A role for proline and acid-rich (PAR) bZIP transcription factors in adaptive response programs.

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We have investigated transcriptional programs associated with low doses of ionizing radiation, epigenetic carcinogen (12-O-tetradecanoyl phorbol-13-acetate, TPA) and basic fibroblast growth factor (bFGF) in a murine carcinogenesis model (JB6 cells) and a normal human skin equivalent model system (MatTek). We observe that the expression of multiple members of the PAR bZIP family, namely hepatic leukemia factor (HLF) and D-site albumin promoter binding protein (DBP), is increased in association with acquisition of anchorage-independent growth properties induced by X-irradiation, TPA and bFGF. HLF and DBP mRNA expression is also increased by 3-10 cGy X-irradiation in normal human skin equivalent cultures. We examined the regulation of apoptosis in JB6 cells transduced with human HLF to determine whether increased HLF expression altered cell fate responses. There are three distinct types of apoptosis signaling, "death by design", "death by neglect" and "death by stress" and we selected stimuli that activated these pathways, namely ionizing radiation (death by stress), serum-starvation (death by neglect) and tumor necrosis factor alpha (TNFα; death by design). Ectopic expression of HLF inhibits apoptosis induced through these pathways. Therefore, we hypothesize that the increase in PAR bZIP factor expression following exposure to low doses of radiation represents a fundamental physiological countermeasure to stress designed to promote cell survival.