APPLICATION OF EMBRYONIC MODELS FOR ELABORATION OF ANTI-CARCINOGENIC PREPARATIONS OF DESIRED ACTION


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Processes of regulation of cell cycle and cell proliferation in carcinogenesis are rather complicated and it is very difficult to specify a certain stage of cell cycle to study effects of different substances on it. Along with it, certain stages of embryonic processes have high level of resemblance with carcinogenic processes giving grounds to extrapolation of the results obtained in embryonic studies to the processes of tumor growth.

On the other hand, the advantage of studying embryonic stages relatively to carcinogenesis concludes in opportunity to analyze molecular mechanisms underlying proliferation and differentiation processes separately within different embryonic stages.
In different animal species engagement of serotonin in regulation of embryonic development has been shown beginning from Buznikov’s studies in 70-ies of last century. It was demonstrated that it adverts on early (pre-nervous) stages of embryogenesis and in more or less degree it is involved in regulation of such morphogenetic processes as cleavage, migration and differentiation in all vertebrate and invertebrate animals (Buznikov, 1987; Azmitia, 2001).
Different researchers demonstrated that serotonin realizes its functions in sub-cellular level through changing activities of single genes and synthesis of specific proteins (Abel & Kandel, 1998). Earlier in the brain cortex of the rats we identified and thereafter purified from the whole brain the novel serotonin-modulating anticonsolidation protein (SMAP), being in direct dependence on serotonin and lacking of species and tissue specificities. Serotonin-modulating nature of SMAP was demonstrated in electrophysiological (on identified command neurons of grapes snails) and biochemical studies, conducted in different models. The goal of this study was analysis of possible role for SMAP in changing rates of different stages of embryonic development of mollusk *Lymnae stagnalis* and in regulation of progression in Lewis sarcoma in mice.
Effects of SMAP on membrane excitability of identified Aplysia neurons LPl1 and PPl1. * - p<0.05 relatively to the original values.
Development of embryos of *Lymnae stagnalis* from the stage of 4 blastomeres (6th day of development)

![Graph showing the dimensions of embryos in mm for different treatments and their significance levels.]

- **Intact**
- **SMAP 1.5 μg/ml**
- **SMAP 7.5 μg/ml**
- **SMAP 50 μg/ml**

*Significance levels:*
- *p = 2 *10^-3*
- **p = 0**

Note: The graph illustrates the comparison of embryo dimensions across different treatments, with significance levels denoted by stars and their corresponding p-values.
Development of embryos of *Lymnae stagnalis* from the stage of pre-metamorphosis (2\textsuperscript{nd} day of development)

*\* p=0.0002*
Impact of SMAP administration on Lewis sarcoma in hybrid mice F1 C57B2/6 x DBA. * - p<0.05
Our studies have shown that SMAP realizes modulating effects on the rates of development of the embryos of *Lymnae stagnalis* and these effects are specific as SMAP effects bore dose-dependent character, disappeared under specific inactivation of SMAP and were opposite directional in the stages of 4 blastomeres and metamorphosis. SMAP brought to developmental retardation of embryos of *Lymnae stagnalis* in the stages of early blastula up to complete (but reversible) cessation of development in 50% of embryos. On the other hand, SMAP accelerated significantly development of the embryos in metamorphosis. Opposite directional character of SMAP effects surmises involvement of different receptor targets and intra-cellular mechanisms in different stages of embryonic development.
The correctness for extrapolation of SMAP effects on embryonic development of *Lymnae stagnalis* on its anti-carcinogenic effects is based on the fact that sarcoma develops from the derivates of embryonic mesoderm (Solovyov, Denisov, 1984). Besides, it was found that embryonic and malignant cells utilize the same regulatory mechanisms of gene expression which determine “embryonic” status of both cellular types. These mechanisms include oncogen Myc and complexes PCR1 и PCR2 (polycomb group repressive proteins), which are present both in embryonic and malignant cells (Wong et al., 2008; Ben-Porath et al., 2008; Shats et al., 2011; Kim, Orkins, 2011).
The revealed effects of SMAP indicating to engagement of serotonergic system into regulation of carcinogenesis are confirmed by the studies of other authors which observed anti-carcinogenic activity for serotonin both *in vivo* and *in vitro* systems. So, injection of serotonin solution directly into sarcoma of mice leads to shrinkage of tumor and significant elongation of life of tumor-transplanted animals (Banik et al., 1996). Application of specific serotonin reuptake inhibitors upregulating serotonin in post-synaptic membrane of the cells delays development of carcinoma of intestine and colon (Tuton, Barkla, 1982), bronchogenic carcinoma and prostate carcinoma in humans (Sheehan et al., 1996). The similar results were obtained in *in vitro* system which demonstrated death of human lymphoma cells subjected to the effects of serotonin in the sample tubes (Serafeim et al., 2002).
Impact of oil on micronuclei amount in erythrocytes (A) and SMAP level in liver (B) in sturgeon juveniles, ** - p<0.01
Impact of sediments and SMAP on micronuclei amount in sturgeon erythrocytes. ** - p<0.01; *** - p<0.001.
Thank you for your attention!