REGIONAL CENTRE FOR BIOTECHNOLOGY
Journal Club

Site-specific DICER and DROSHA RNA products control the DNA-damage response

Sofia Francia et al. (2012)Nature, Volume 488, 231-235.

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Wednesday, September 12, 2012
4:00 pm
Seminar Room

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Non-coding RNAs (ncRNAs) are involved in an increasingly recognized number of cellular events1. Some ncRNAs are processed by DICER and DROSHA RNases to give rise to small doublestranded RNAs involved in RNA interference (RNAi)2. The DNA-damage response (DDR) is a signalling pathway that originates from a DNA lesion and arrests cell proliferation3. So far, DICER and DROSHA RNA products have not been reported to control DDR activation. Here we show, in human, mouse and zebrafish, that DICER and DROSHA, but not downstream elements of the RNAi pathway, are necessary to activate the DDR upon exogenous DNA damage and oncogene-induced genotoxic stress, as studied by DDR foci formation and by checkpoint assays. DDR foci are sensitive to RNase A treatment, and DICER- and DROSHA-dependent RNA products are required to restore DDR foci in RNase-A-treated cells. Through RNA deep sequencing and the study of DDR activation at a single inducible DNA double-strand break, we demonstrate that DDR foci formation requires site-specific DICER- and DROSHA-dependent small RNAs, named DDRNAs, which act in a MRE11–RAD50–NBS1- complex-dependent manner (MRE11 also known as MRE11A; NBS1 also known asNBN).DDRNAs, either chemically synthesized orin vitro generated by DICER cleavage, are sufficient to restore the DDR in RNase-A-treated cells, also in the absence of other cellular RNAs. Our results describe an unanticipated direct role of a novel class of ncRNAs in the control of DDR activation at sites of DNA damage.