Obesity alters sumoylation-dependent proteomic response in ovaries of mice exposed to 7,12-dimethylbenz[a]anthracene.

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Small **u**biquitin-like **mo**difiers (SUMOs) are present in all eukaryotes, and protein sumoylation is a post-translational modification that functions in chromatin-associated processes including DNA repair. Additionally, SUMOs and SUMO ligase enzymes (PIAS) localize at DNA double strand breaks. Further, ovarian roles for SUMOs have been recently described. We have previously discovered that exposure to the genotoxicant 7,12-dimethylbenz[a]anthracene (DMBA; 1 mg/kg for 7 d), in adult lean and obese mice altered the abundance of ovarian SUMO proteins thus, the hypothesis tested was that exposure to DMBA would increase sumoylation of proteins as a mode of ovotoxicity and that obesity would alter this response. Lean and obese mice (KK.Cg-a/a and KK.Cg-Ay/J) were exposed to either corn oil (CT) or DMBA (1 mg/kg) for 7d via intraperitoneal injection (n = 4/treatment) and ovaries were flash-frozen on day 2 of diestrus and stored in −80°C. Protein isolation was performed followed by immunoprecipitation of SUMO2/3 substrates using a SUMO2/3 polyclonal antibody. Precipitated proteins were digested with trypsin and labeled with tandem mass tags for liquid chromatography tandem mass spectrometry (LC-MS/MS). A total of 114 SUMO protein targets were identified and quantified between treatment groups. Obesity alone altered the abundance of 67 sumoylated proteins ($P < 0.1$). Exposure to DMBA differentially affected the level of 54 sumoylated proteins in obese compared to lean females ($P < 0.1$). Approximately two-thirds (44 proteins) of differentially abundant sumoylated proteins were decreased in obese ovaries, but in DMBA-exposed mice, the reverse trend was observed with ~one-third (12 proteins) being reduced in obese mice, suggesting an alteration of the sumoylation-dependent proteomic response. In lean females, exposure to DMBA altered 13 sumoylation-dependent proteins ($P < 0.1$) while 33 sumoylation-dependent proteins were affected in obese mice ($P < 0.1$), supporting that the physiological status effect is greater than the DMBA exposure effect. The large proline-rich protein BAG6, which functions in DNA damage-induced apoptosis, and bromodomain-containing protein 1, which is a scaffold subunit of histone acetyltransferases, were decreased in DMBA-exposed lean mice by 1.7-fold and 2.5-fold, respectively ($P < 0.01$); increased in obese DMBA-treated mice by 1.9-fold and 2.4-fold, respectively ($P < 0.01$) and increased in obese relative to lean control mice by 0.8-fold and 1.2-fold, respectively ($P < 0.05$). These findings suggest differential epigenetic control of the DNA damage response due to metabolic status, identify ovarian SUMO target proteins, and elucidate the dynamic interplay of sumoylation as a response to ovotoxicity induced by DMBA exposure. Supported by 1R01ES030341 from NIEHS.