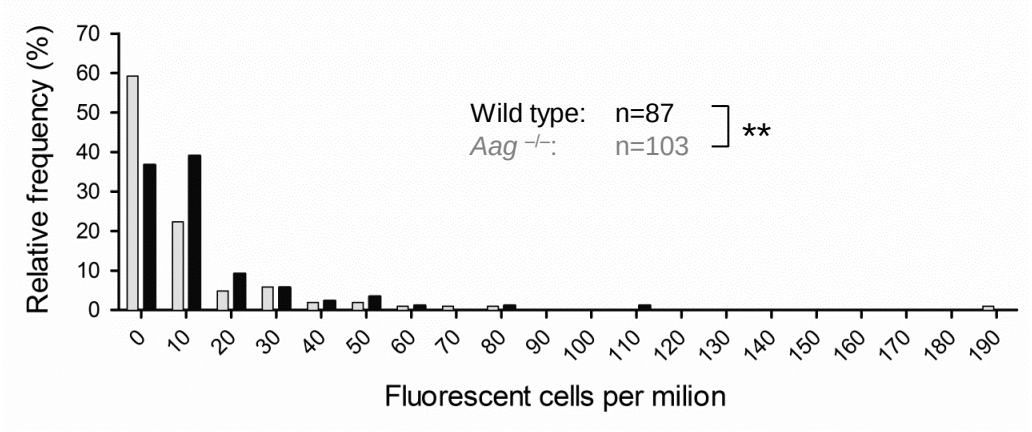
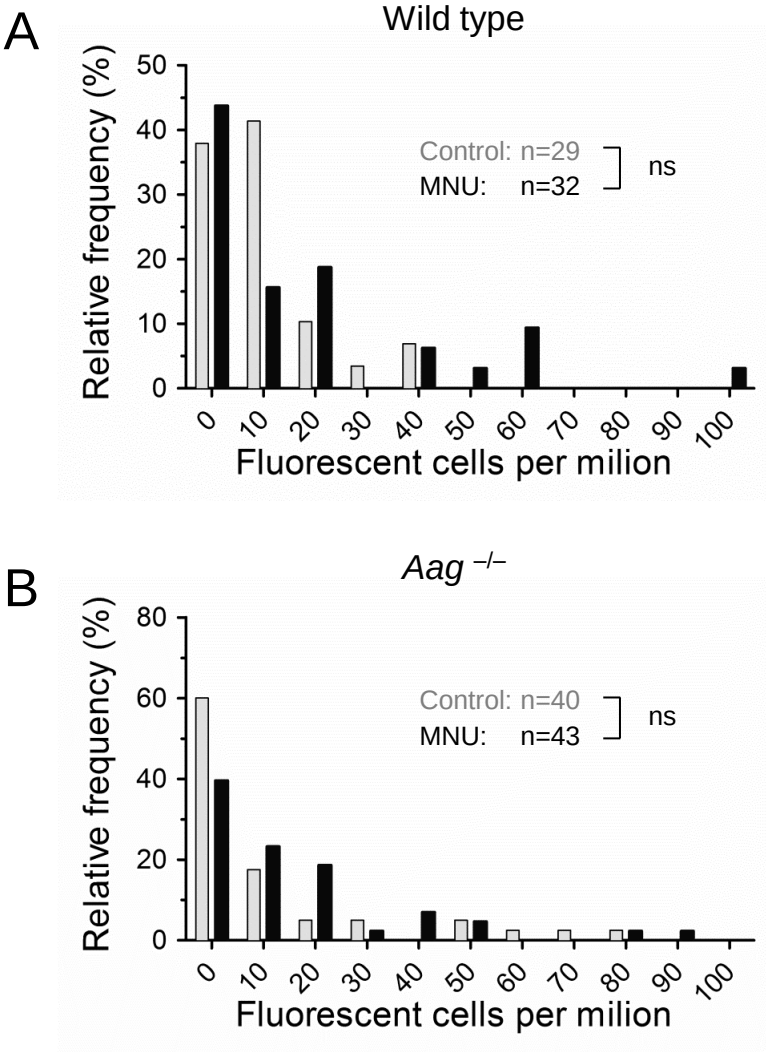
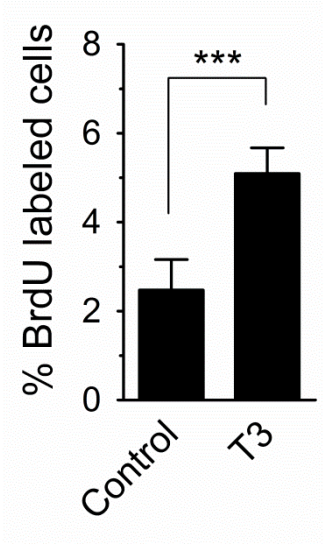


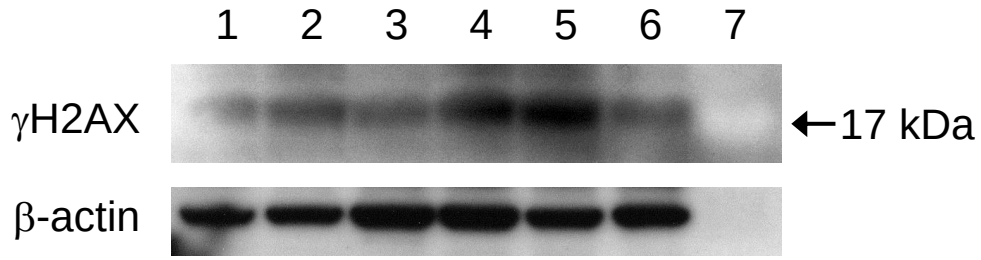
Supplementary Figure 1. Aag glycosylase activity promotes spontaneous HR detected by flow cytometry. The frequencies of fluorescent cells per million cells in disaggregated pancreata were determined by flow cytometry for each animal. The relative frequencies of mice having the indicated fluorescent cell frequencies are shown for wild type mice (n=87) and *Aag*$^{-/-}$ mice (n=103). The frequency distribution in *Aag*$^{-/-}$ mice (light bars) is shifted to the left compared to wild type mice (dark bars). ** $P < 0.01$ (Mann–Whitney *U*-test).



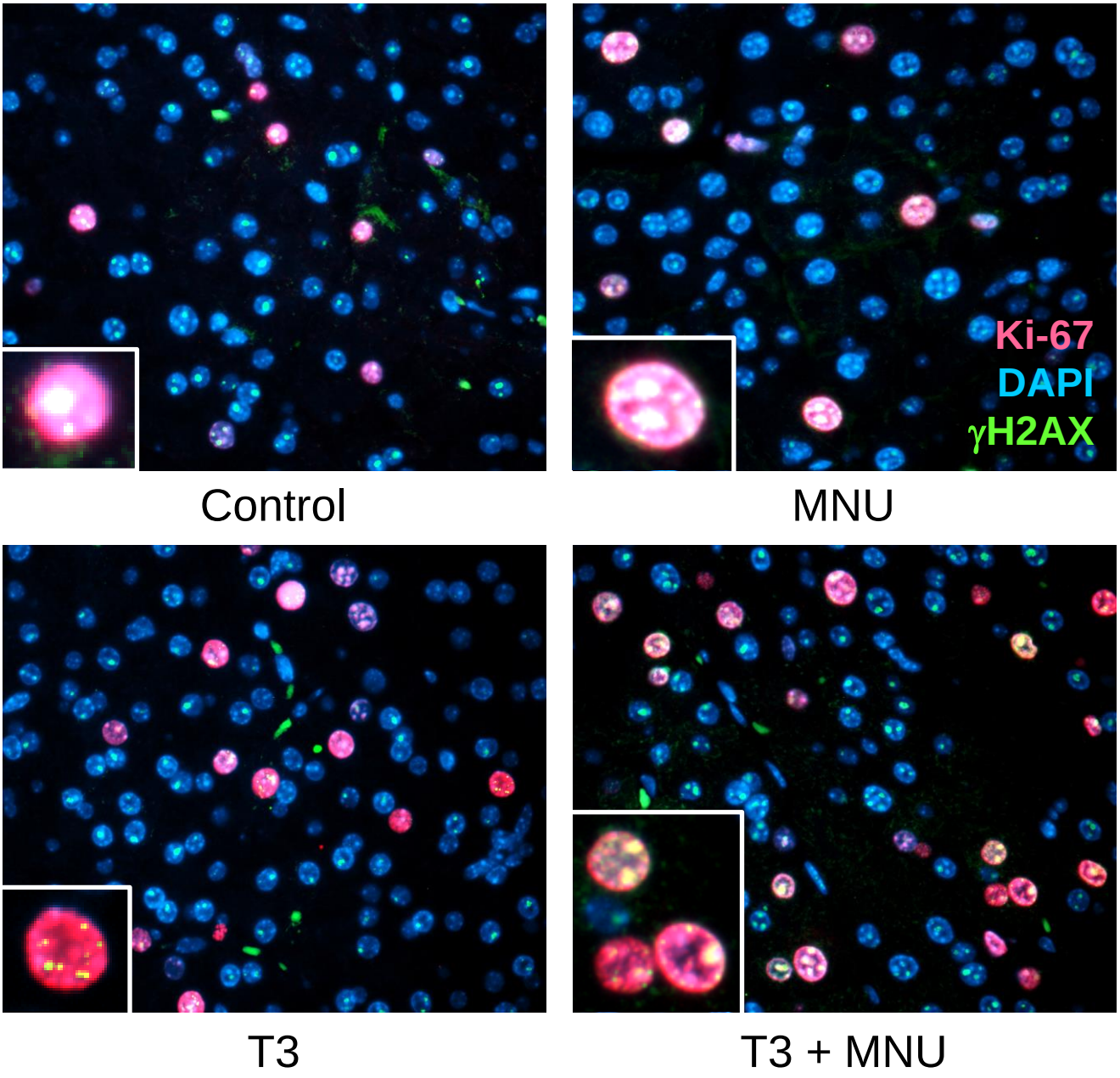
Supplementary Figure 2. Damage-induced HR in wild type and *Aag*$^{-/-}$ mice detected by flow cytometry. Mice were treated with the methylating agent MNU or control treatment, and the frequencies of fluorescent cells per million cells in disaggregated pancreata were determined by flow cytometry. (**A**) Relative frequencies of mice with the indicated fluorescent cell frequencies in control (n=29, light bars) and MNU-treated (n=32, dark bars) wild type mice. (**B**) Relative frequencies of mice with the indicated fluorescent cell frequencies in control (n=40, light bars) and MNU-treated (n=43, dark bars) *Aag*$^{-/-}$ mice. ns, not statistically significant (Mann–Whitney *U*-test).



Supplementary Figure 3. Hormone-induced cell proliferation in the pancreas. BrdU labeling indicates increased cell proliferation in T3-treated mice (n=11) compared to control mice (n=10). Animals received BrdU (75 mg/kg *i.p.*) 4 h before harvesting pancreata. The frequencies of BrdU positive cells in disaggregated pancreata were determined by antibody staining and flow cytometry. Data are mean ± SEM. *** $P < 0.001$ (Student's *t*-test).



Supplementary Figure 4. Time course of DSB induction after T3+MNU treatment. At the peak of T3-induced cell proliferation, mice were treated with MNU and pancreata were harvested at different times after MNU injection. H2AX phosphorylation was determined by Western blotting in tissue extracts. Lane **1**: control (no T3, no MNU). Lane **2**: 0.5 h after MNU treatment. Lane **3**: 1 h after MNU treatment. Lane **4**: 2 h after MNU treatment. Lane **5**: 6 h after MNU treatment. Lane **6**: 13.5 h after MNU treatment. Lane **7**: Molecular weight marker (γH2AX is 15.1 kDa).

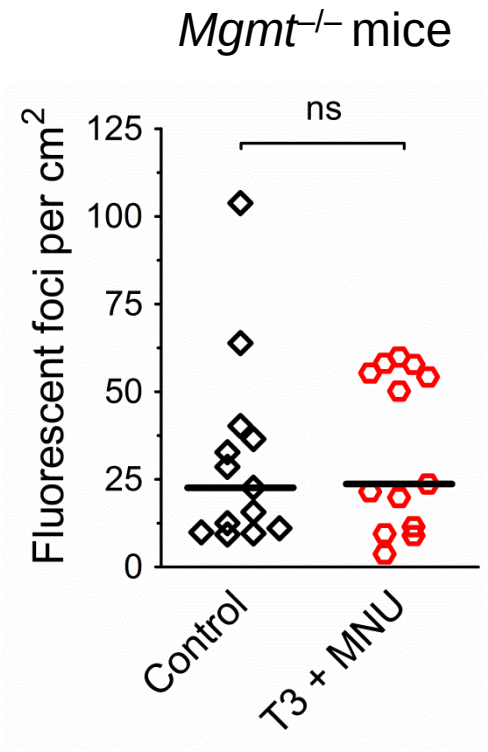


Supplementary Figure 5. DSBs induced by DNA damage and cell proliferation. Staining for the DSB marker γH2AX (green) and the proliferation marker Ki-67 (red) in pancreas sections. Mice were treated with thyroid hormone (T3) to induce cell proliferation in the pancreas. At the peak of T3-induced cell proliferation, mice were treated with MNU (25 mg/kg *i.p.*) or mock treatment. 6 hours after MNU injection, pancreata were harvested for analysis. A representative image from each treatment group is shown. Original magnification, ×40. Insets show nuclei at higher magnification. Fluorescence is pseudocolored.

Supplementary Table 1. LD_{50} values for MNU in wild type, *Aag*$^{-/-}$ and *Mgmt*$^{-/-}$ mice.

Genotype	LD_{50} (mg/kg)
Wild type	140
Aag$^{-/-}$	130
Mgmt$^{-/-}$	2

LD_{50} values were determined according to the method of Deichmann and LeBlanc (ref. 21). Experiments were repeated two or three times, and average values are reported.



Supplementary Figure 6. Combined DNA damage and cell proliferation has no effect on HR in the pancreata of *Mgmt*$^{-/-}$ mice. Mice were fed a diet with thyroid hormone (T3) or control diet, and received MNU (0.4 mg/kg *i.p.*) or control treatment at the peak of T3-induced cell proliferation. The MNU dose is the same percentage of the LD_{50} as in wild type and *Aag*$^{-/-}$ mice. Sequence rearrangements were measured 3 to 4 weeks after MNU injection. Frequencies of fluorescent foci per cm^2 pancreatic tissue in control (n=13) and T3+MNU treated (n=13) mice are not significantly different.