Alteration of the DNA damage response in colorectal tumor progression. （要約）

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Recent studies have demonstrated increased levels of DNA double-strand breaks (DSBs) and activation of the DNA damage response (DDR) in precancerous lesions during cancer development. Those observations have not been fully elucidated using paraffin-embedded tissues of colorectaltumors. The aims of this study were to analyze the presence of DSBs and DDR activation mediated by p53-binding protein 1 (53BP1), which is a conserved checkpoint and DNA repair protein, and to clarify their association with colorectal tumor progression. We used immunohistochemical staining to investigate the expression of γH2AX, a sensitive marker for DSBs, in 152 colorectal tumors (46 low-grade adenomas, 25 high-grade adenomas, 25 intramucosal carcinomas, and 56 invasive carcinomas). The colocalization of γH2AX and 53BP1, which is strongly associated with the DSB repair process, was analyzed using double-label immunofluorescence. Elevated γH2AX expression was identified in 16 (16.7%) of 96 intramucosal neoplasias and in 19 (33.9%) of 56 invasive carcinomas. Double-label immunofluorescence occasionally revealed cells, particularly in invasive carcinoma, with γH2AX foci that did not colocalize with 53BP1. The percentage of tumor cells with γH2AX foci that colocalized with 53BP1 was significantly lower in invasive carcinoma than in intramucosal neoplasia (median percentage, 54.8% and 88.5%, respectively; P = .001). In conclusion, the number of cells with DSBs increases in intramucosal neoplasia and invasive carcinoma. The decreasing number of cells with colocalization of γH2AX and 53BP1 during the progression from intramucosal neoplasia to invasive carcinoma suggests that DDR, at least mediated by 53BP1, is inefficient during the process of cancer invasion.