

CHANGES IN APOPTOTIC ACTIVITY DRIVEN BY DNA METHYLATION EPIMUTATIONS IN HUMAN CANCER

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Apoptosis is one of the fundamental biological phenomena, well known to be crucial in cancer development for its vital role in a subtle interplay between proliferation and cell death. Programmed cell death is indeed a powerful physiological frontier cancer cells have to overcome along the way of fulfilling their full malignant potential. Therefore, complex signalling networks developed in the frame of apoptosis which can be crashed not only by gene mutations but disruption in gene expression regulation as well. DNA methylation is one of the most prominent epigenetic mechanisms strongly effecting gene expression by organizing chromatin status and its permissiveness to transcription. Aberrant DNA methylation is an epimutation already recognized as an early event, sometimes even preceding other well-known molecular carcinogenic incidences. Reports from literature, which will be discussed in this lecture, point to DNA methylation epimutations as underlying mechanism of aberrant apoptotic gene expression resulting in a breach of cell homeostasis regulatory mechanisms toward carcinogenesis.

Keywords: Epigenetics; DNA methylation; apoptosis; epimutation; cancer.

APOPTOSIS AND COLORECTAL CANCER

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Programmed cell death, or apoptosis, is a fundamental mechanism of tissue homeostasis. In the normal colon, as much as 10^{10} cells per day undergo apoptosis and are shed into the lumen. One of the hallmarks of cancer is escape from mechanisms regulating apoptosis, such as cellular response to extrinsic growth factors

and telomere shortening. Escape from apoptosis also makes cancer cells resistant to chemotherapy and radiation. The molecular machinery of apoptosis is a potential target for drugs that could promote cell death in colorectal cancer cells. The intrinsic (mitochondrial) pathway of apoptosis is regulated mainly the the Bcl-2 protein family, which are activated by various stimuli, including growth factor withdrawal and cellular damage. Under such circumstances, the antiapoptotic factors (eg. Bcl-2, Bcl-XL, Bcl-W, Mcl-1) release the proapoptotic factors (eg. BAK, BAX), which in turn increase mitochondrial membrane permeability, leading to cytochrome C release and Caspase 9 activation and consequently, via Caspase 3 activation, to apoptosis. In cancer antiapoptotic Bcl-2 family members are overexpressed, while the proapoptotic factors are underexpressed. "BH-3 mimetics" are a class of small molecules inhibitors of certain antiapoptotic Bcl-2 family members. Navitoclax is a potent inhibitor of Bcl-2, Bcl-W and Bcl-XL, with in vitro evidence of apoptosis induction in colorectal cancer cells, and demonstrated safety in a phase I clinical trial in combination with established therapy regimes. Obatoclax is a promising pan-Bcl-2 inhibitor. HA14-1 is a small molecule selectively targeting Bcl-2. Oblimersen is an antisense oligonucleotide targeting Bcl-2, and has shown safety in phase I trials. In summary, several new drugs focusing on apoptosis induction in colorectal cancer are currently being studied, which will hopefully lead to better therapies in the future.

Keywords: apoptosis; colorectal cancer; therapy; new drugs.

KIDNEY TUMOR EMPERIPOLESIS

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Emperipolesis means active penetration of one cell by another which remains intact. Main cells participating in emperipolesis usually are histiocytes, but other cell types may participate. Emperipolesis can also be found in some cancers.

The exact mechanism for emperipolesis is not fully known but it is believed that the pathway of lizosom degradation mediated NK ("natural killer") cells is crucial in this process. It was noted that NK cells use emperipolesis when leading tumor cells to programmed cell death. Process similar to emperipolesis, called entosis was also described, but with the different ultrastructural pathways and molecules in-