CHOP-dependent regulation of p21/waf1 underlines the transition from the pro-survival to the pro-apoptotic activity of ER stress response
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Introduction CHOP/GADD153, a pro-apoptotic transcription factor, is induced during the Unfolded Protein Response (UPR) and is associated with Endoplasmic Reticulum (ER)-stress. p21/waf1 is an established tumor suppressor, however, it also exhibits a pro-survival function as it protects from induction of apoptosis.

Aim We sought to explore the potential involvement of p21/waf1 in the induction of ER-stress associated apoptosis. Furthermore we studied if CHOP-dependent regulation of p21/waf1 is involved in this process.

Materials and Methods We have performed in vitro experiments in mouse Embryonic Fibroblasts (MEFs) isolated from CHOP-deficient or wild type (wt) mice. Cell proliferation was assessed by cell counting and ER stress was facilitated by tunicamycin, an inhibitor which induces ER-stress.

Results Expression of CHOP or induction of ER stress by tunicamycin, suppressed p21 mRNA and protein levels in wt MEFs. Similar results were also obtained by experiments involving A549 human lung cancer cells. CHOP-deficient cells were more resistant to tunicamycin than their wt counterparts but their sensitivity was restored by knocking-down p21 expression by siRNA.

Conclusions Our findings indicate that CHOP relieves the anti-apoptotic activity of p21 during ER stress. Thus, p21 is implicated in the regulation of the UPR by inhibiting induction of apoptosis. Accordingly, our study provides hints for understanding the role of CHOP in ER stress-mediated apoptosis since malfunction of this homeostatic mechanism has been implicated in a variety of common diseases such as diabetes and cancer.