

P058 Human MDC1 regulates the metaphase-to-anaphase transition

Kelly Townsend¹, Helen Dyson¹, Andrew N. Blackford¹, Edward S. Miller¹, Garry G. Sedgwick¹, Giancarlo Barone¹, Andrew S. Turnell¹, Grant S. Stewart¹.

¹School of Cancer Sciences, The University of Birmingham, Edgbaston, Birmingham. B15 2TT. UK.

Human Mediator of DNA damage checkpoint 1 (hMDC1) is a critical regulator of the cellular response to DNA double strand breaks and contributes to this process through its ability to recruit DNA repair and checkpoint proteins to sites of damage marked by phosphorylated histone H2AX. Here, we show that hMDC1 also regulates normal metaphase-to-anaphase transition, through its ability to bind the anaphase-promoting complex/cyclosome (APC/C) and modulating its E3 ubiquitin ligase activity. In support of a role for hMDC1 in controlling mitotic progression, depletion of hMDC1 by siRNA results in a metaphase arrest that is independent of both spindle checkpoint and ATM/ATR activation. Mitotic cells lacking hMDC1 exhibit markedly reduced levels of APC/C activity characterised by reduced levels of Cdc20, and a failure of Cdc20 to bind the APC/C and CBP. In addition, we observed a metaphase arrest following ionising radiation that was similarly characterised by the reduced capacity of Cdc20 to bind the APC/C, CBP and hMDC1. We suggest that hMDC1 functionally regulates the normal metaphase-to-anaphase transition, and possibly also a mitotic damage response, by modulating Cdc20-dependent activation of the APC/C.