Annual highlight

Maiani *et al*., *Nature* 2021 Apr;592(7856):799-803. doi: 10.1038/s41586-021-03422-5.
Simoneschi *et al*. *Nature* 2021 Apr;592(7856):789-793. doi: 10.1038/s41586-021-03445-y.
Maiani *et al., Autophagy* 2021 Dec;17(12):4506-4508. doi: 10.1080/15548627.2021.1985917.

We identified AMBRA1 as an upstream factor regulating key cell-fate decision parallel pathways of Myc and cyclin D/CDK-pRB. By means of an AMBRA1 nervous system conditional KO mouse we demonstrated that Cyclins D could represent a key target of AMBRA1 in the regulation of cell cycle and proliferation. Given the established oncogenic role of cyclins D, these data have implications in clinical practice, opening new scenarios for translational biomarkers in embryonal neuroectodermal tumors. We also discovered that AMBRA1 downregulation associated with enhanced DNA replication stress (RS) and that this phenotype could be exploited to selectively kill cancer cells, by treatments with CHK1 inhibitors. Moreover, the RS phenotype was independent of AMBRA1 role in autophagy and relied on its control of the cell cycle progression and, most importantly, AMBRA1-mediated regulation of c-MYC was not enough to explain such an effect. Interestingly, this molecular mechanism is extremely conserved in many cell types with different genetic backgrounds, supporting not only the relevance of this pathway in mammalian cells homeostasis but also suggesting promising translational application in different cancer subsets.

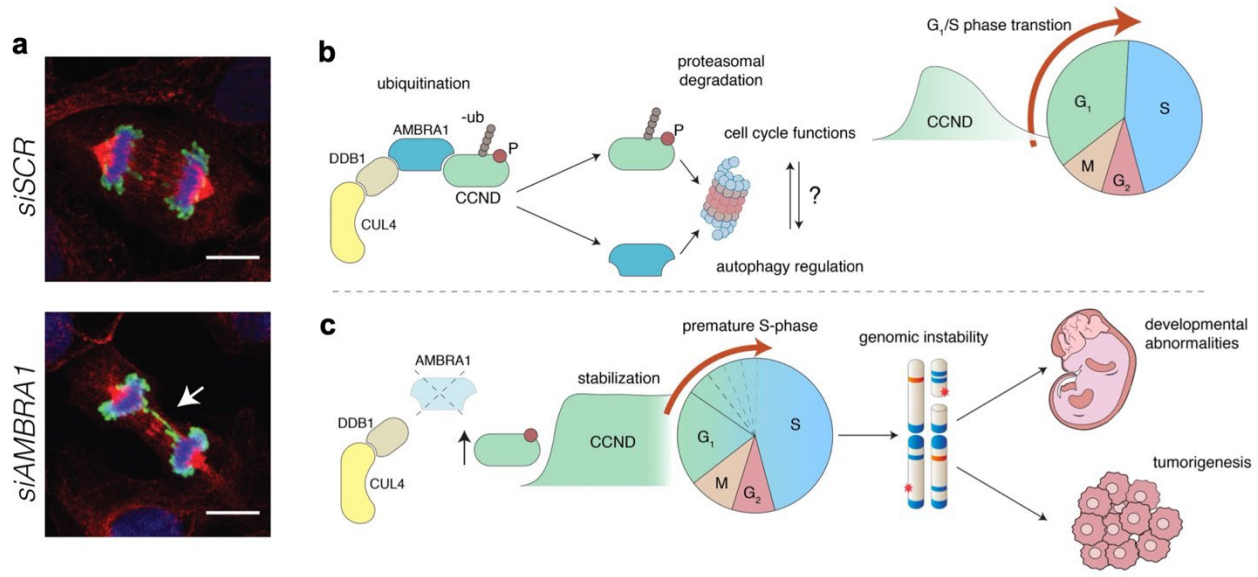

Fig. 1 AMBRA1 regulates cell cycle and genomic integrity through the CUL4-DDB1 complex. (a) AMBRA1-silenced and control U2OS cells stained for γ-tubulin (red), histone H3 phosphorylated at Ser10 (H3(pS10); green) and Hoechst (blue). Arrow indicates chromosomal abnormality. (b) in physiological conditions, AMBRA1 acts as a DCAF substrate receptor protein for recognition of CCNDs and ubiquitination by the DDB1-CUL4 complex. Once ubiquitinated, both AMBRA1 and CCNDs are primed for proteasomal degradation, with this influencing both cell cycle orchestration and autophagy. (c) The absence of AMBRA1 impairs CCND degradation, thereby provoking premature S-phase entry and replication stress that leads to genomic instability, ultimately affecting both neurodevelopment and cancer onset and aggressiveness