

Материалы III съезда ВОГиС

**«Генетика в XXI веке: современное состояние и перспективы развития».**

Т.2.– 6-12 июня, 2004.– Россия, Москва.– С.452.

## **SOME ASPECTS OF APPLYING ANTIMUTAGENS AS ANTICARCINOGENS**

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Carcinogenesis is a long-lasting multi-staged process; DNA damage and “epigenetic alterations” in gene expression contribute to malignant growth. Chemopreventive strategy should be based on understanding mechanisms, which favour or prevent stages of initiation, promotion and progression of cancer. In this respect, data on antimutagens as anticarcinogens seem to be very interesting and promising. Experience of such investigations was summed up at the VIII International Conference on Mechanisms of Antimutagenesis and Anticarcinogenesis (4–8 October, 2003, Pisa, Italy). Tumor incidences are known to correlate with DNA adducts induced by a range of promutagens and oxidative stress. Spontaneous DNA damage (e.g., 8-oxoguanine) appears also to contribute to carcinogenesis. So, information on inhibition of a spontaneous mutation process is of novel importance. Specifically, we observed 3–5-fold reduction in mutation frequency in *Drosophila* germ cells due to their pretreatment with antioxidants of 1,4-dihydropyridine (1,4-DHP) series. At the initiation stage, inhibition of spontaneous and induced mutations by antimutagens can be achieved (1) by scavenging reactive oxygen species; (2) by induction of the antioxidant enzymes; (3) by modulation of mutagen/carcinogen metabolism including impact on gene expression or transcription factors involved in this process. At the promotion stage, inflammation is the important event, which is regulated by cyclooxygenase 2, therefore different antioxidants including 1,4-DHP derivatives, which possess anti-inflammatory properties

might inhibit this stage. The role of excision DNA repair (global genome and transcription-coupled repair) for removing DNA damage and adducts of different nature and origin is well known. Contribution of this and other repair systems in anticarcinogenesis is the object of current studies. In this context, we would like to emphasize that the antimutagens of 1,4-DHP series are able to modulate DNA repair involved in chemical and radiation mutagenesis in *Drosophila* germ cells and human lymphocytes. A protective role of apoptosis is undoubted, especially at the promotion stage. Chemical analogy of 1,4-DHP derivatives to dihydronicotinamide allows us to expect the impact of these compounds on PARP and apoptosis; the latter is supported by our experiments in human lymphocytes. Angiogenesis promotes tumor progression and metastasis; antimutagens successfully inhibit tumor growth and metastasis due to modulating this process. Analysis of current data on antimutagens/anticarcinogens indicates that they affect practically all known molecular targets responsible for anticarcinogenesis. Epigallocatechingallate and N-acetylcysteine may be attributed to multitarget agents. Antimutagens of 1,4-DHP series also show multiple mechanisms of action and seem to modulate expression of genes controlling cell response to genotoxic stress. These compounds are promising for prevention and inhibition of tumor growth at different carcinogenesis stages.

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