

Molecular mechanisms of post-Chernobyl thyroid tumors

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Abstract

Over the last 25 years, a large body of knowledge has been accumulated on molecular landscape of post-Chernobyl thyroid cancer and benign diseases, leading to better understanding of basic mechanisms of thyroid carcinogenesis associated with exposure to ionizing radiation. Multiple studies of thyroid cancers in children and young adults living in the areas contaminated as a result of the Chernobyl accident have shown that chromosomal rearrangements rather than point mutations represent a common genetic mechanism of these cancers. A prototypic example of such chromosomal rearrangements is *RET/PTC*, seen in 30–80% of these cancers. More recently, another rearrangement, *ETV6/NTRK3* has been found to be common and detectable in ~15% of these tumors. These rearrangements appear to be associated with I-131 dose received after Chernobyl and can be induced in cultured human thyroid cells exposed to various types of ionizing radiation. It has also been shown that genes participating in *RET/PTC* rearrangements are located close to each other in the nuclei of normal thyroid cells, providing structural basis for mis-joining free DNA ends located in proximity to each other. However, it remains unknown if such oncogenic chromosomal rearrangements are formed as a direct result of double-strand DNA breaks induced by exposure to radiation or indirectly and via what mechanism of DNA repair. In addition to chromosomal rearrangements and point mutations, significant knowledge has been accumulated on other genetic alterations, such as DNA copy number variations (e.g. recurrent gain of 7q11) and mRNA dysregulation in post-Chernobyl tumors. These studies allowed better understanding of the genetic mechanisms of radiation-associated thyroid cancer and should eventually help to develop measures for preventing or alleviating carcinogenic consequences of radiation exposure.