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The Role of Dicer in DNA Repair and Colon Cancer Chemotherapy

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Abstract

Dicer is that the key component of the RNA interference pathway. In 2008, our group reported that Dicer knockdown led to DNA damage accumulation in mammalian cells. Subsequently, two groups showed that Dicer-dependent small RNAs produced from the sequences in the vicinity of DNA double-strand break (DSB) sites were essential for homologous recombination-mediated DSB repair. Recently, we found that Dicer is associated with SIRT7 and is required for DNA damage-induced chromatin relaxation by promoting H3K18Ac DE acetylation, decreased Dicer expression inhibited non-homologous end joining by preventing chromatin relaxation at DSB sites. Moreover, we demonstrated that Dicer knockdown and overexpression increased and decreased respectively, the chemo sensitiv¬ity of colon cancer cells, and that Dicer protein expression in colon cancer tissues of patients was directly correlated with chemo resis¬tance. Our findings suggest that manipulation of Dicer expression may improve chemotherapy effects for patients with colon cancer, and possibly other cancers.

DNA Damage is accumulated in Dicer-Deficient Cells:
The RNAi hardware assumes significant jobs in the guideline of heterochromatin structure and capacity.In particular, loss of has been appeared to bring about DE condensation of heterochromatin as well as gathering of extra chromosomal round rehashed DNAs (eccDNA) . Ligase IV, a fundamental controller of non-homologous end joining, maybe alongside other DNA harm fix apparatus, have been recommended to take an interest in the eccDNA development in - insufficient cells . These discoveries infer that notwithstanding expanded openness of DNA fix and recombination proteins to rehashed DNA brought about by heterochromatin DE-condensation, initiation of DNA harm reaction (DDR) may likewise add to the eccDNA arrangement in - freak cells.

Sub-atomic Mechanisms by Which Loss of Dicer Leads to DNA Damage:
Amassing of DNA Damage in Dicer-Deficient Cells Is Attributed to Reduced Efficiency of DNA Damage Repair: These RNAs have been alluded to as DSB-incited little RNAs (diRNAs) or Dicer-and Drosha-subordinate little RNAs (DDRNAs). Additionally, Francia and associates detailed that DDR foci arrangement was delicate to RNase A treatment and that DDRNAs, either synthetically blended or produced in vitro by Dicer cleavage, were adequate to reestablish DDR in RNase-A-rewarded cells . Wei and partners additionally recommended that diRNAs may work as guide particles to coordinate either chromatin adjustments or the enrollment of protein edifices to DSB destinations to encourage fix. In view of these perceptions, we propose that the aggregation of DNA harm in Dicer-lacking cells might be ascribed to decreased proficiency of DNA harm fix.

Is Accumulation of DNA Damage in Dicer-Deficient Cells the Consequence of Heterochromatin De-condensation?:
It has been exhibited that chromatin assumes urgent jobs in DDR and that interruption of chromatin structures prompts genome shakiness . In particular, Peng and Karpen announced that Drosophila cells coming up short on the H3K9 methyltransferase Su(var)3-9 demonstrated essentially raised frequencies of unconstrained DNA harm in heterochromatin and that the gathering of such DNA harm related with chromosomal deformities, for example, translocations and loss of heterozygosis . Likewise, our gathering showed that restraint of DNA methylation by 5-aza-2′-deoxycytidine incited DNA harm in human cells.

Is Accumulation of DNA Damage in Dicer-Deficient Cells the Consequence of Transposon Activation?:
The RNAi hardware has been proposed to work as the invulnerable arrangement of the genome to safeguard against atomic parasites, for example, transposons and infections . Loss of the key segments of the RNAi pathway was appeared to enact transposition, which thusly produced twofold strand DNA breaks and evoked DDR. Along these lines, we have suggested that actuation of transposition may add to DNA harm collection in Dicer-knockdown cells. We contemplated that loss of Dicer settles the transcripts got from transposons and retro transposons, along these lines causing an elevated level of transposition and producing twofold strand DNA breaks. Notwithstanding, regardless of whether Dicer can process transposons-and retro transposons-inferred transcripts stays to be explained. While it has been accounted for that endogenous siRNAs got from SINE/B1 RNAs may exist in mouse cells and that diminished Dicer articulation prompted collection of Alu RNAs in human retinal pigmented epithelium cells.

Is Accumulation of DNA Damage in Dicer-Deficient Cells the Consequence of miRNA Downregulation?:
In light of DNA harm brought about by ionizing or UV radiation, the outflow of cell miRNAs experiences worldwide adjustment. DDR can control miRNA articulation at the transcriptional level; for instance, the miR-34a essential transcript has been demonstrated to be legitimately transactivated by p53 following DNA harm. DDR can likewise manage miRNA articulation by tweaking the miRNA handling and development steps. Suzuki and partners detailed that in light of DNA harm, p53 connected with the Drosha/DGCR8 preparing complex by means of a

relationship with the RNA helicase p68 and encouraged the handling of pri-miRNAs to pre-miRNAs.

Dicer, DNA Damage, and Tumorigenesis:
Contrasted with typical tissues, tumor tissues display a general down regulation of miRNAs . Also, the Dicer mRNA and protein levels, albeit still disputable, have been every now and again saw as down regulated in tumor tissues. The investigation of human malignant growth genome duplicate number information has likewise uncovered incessant erasure of Dicer . What's more, Heravi-Moussavi and partners as of late announced that transformations in the RNase IIIb area of Dicer are habitually connected with non-epithelial ovarian tumors , in which the changes are confined to codons encoding metal-restricting destinations inside the RNase IIIb reactant focuses that are basic for microRNA biogenesis .Signs of DDR, including phosphorylation of histone H2AX and Chk2, accumulation of p53, and focal staining of p53-binding protein 1, have been widely observed in clinical specimens from different stages of human tumors and precancerous lesions, but not in normal tissues.

Discussion:
Here, by promoting the synthesis of DDRNAs with a pharmacological treatment we were able for the first time to positively modulate DDR activation and DNA repair. We took advantage of the small molecule enoxacin, recently found to improve the endoribonuclease activity of the DICER-complex, by facilitating the interaction of TRBP to the RNA substrates. Specifically, we discovered that enoxacin treatment of cultured cells exposed to DNA damage strongly increases DDR activation. Importantly, we demonstrated that this effect, while relying on TRBP activity, does not require the functions of the GW182 protein family, necessary effectors for miRNA-guided gene-silencing.

Results:
Enoxacin boosts DDR via TRBP activity: Since it has been previously shown that DICER endoribonuclease activity is crucial for DDR activation, we tested whether the enhancement of DICER processing by a pharmacological treatment could promote DDR activation. Thus, we treated HeLa cells with 50 μM enoxacin (or DMSO as vehicle-only control) for 48 hours before exposure to ionizing radiation (IR). We then analysed the activation of DDR at different time points after IR by quantitative immunofluorescence (IF) for γH2AX, pATM, 53BP1, MDC1 and pS/TQ (the substrate of active ATM). Cells treated with enoxacin prior to IR mounted stronger DDR activation than control cells treated with DMSO, as measured by the intensity of DDR foci per nucleus.