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NF-κB1 AND NF-κB2 REGULATE SUSCEPTIBILITY TO DNA DAMAGE INDUCED INTESTINAL EPITHELIAL APOPTOSIS IN VIVO

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Introduction The five members of the Nuclear Factor kappa B (NFκB) family of transcription factors signal via two pathways (classical and alternative) and play crucial roles in regulating gastrointestinal inflammation and carcinogenesis. Several mechanisms are likely to be involved including modulation of the key cellular processes of proliferation and apoptosis. NFκB1 has previously been shown to regulate radiation-induced apoptosis in the murine small intestine, but the involvement of other family members, particularly those involved in alternative pathway signalling, in regulating gastrointestinal

epithelial apoptosis and proliferation has not previously been investigated.

Methods Apoptosis was induced in groups of 6 male 10–12 weeks old c-Rel-null, NFκB1(p50)-null and NFκB2(p52)-null mice and their wild-type (C57BL/6) counterparts by two DNA damage inducing stimuli, namely 8Gy γ-irradiation and a single 250 mg/kg intraperitoneal injection of the chemotherapeutic drug Irinotecan. H and E sections were prepared from formalin fixed small intestine and distal half of the colon and cell number, apoptosis and mitosis were assessed on a cell positional basis.

Results Significant increases in crypt cell number were observed in NFκB1-null and NFκB2-null small intestine and in NFκB1-null and c-Rel-null colon. No significant differences were observed in baseline small intestinal and colonic crypt mitosis between any strains of mice. However, NFκB2-null mice demonstrated a significant increase in spontaneous small intestinal crypt apoptosis. In addition, small intestinal and colonic crypt apoptosis were both significantly increased (up to 3-fold) in NFκB1-null and NFκB2-null mice at 4.5 h following 8Gy γ-irradiation and 6 h following 250 mg/kg Irinotecan relative to wild-type and c-Rel-null mice. Although mitosis was suppressed in the small intestinal and colonic crypts of all strains of mice following DNA damaging stimuli, this suppression occurred to a significantly greater extent in the colonic crypts of NFκB1-null and NFκB2-null mice compared to C57BL/6 mice following Irinotecan treatment.

Conclusion Individual members of the NFκB family of proteins therefore play specific roles in regulating crypt cell number, apoptosis and mitosis in murine intestinal epithelia. Whereas c-Rel appears to play only a minor role in regulating these processes, disruption of the classical and alternative signalling pathways by deletion of NFκB1 and NFκB2, respectively both increased susceptibility to apoptosis and suppression of mitosis. NFκB1 and NFκB2 may therefore play important roles in regulating inflammatory and neoplastic disease development in intestinal epithelia.

Competing interests None.

Keywords apoptosis, nuclear factor kappa B, radiation.