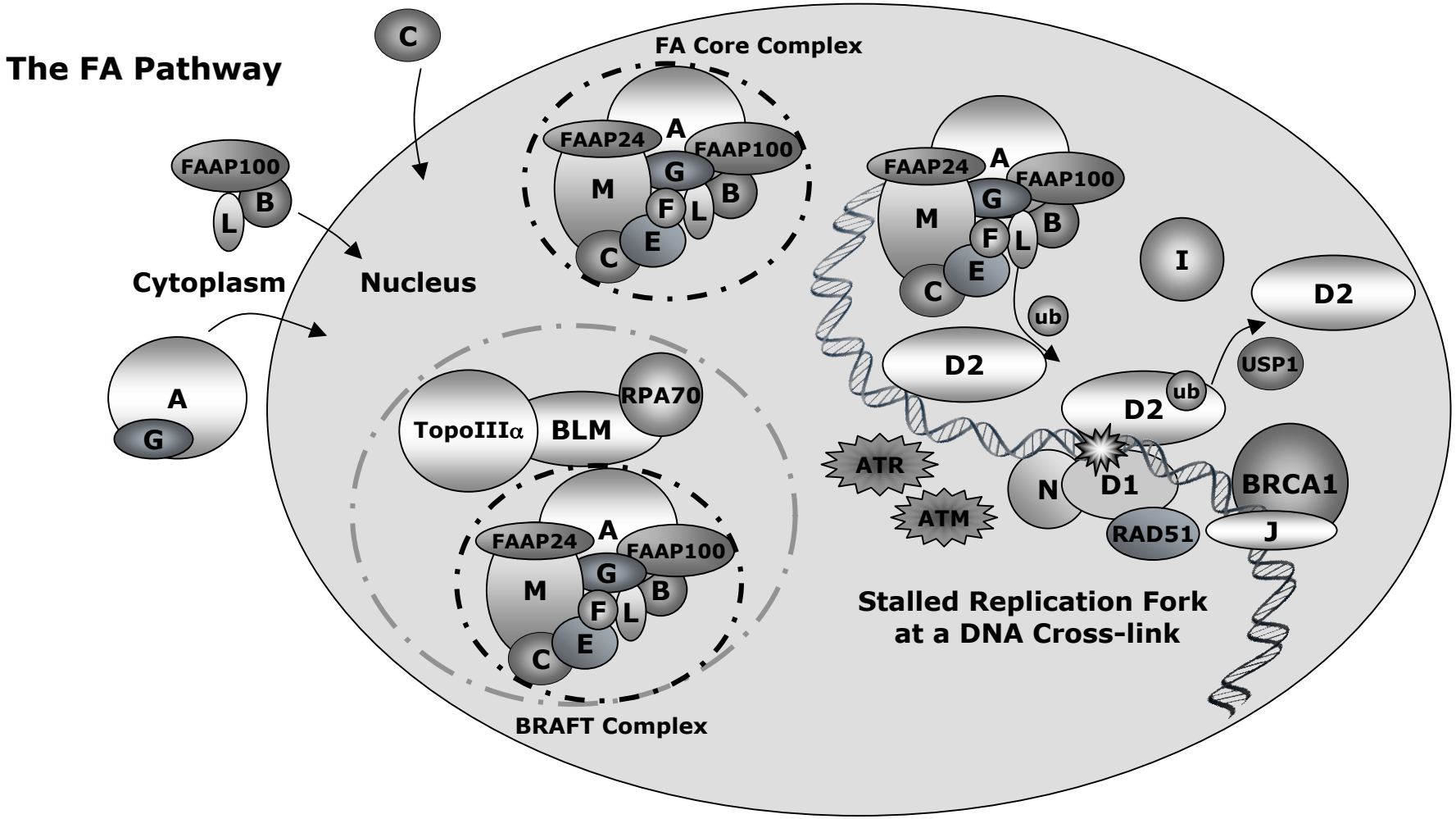

Fig 1. Model for the sequential assembly of the FA core complex proteins. In the nucleus, DNA cross-links or lesions that are caused by either endogenous or exogenous DNA-damaging agents are encountered by the advancing replication fork during S phase. The Fanconi Anemia (FA) nuclear core complex (consisting 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 protein. Following its monoubiquitylation, FANCD2 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. The nuclear BRAFT complex is composed of the FA core complex and the BLM protein along with BLM interacting proteins TOPOIIIα and RPA70. Though the BLM complex has DNA unwinding activities its function in combination with the FA core complex remains elusive. In the cytoplasm FANCA and G form a dimer, FANCB, L and FAAP100 form a trimer and FANCC may enter the nucleus via a carrier protein. These subcomplexes translocate to the nucleus independently where together with FANCE, F, M and FAAP24 form the FA core complex.