Artemia Diapause, An Excellent Model for Studying Cell Quiescence and Tumor Dormancy

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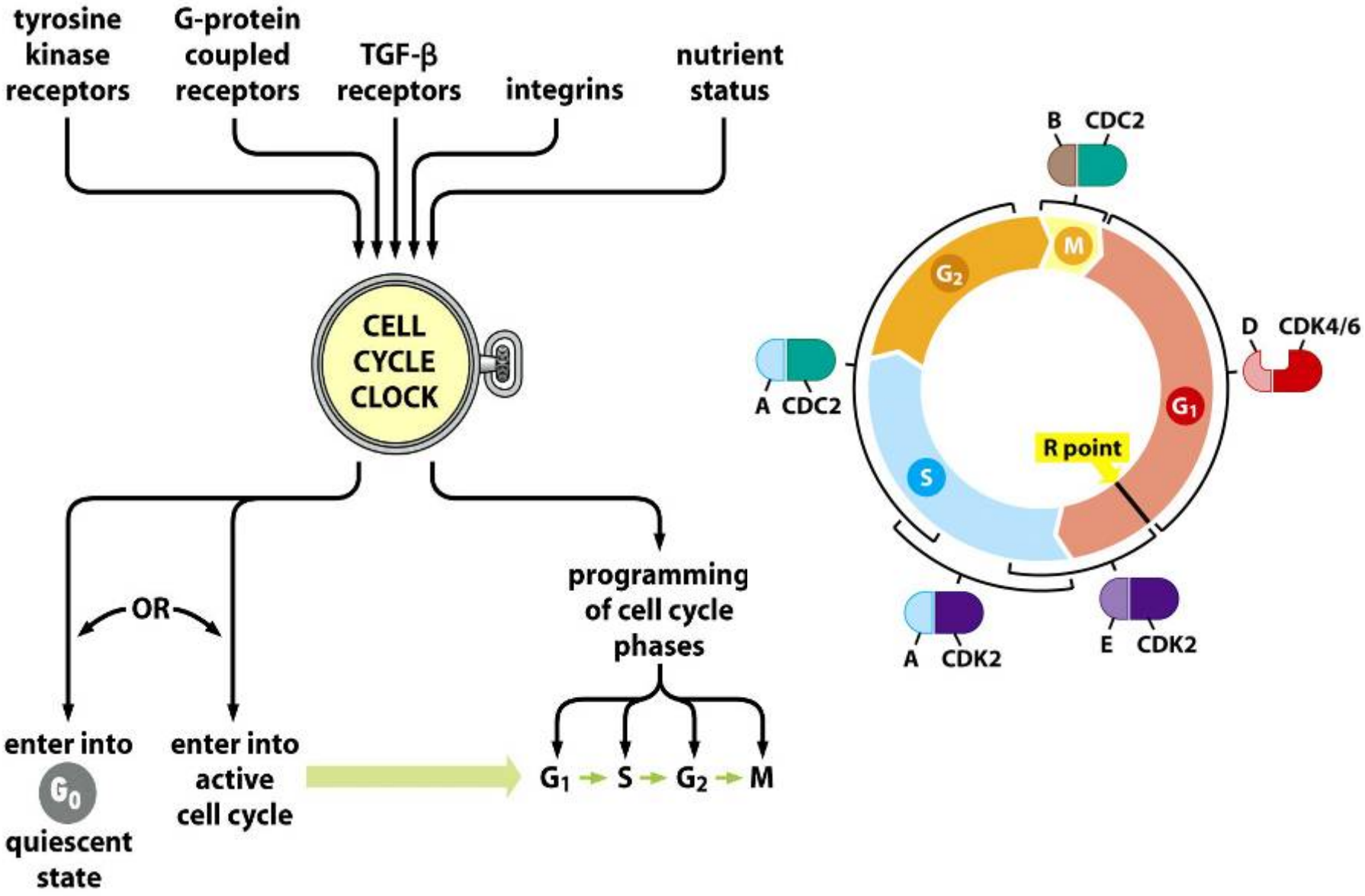
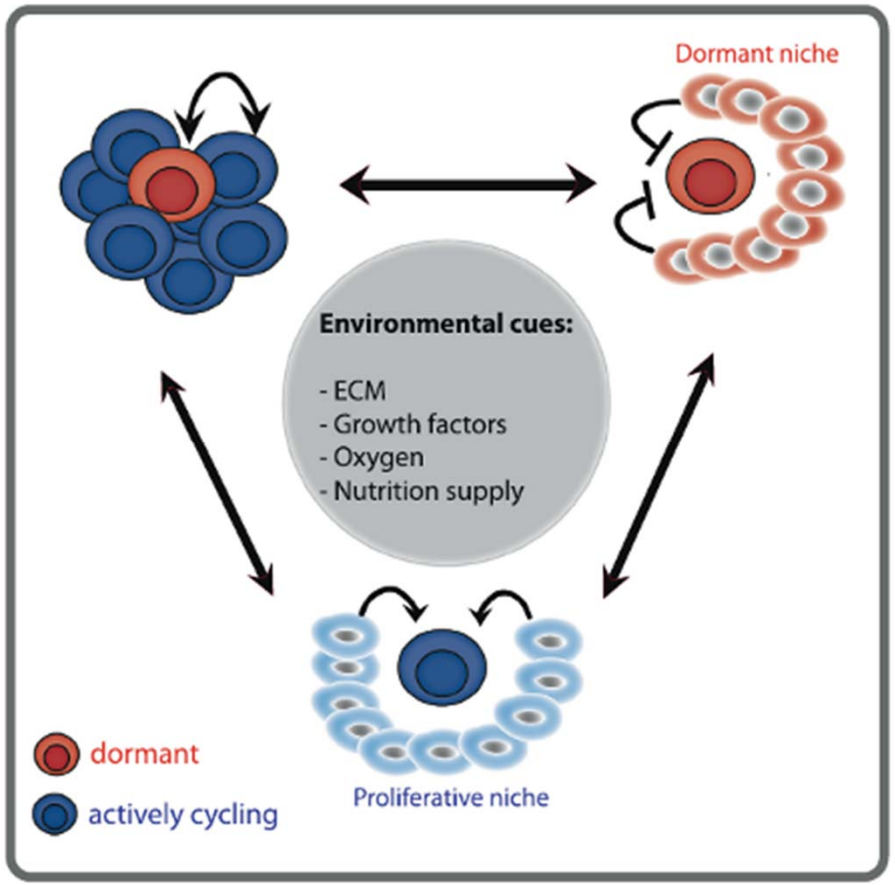
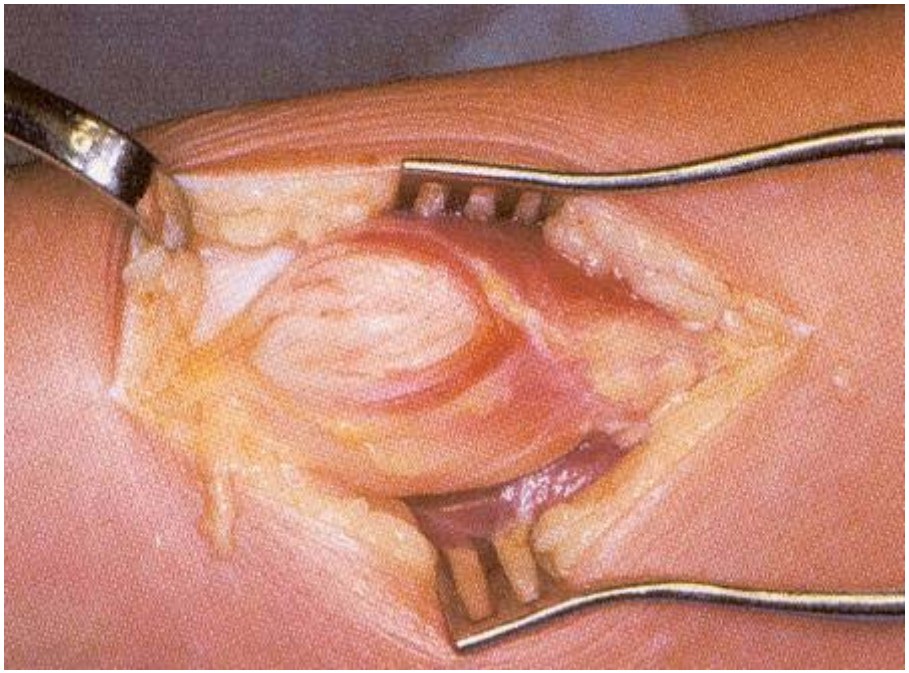
Dormancy is a period in an organism's life cycle when growth, development, and physical activity are temporarily slowed, or even stopped, and these tend to be closely associated with certain environmental conditions

Quiescent cells have an extremely low metabolic rate, and DNA replication, transcription, and translation are greatly depressed or switched off.

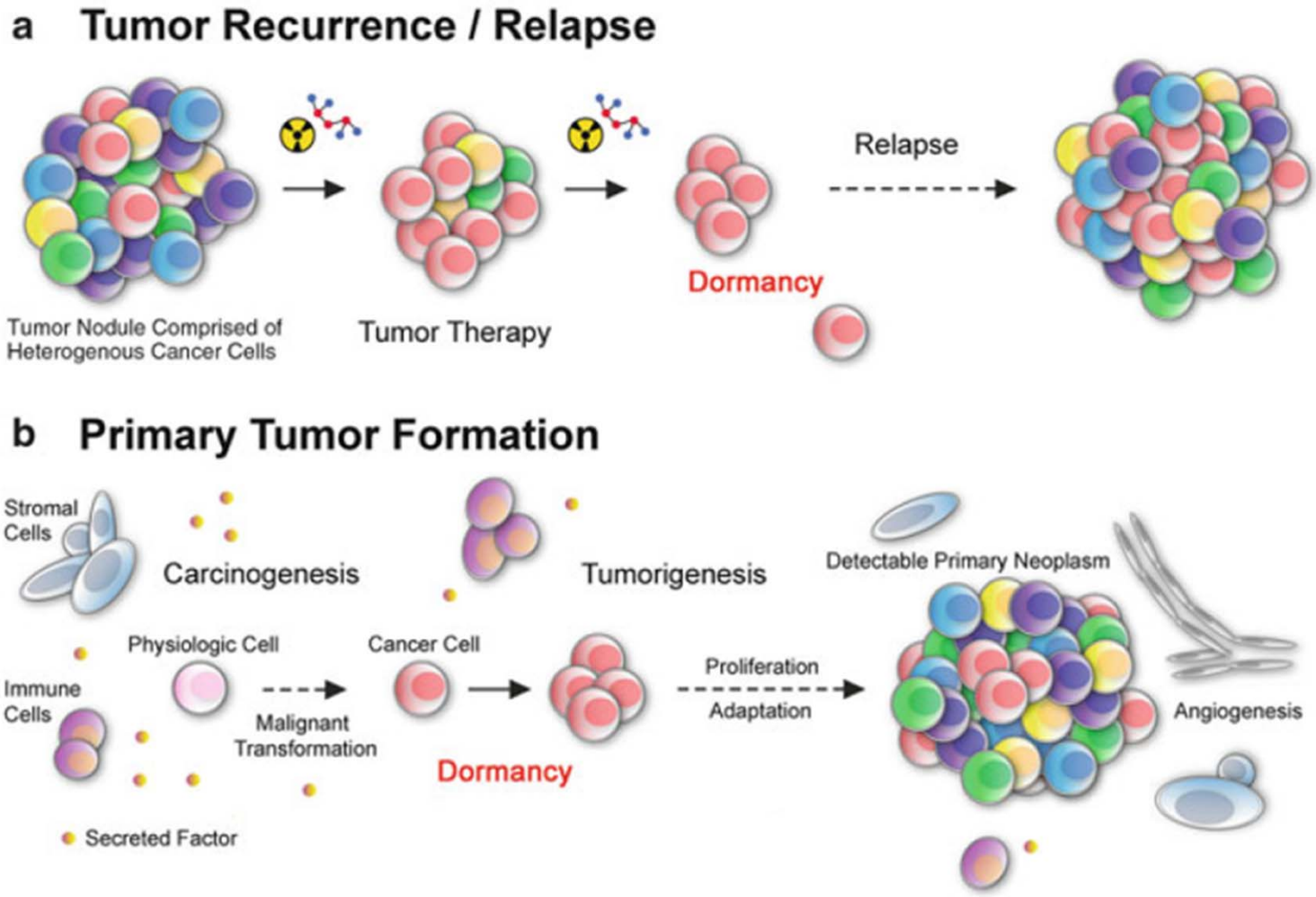


There is now growing evidence that cell dormancy occurs early in tumor development, indicating that tumor growth is not continuous and may pass through a long period. The possibility that cancers may lie dormant in the body for prolonged periods of time without causing overt neoplasia has been recognized for many decades.

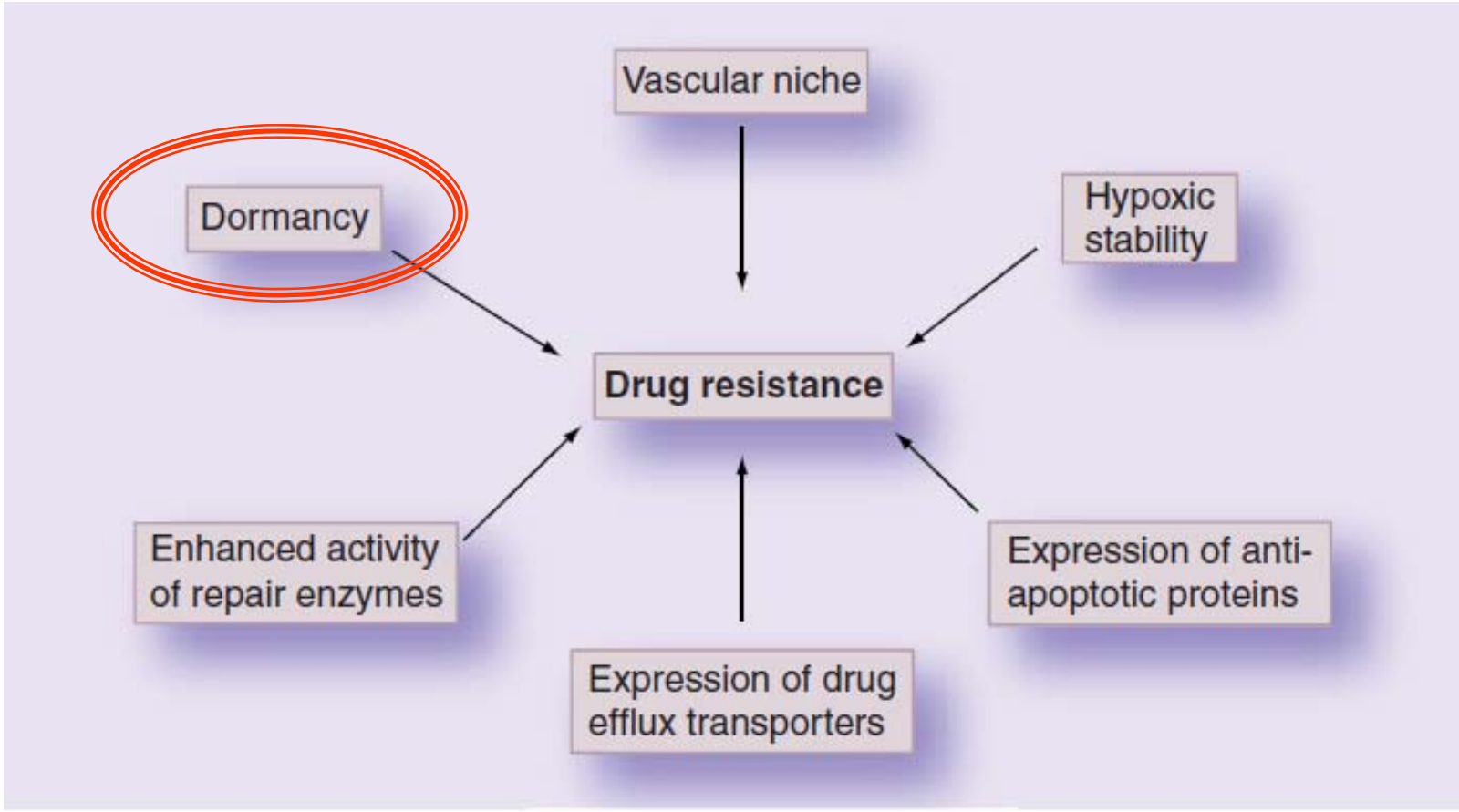




During the process, cellular dormancy can occur when tumor cells enter a state of quiescence through a G0 arrest of the cell cycle. Experimentally, this quiescent state is commonly defined by absence of proliferation and lack of programmed cell death

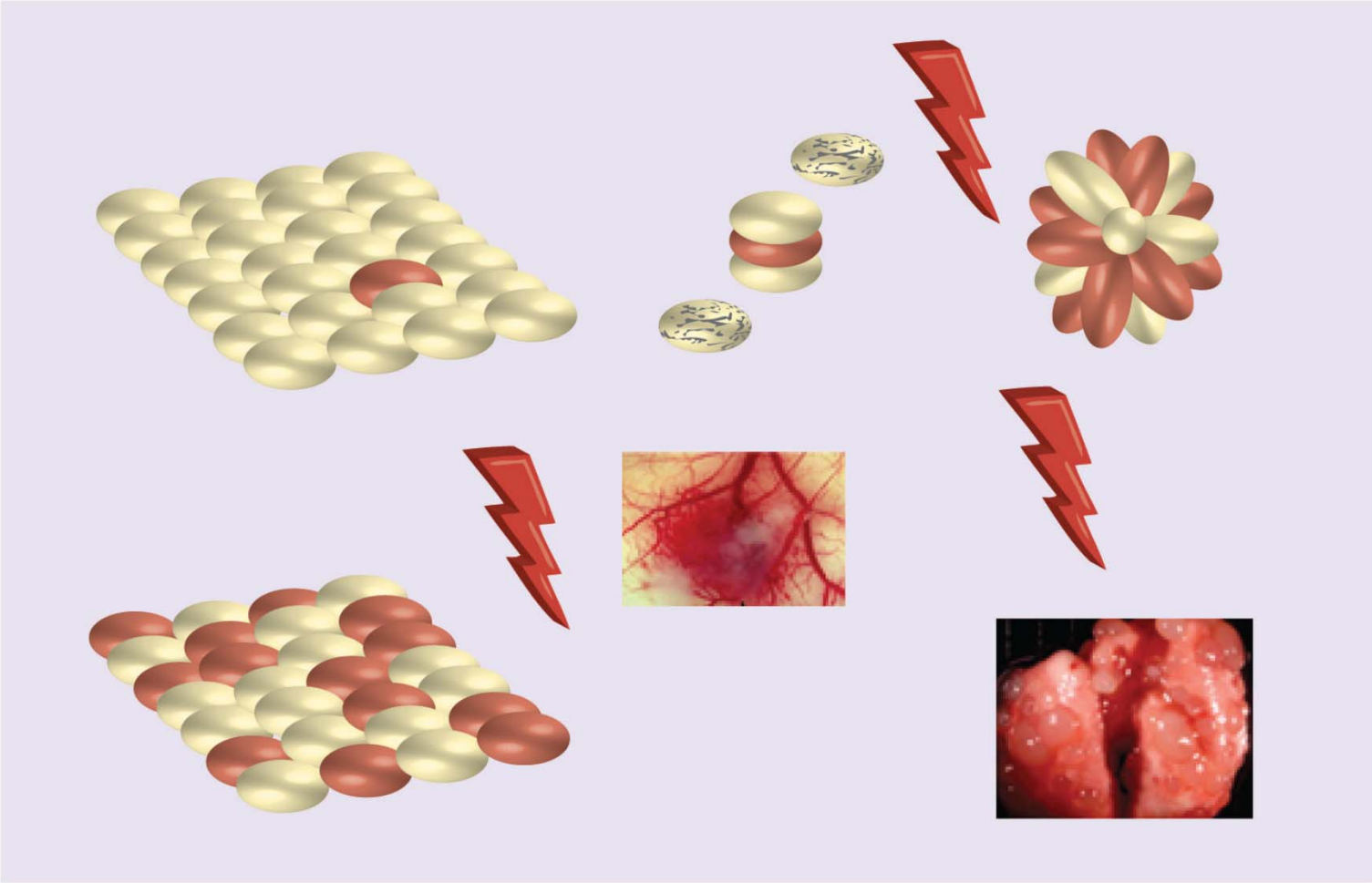


Recently, the occurrence of quiescence in tumor cells, especially in cancer stem cells (CSC) has been reported and proposed that could resist the radiation and chemical treatments in clinic to surviving using the strategy of cell quiescence



Serguei Vinogradov* & Xin Wei,
Nanomedicine (2012) **7**(4), 597–615

Principal steps in the survival of cancer stem cells after tumor treatment, metastasis and tumor relapse following the therapy



Serguei Vinogradov* & Xin Wei,
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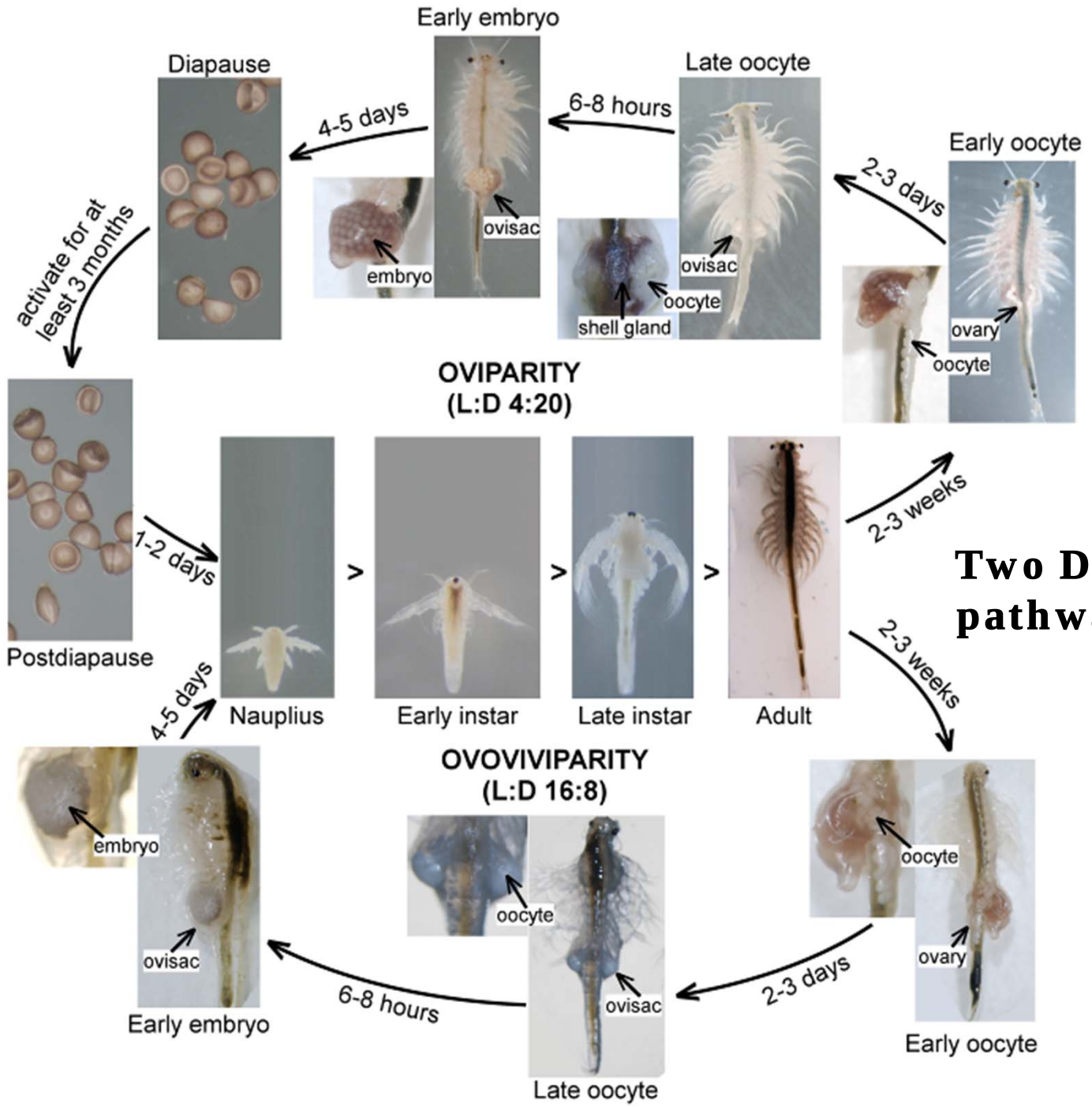
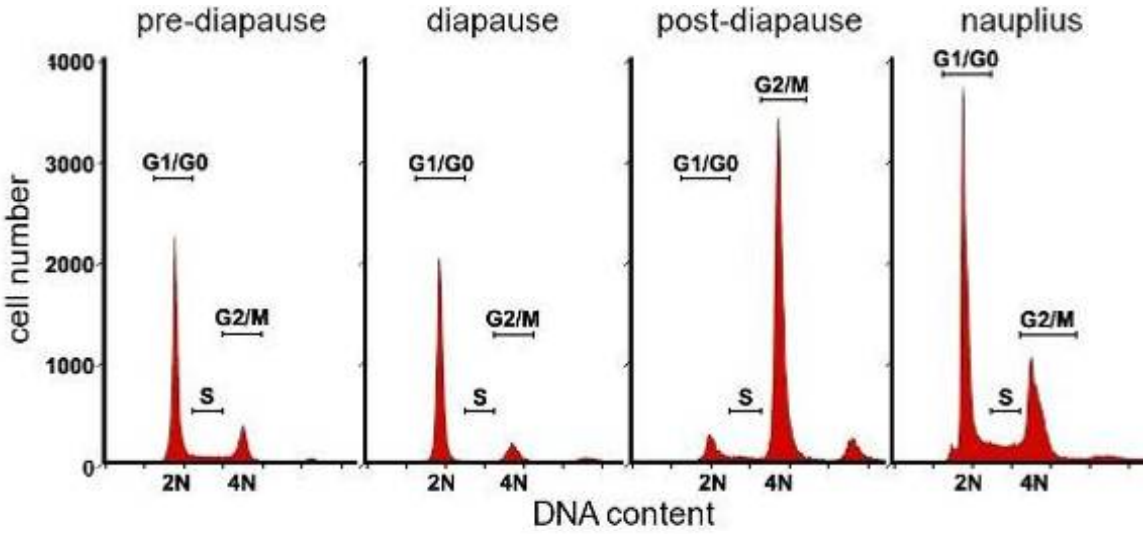
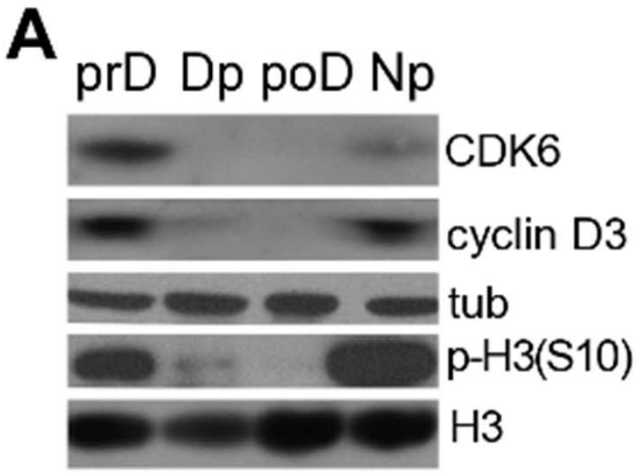
As outlined above, cell quiescence is a key regulator of the tumor dormant state, particularly in response to various forms of tumor therapy. However, very little is known the cell quiescence is regulated to persist for extended periods of time and then give rise to the malignant state.

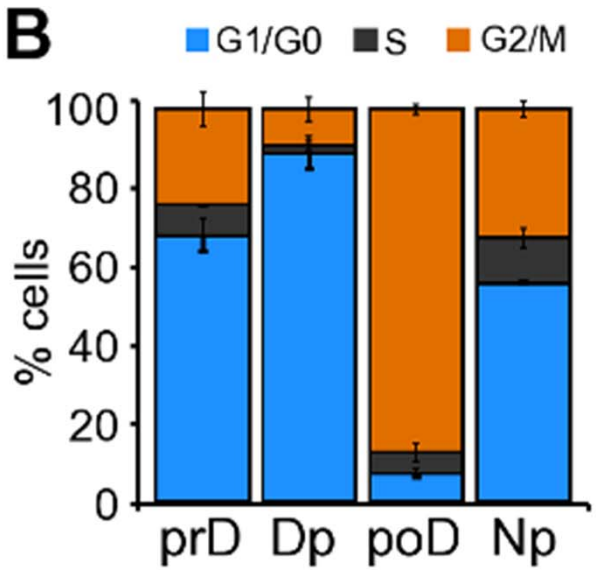


Two Developmental pathways of Artemia

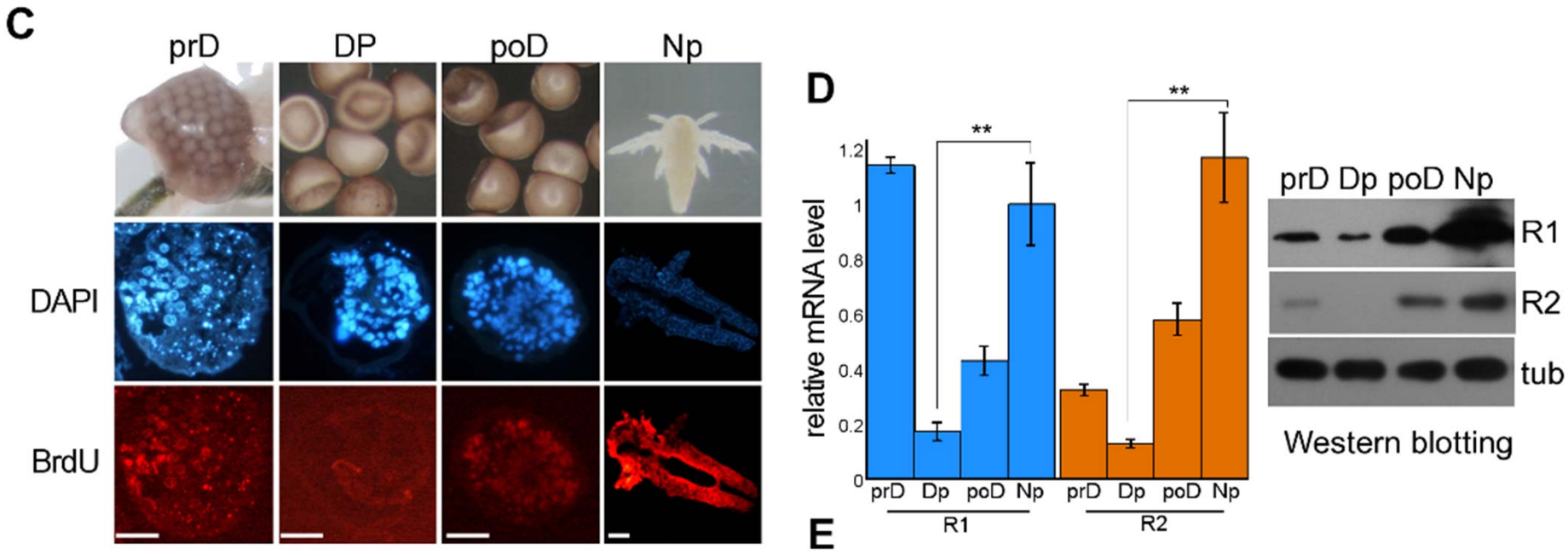
Cell Cycle at pre-diapause, diapause, post-diapause and nauplius stages



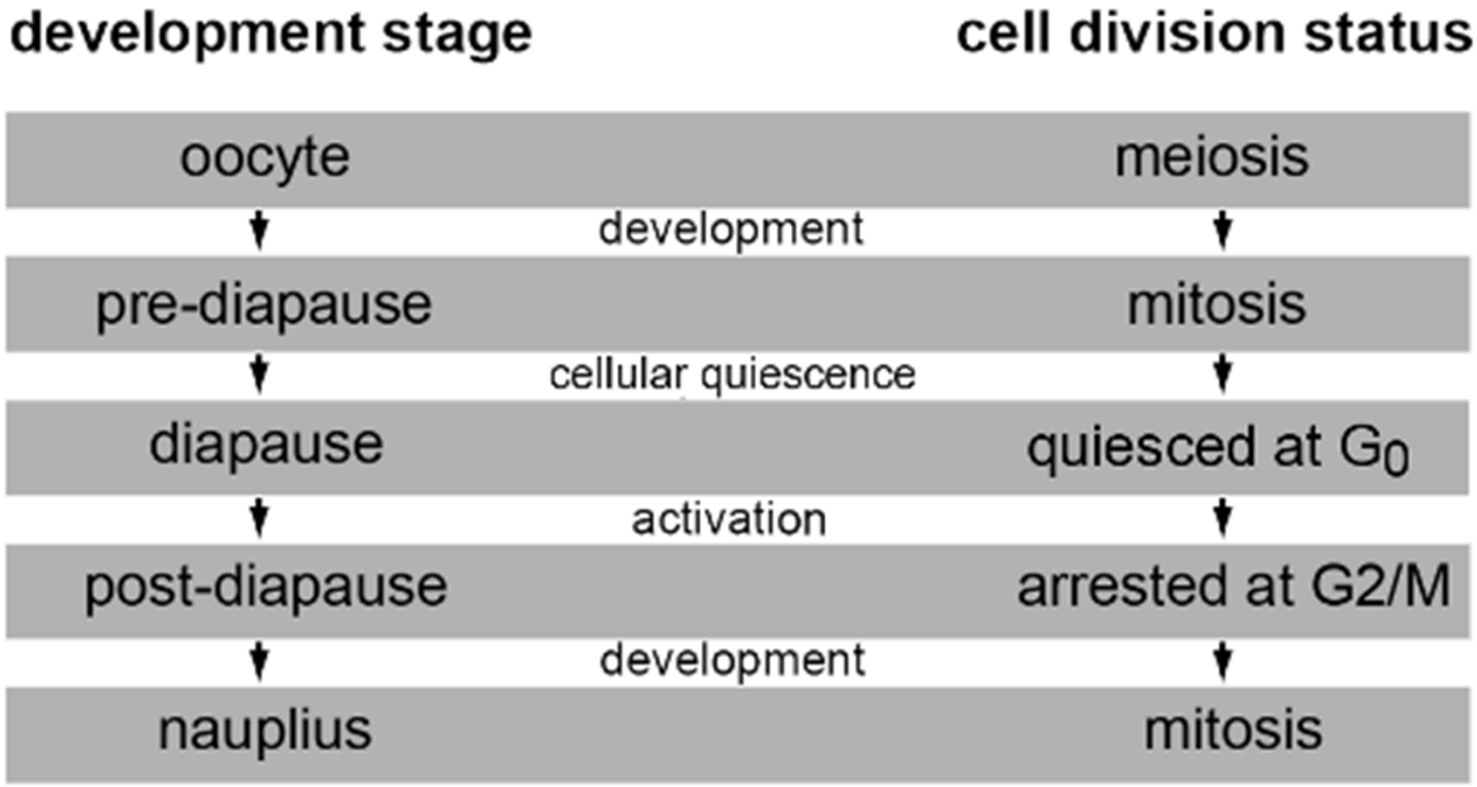




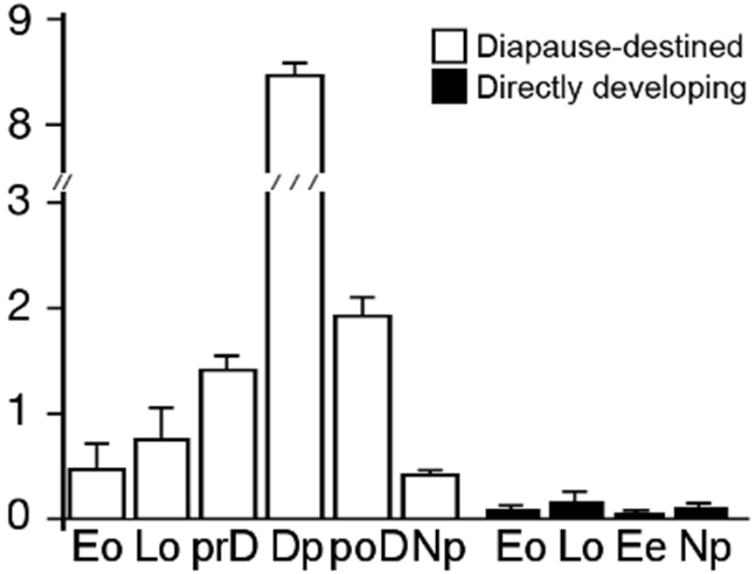
Cell Cycle at pre-diapause, diapause, post-diapause and nauplius stages

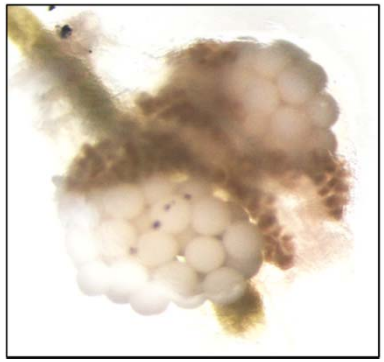


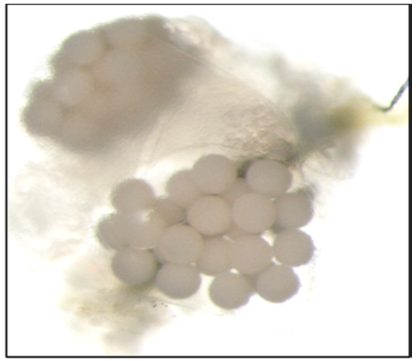
Cell Cycle at pre-diapause, diapause, post-diapause and nauplius stages



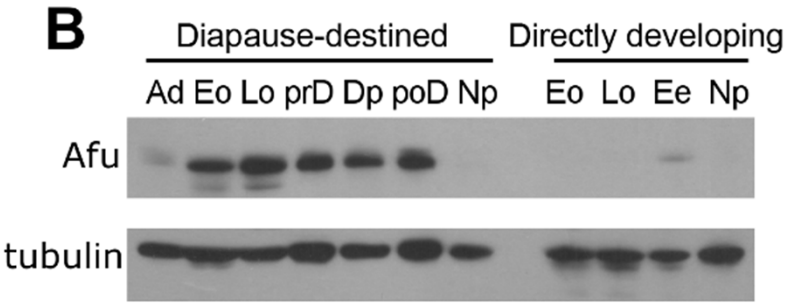
Characterization of *Afu* gene expression in diapause-destined reproduction pathway and directly developing reproduction pathway of *Artemia*.

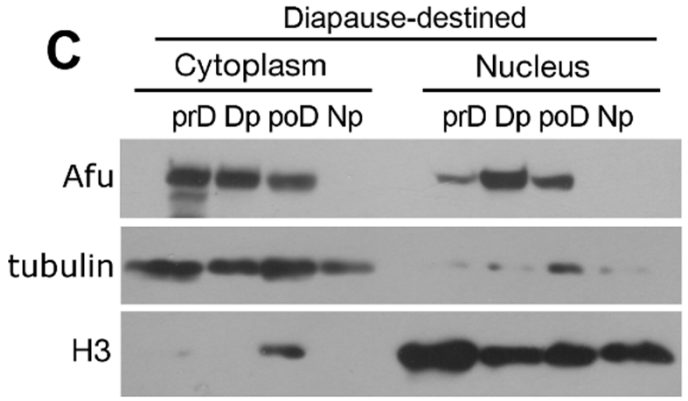




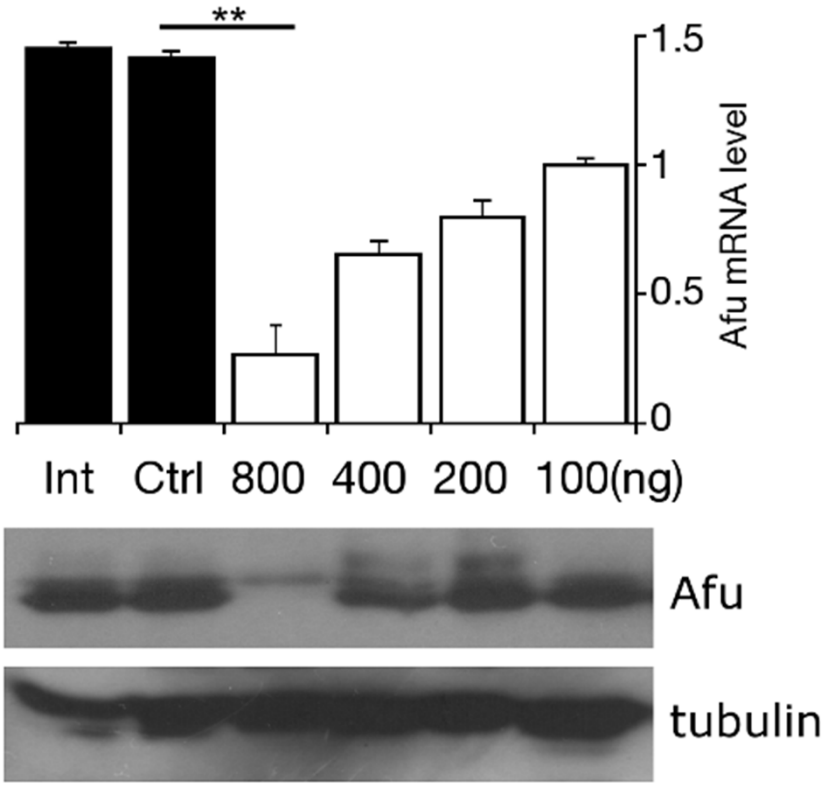


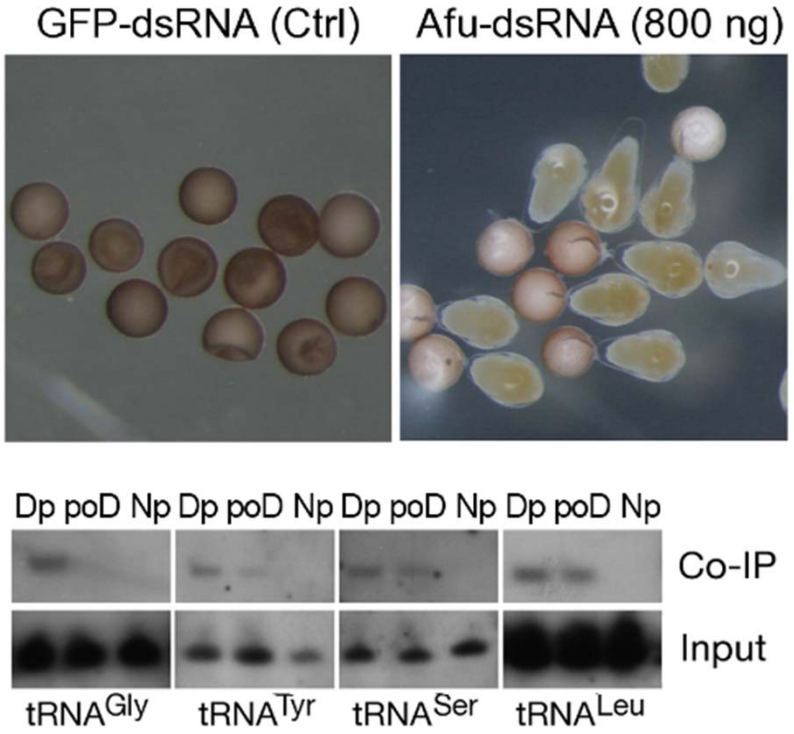
Oviparity **Ovoviviparity**



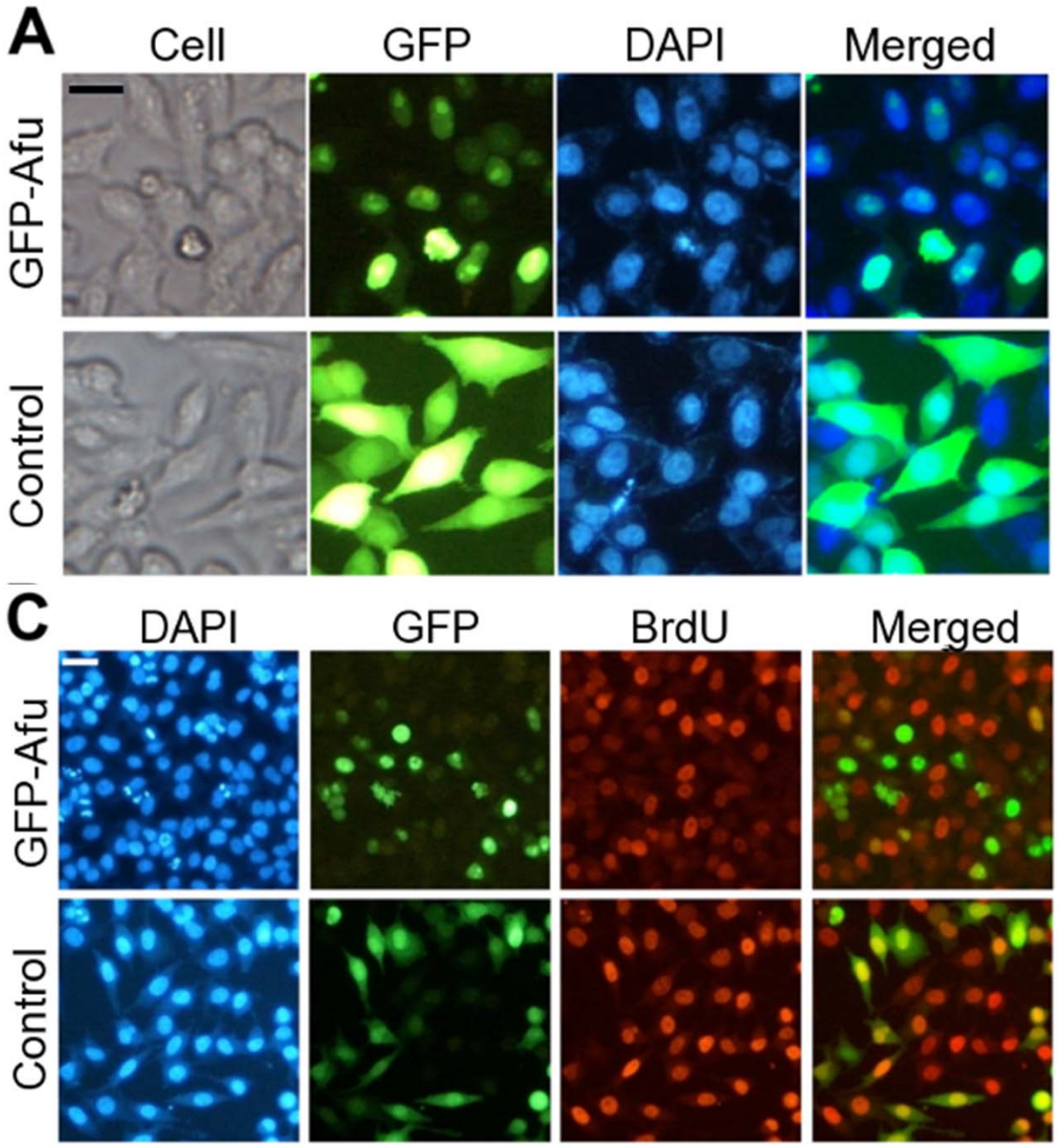


RNAi was used to knockdown *Afu* gene expression by treatment with a series of *Afu*-dsRNA dose injections





Afu localizes to the nucleus and results in quiescence in HeLa cells



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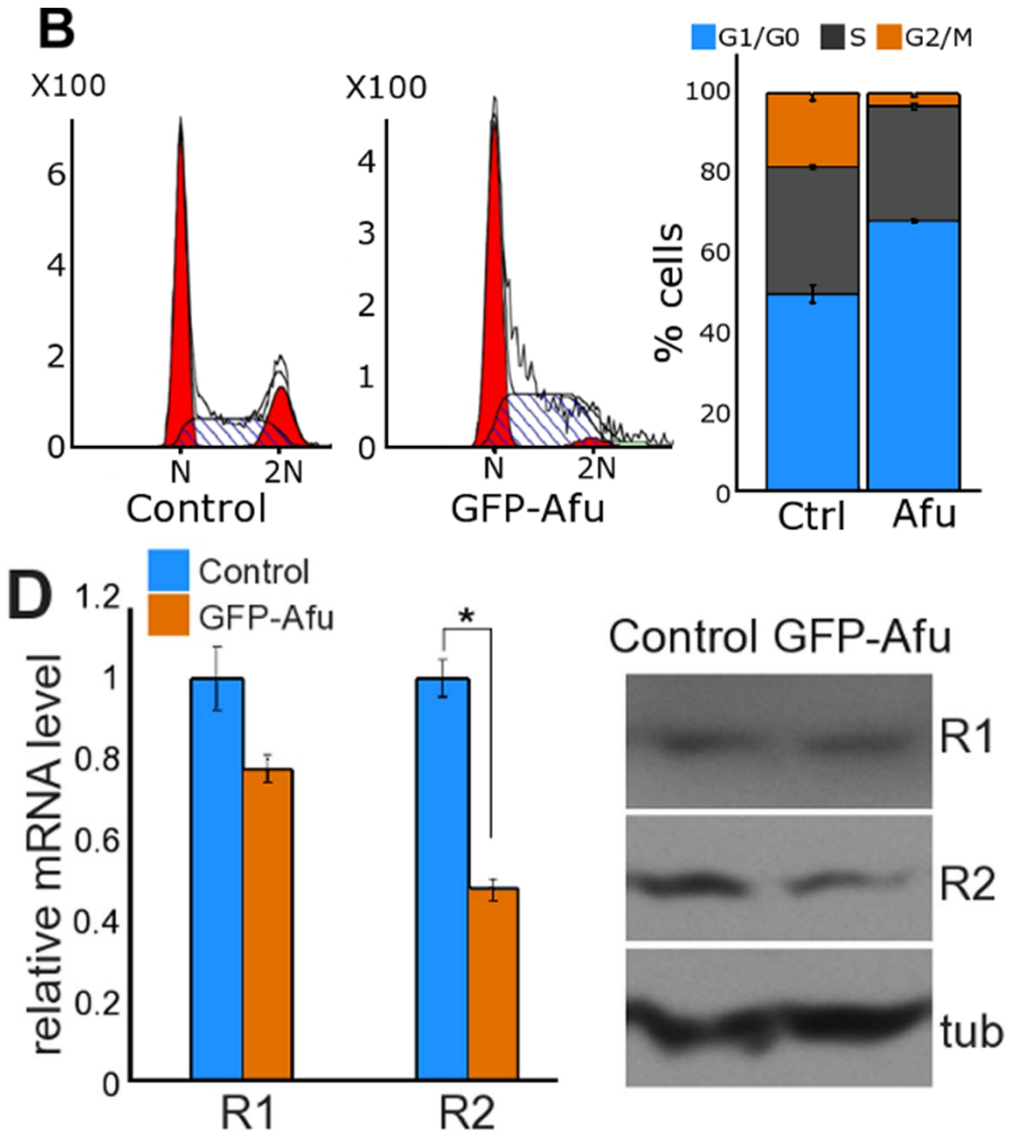

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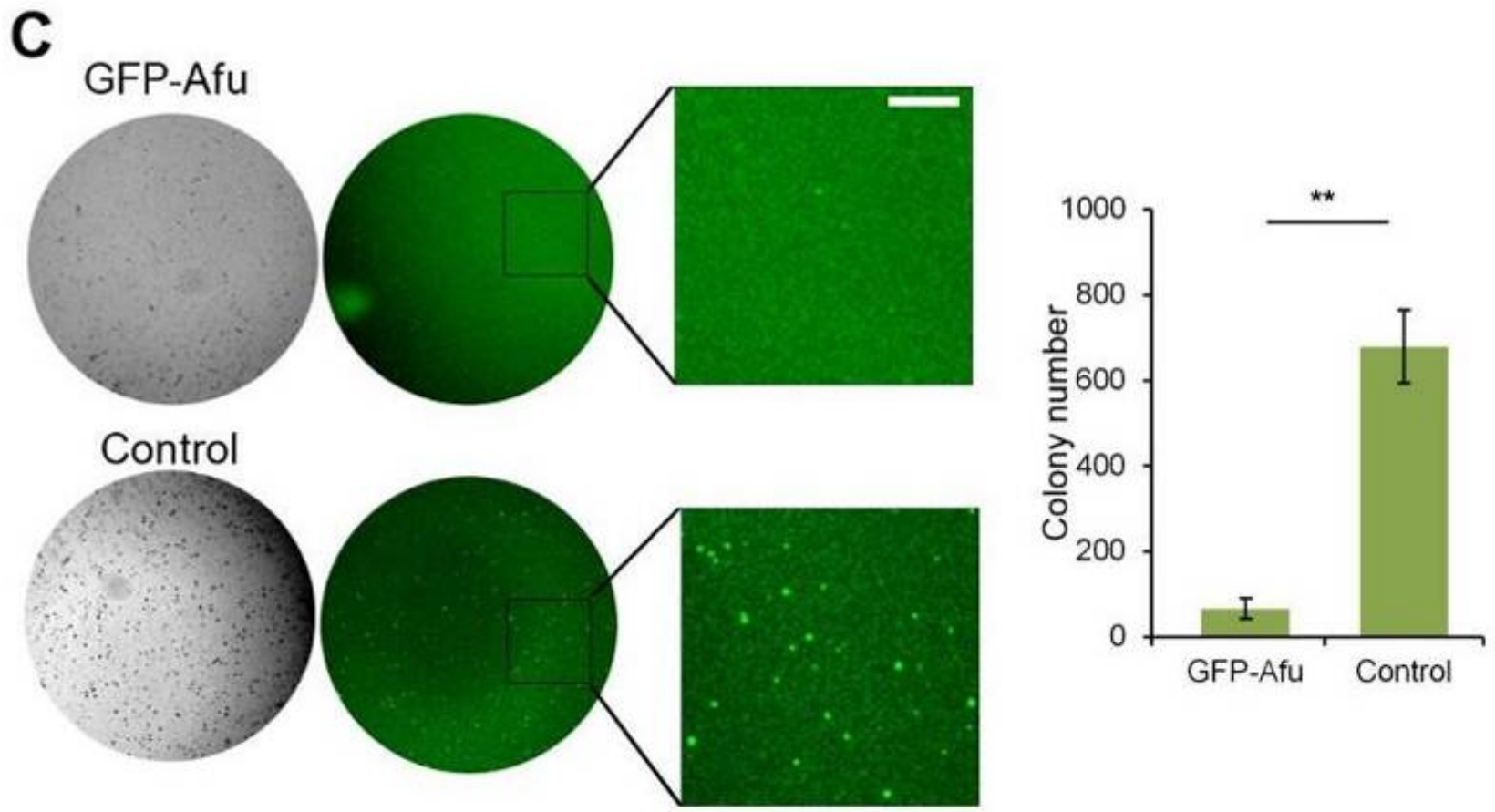
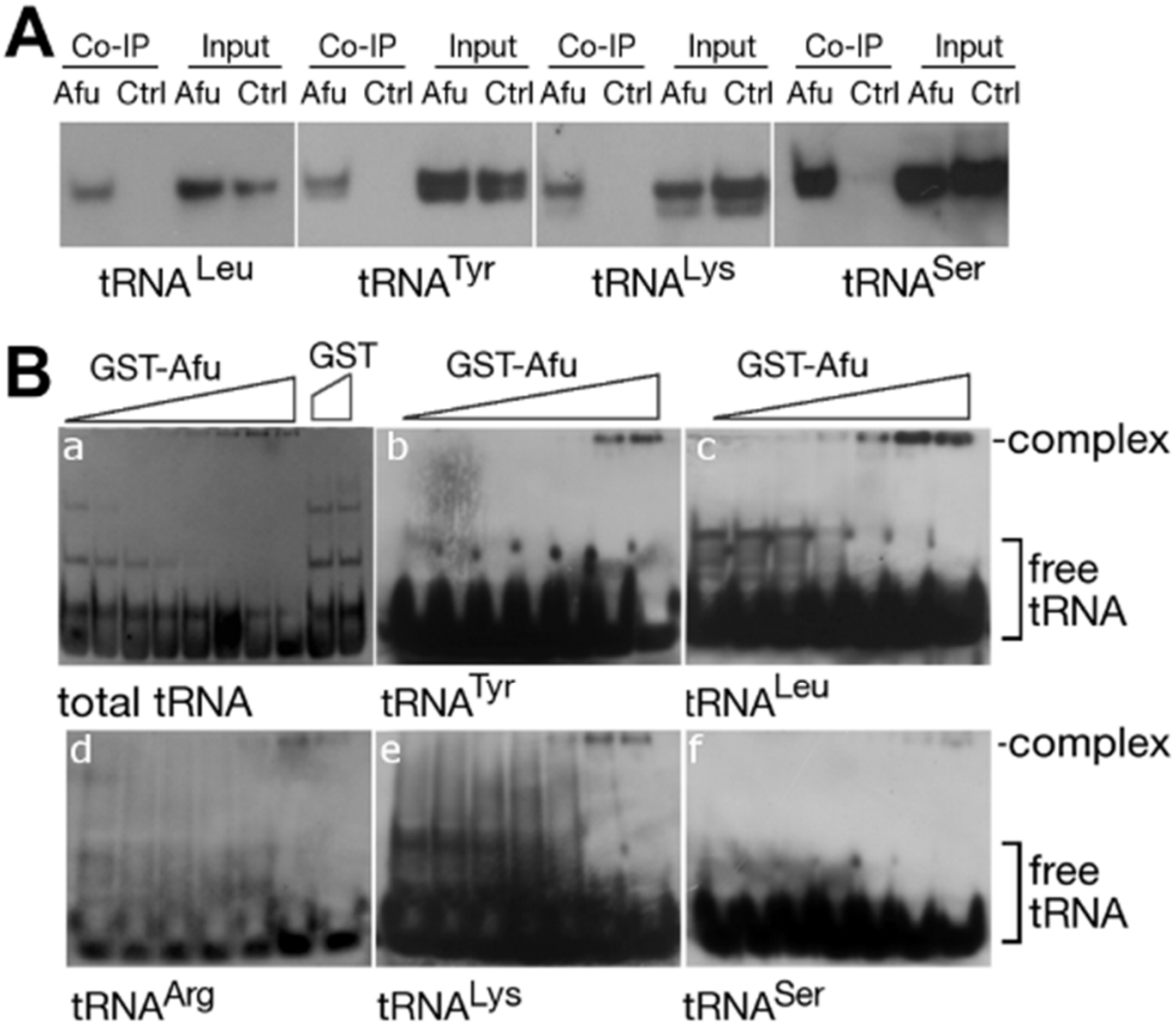


Afu binds to tRNAs in the nuclei and controls tRNA trafficking in HeLa cells



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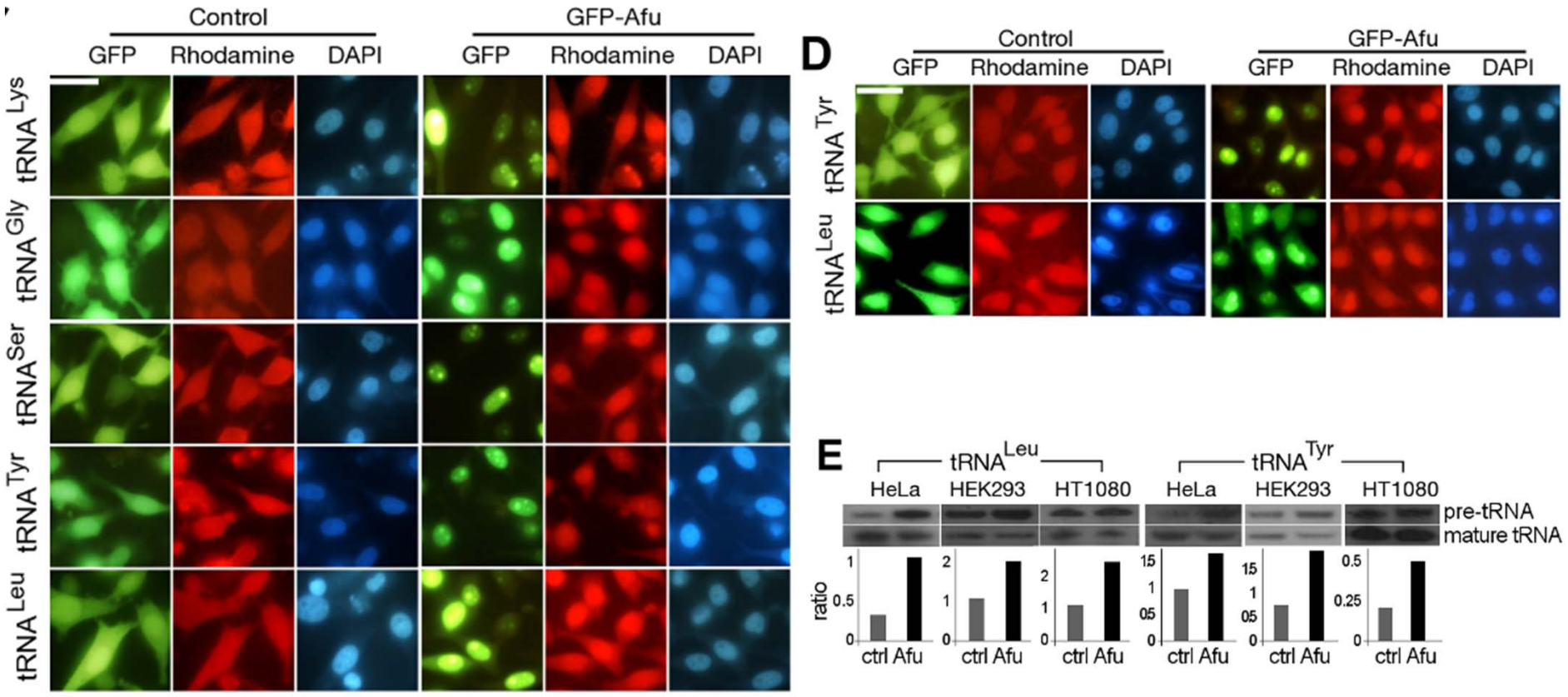
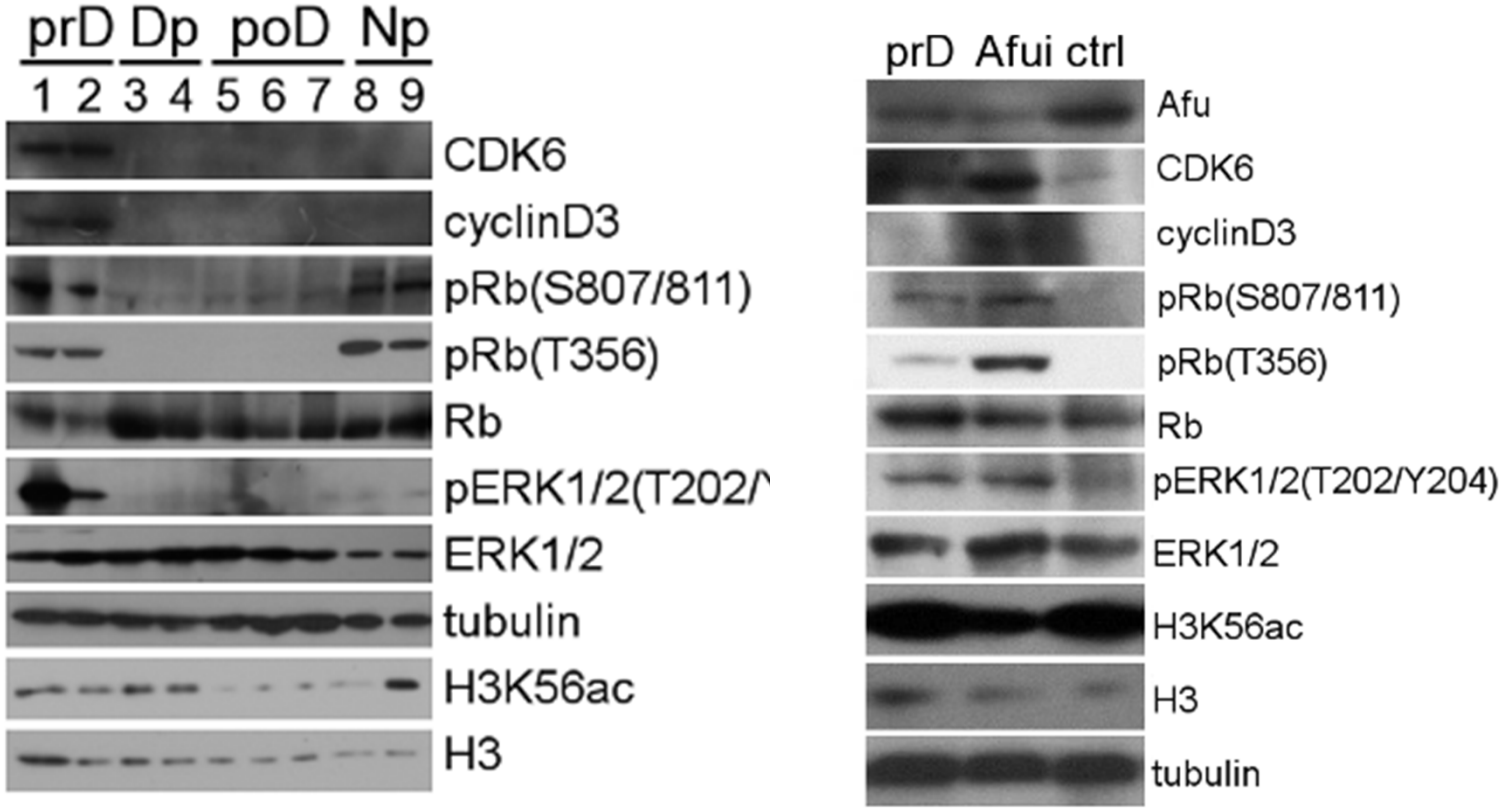


the signaling pathways linking tRNA trafficking to the cell cycle checkpoint



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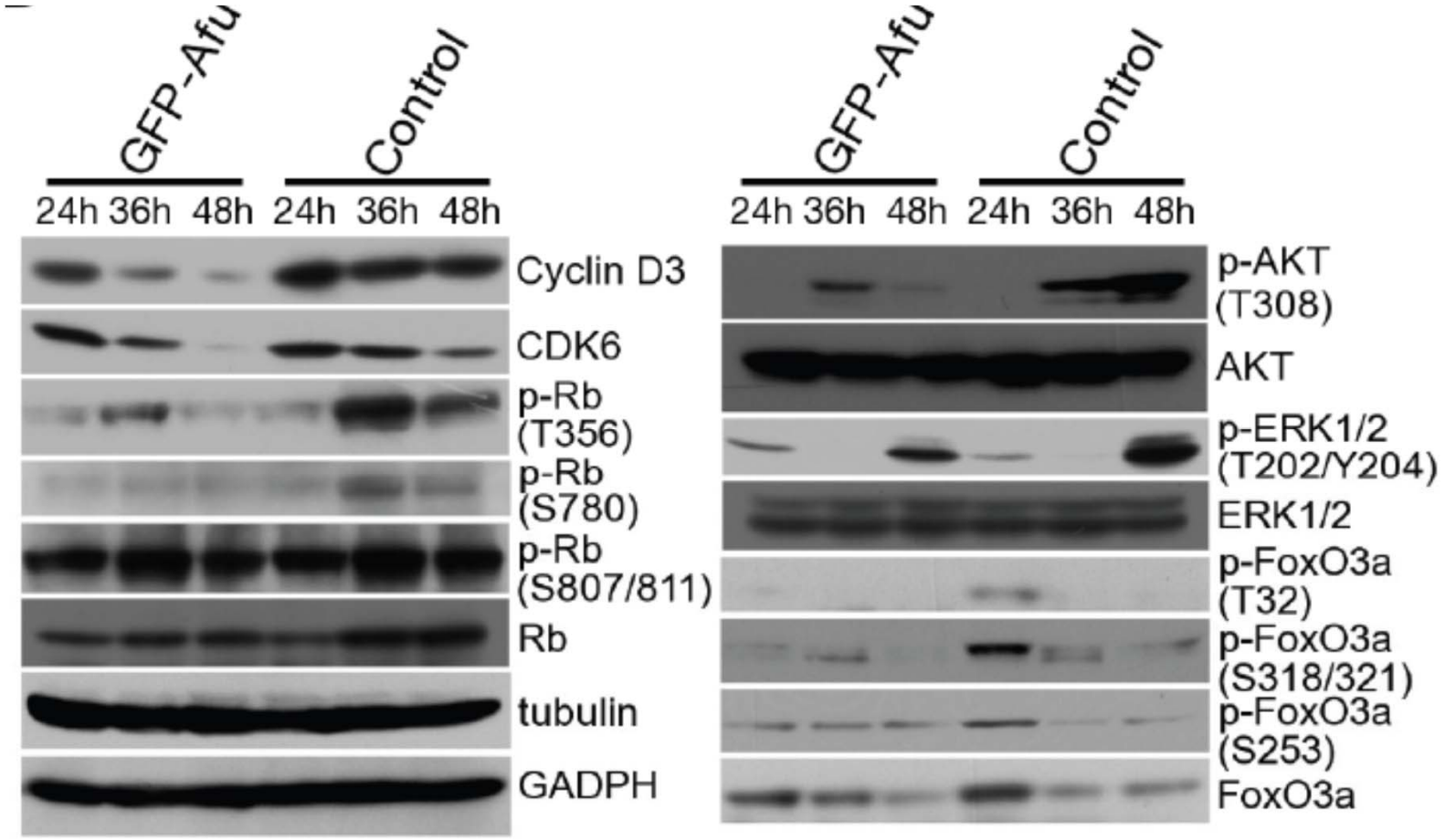
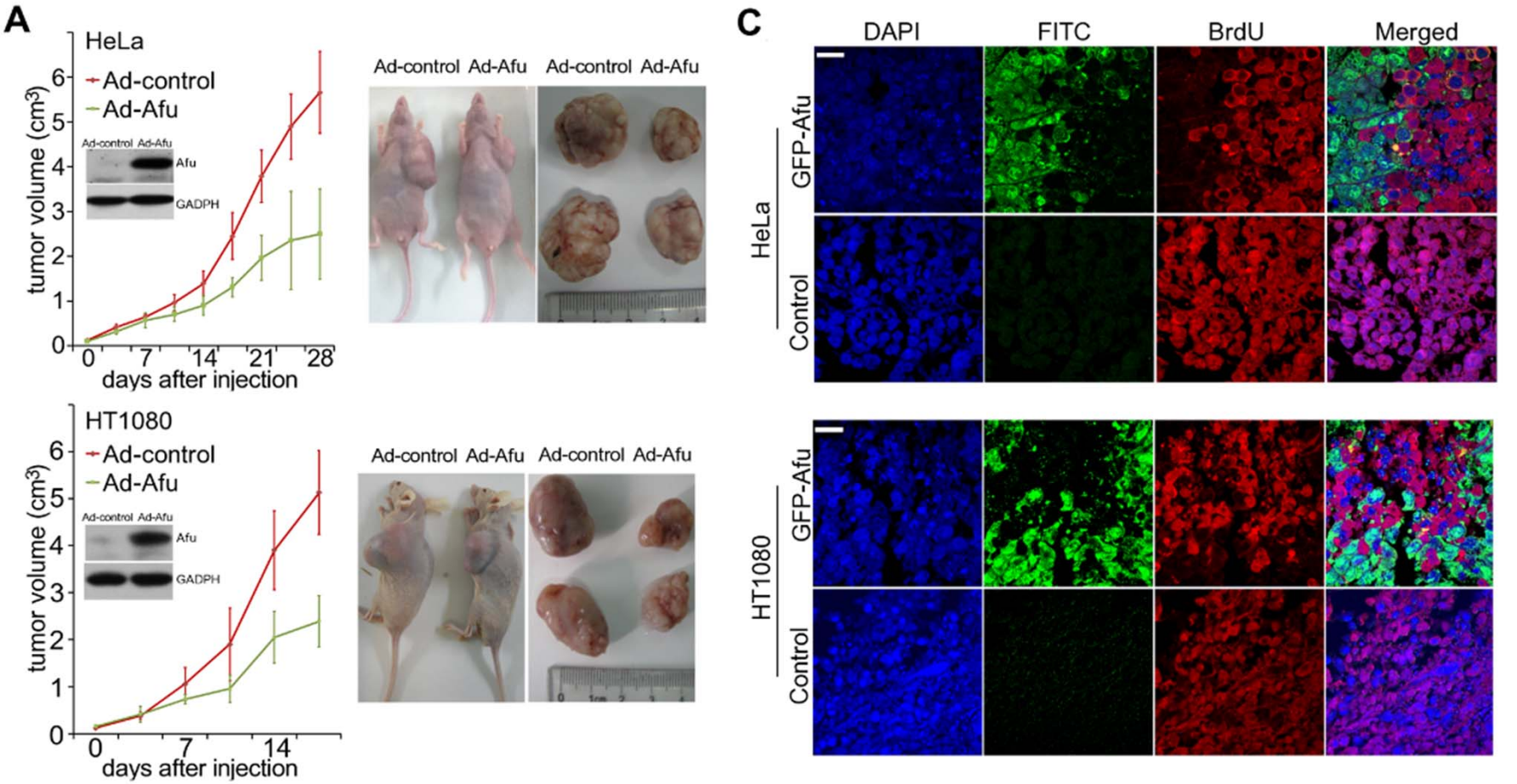
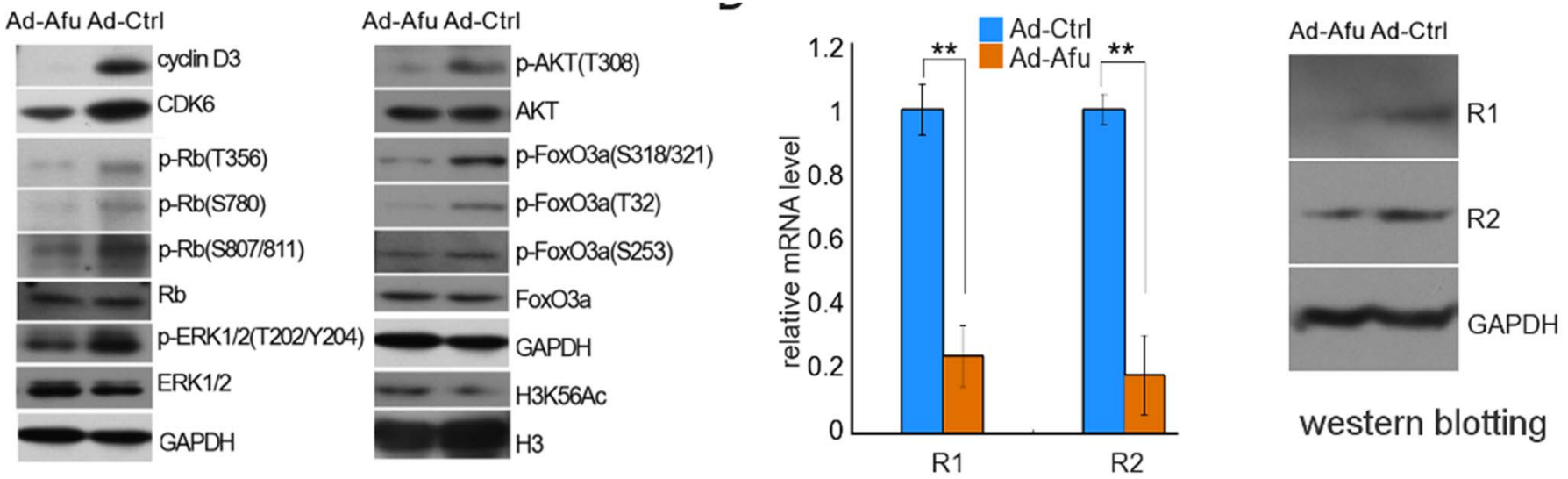


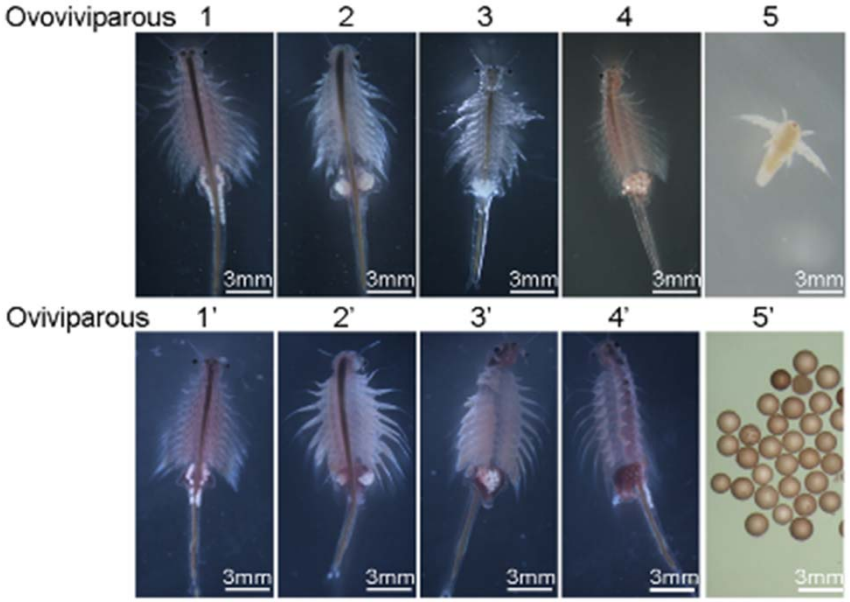
Afu inhibits mitosis of Hela and HT1080 cells in mouse xenograft tumor model

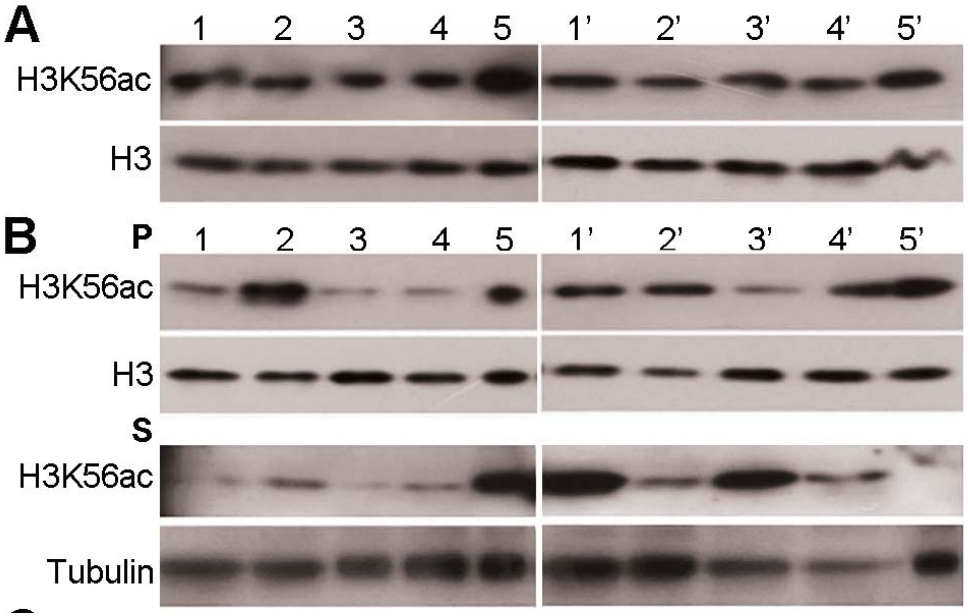


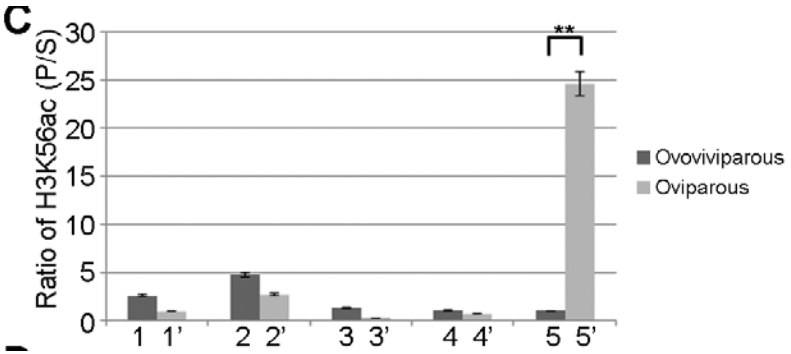
Afu was capable of causing the cell quiescence at G0 in tumor

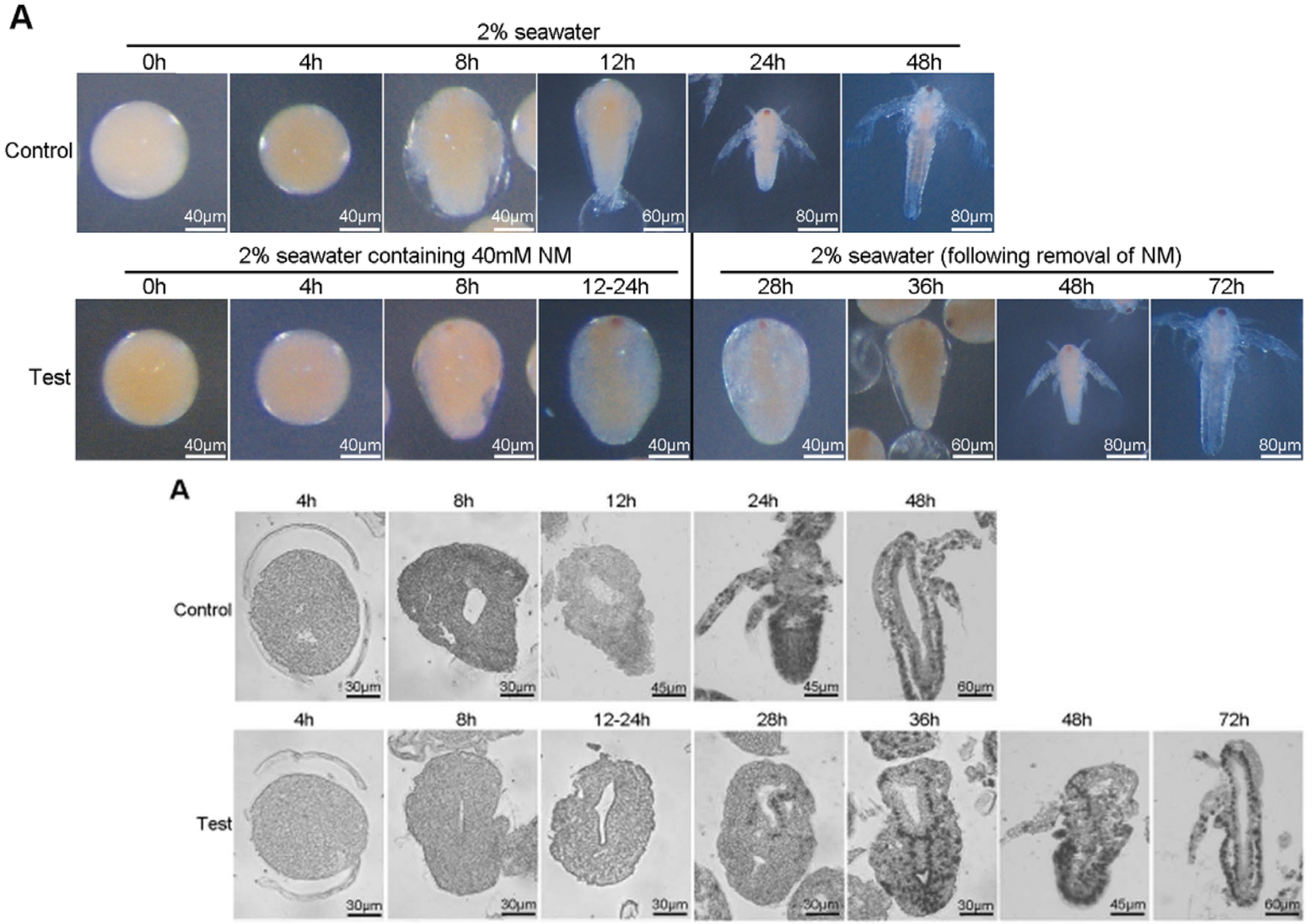


Accumulation of H3K56ac on chromatin in *Artemia* diapause embryos








A
2% seawater
0h
4h
8h
12h
24h
48h
Control
40μm
40μm
40μm
60μm
80μm
80μm
2% seawater containing 40mM NM
2% seawater (following removal of NM)
0h
4h
8h
12-24h
28h
36h
48h
72h
Test
40μm
40μm
40μm
40μm
40μm
60μm
80μm
80μm
A
4h
8h
12h
24h
48h
Control
30μm
30μm
45μm
45μm
60μm
4h
8h
12-24h
28h
36h
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Test
30μm
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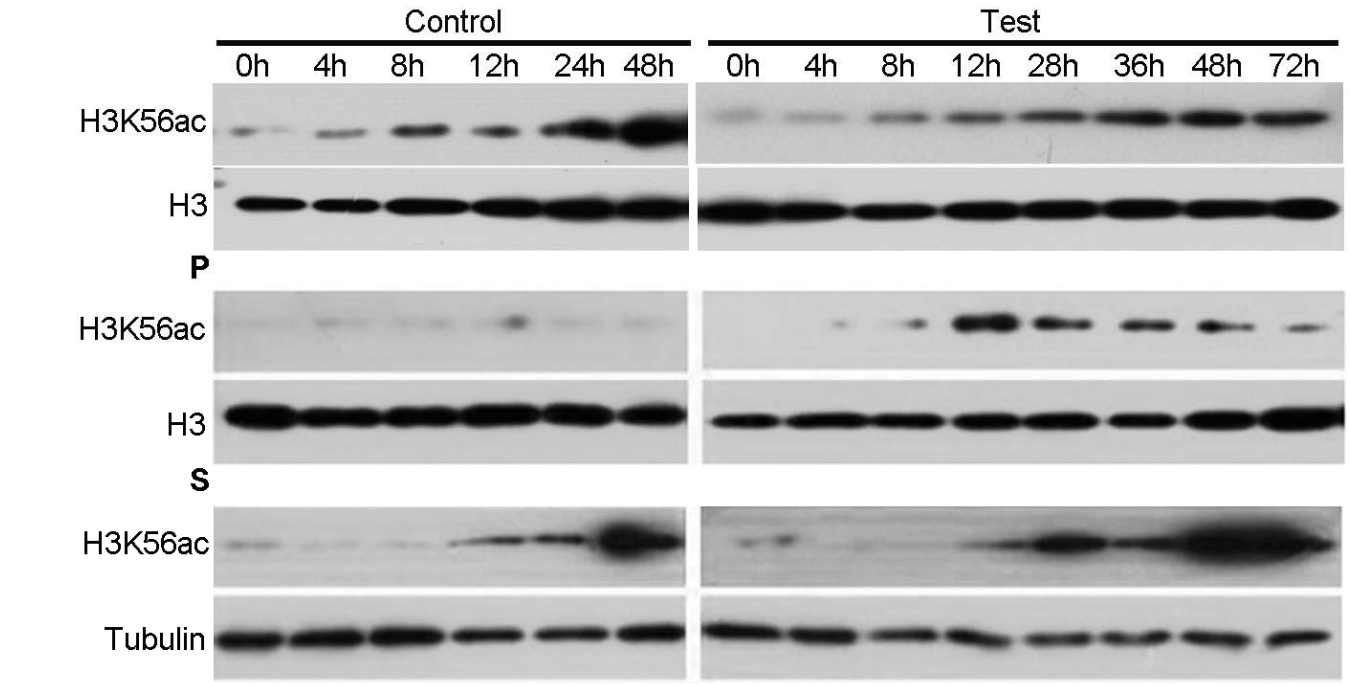
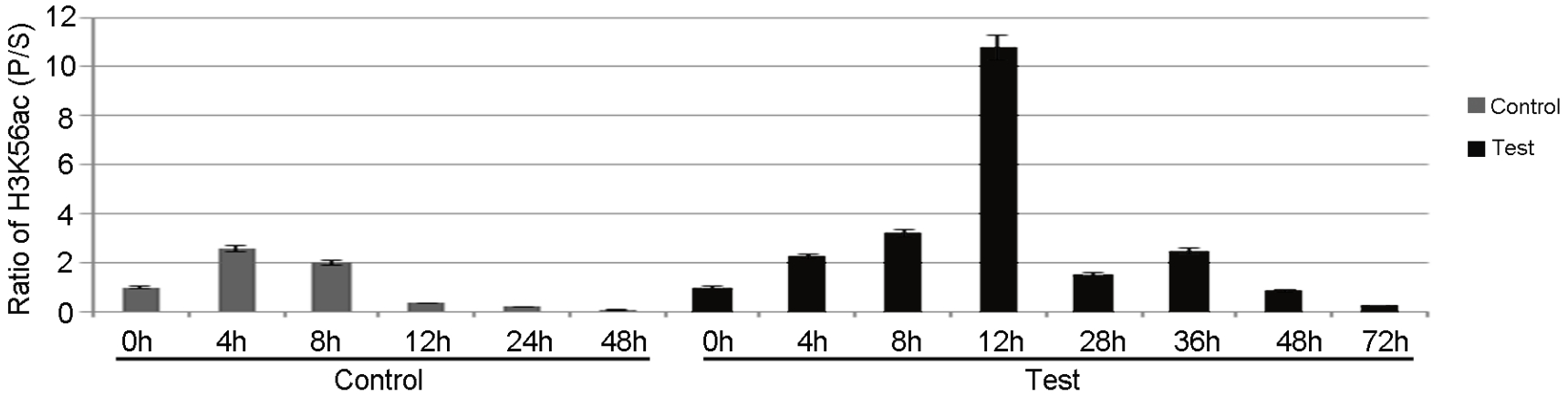
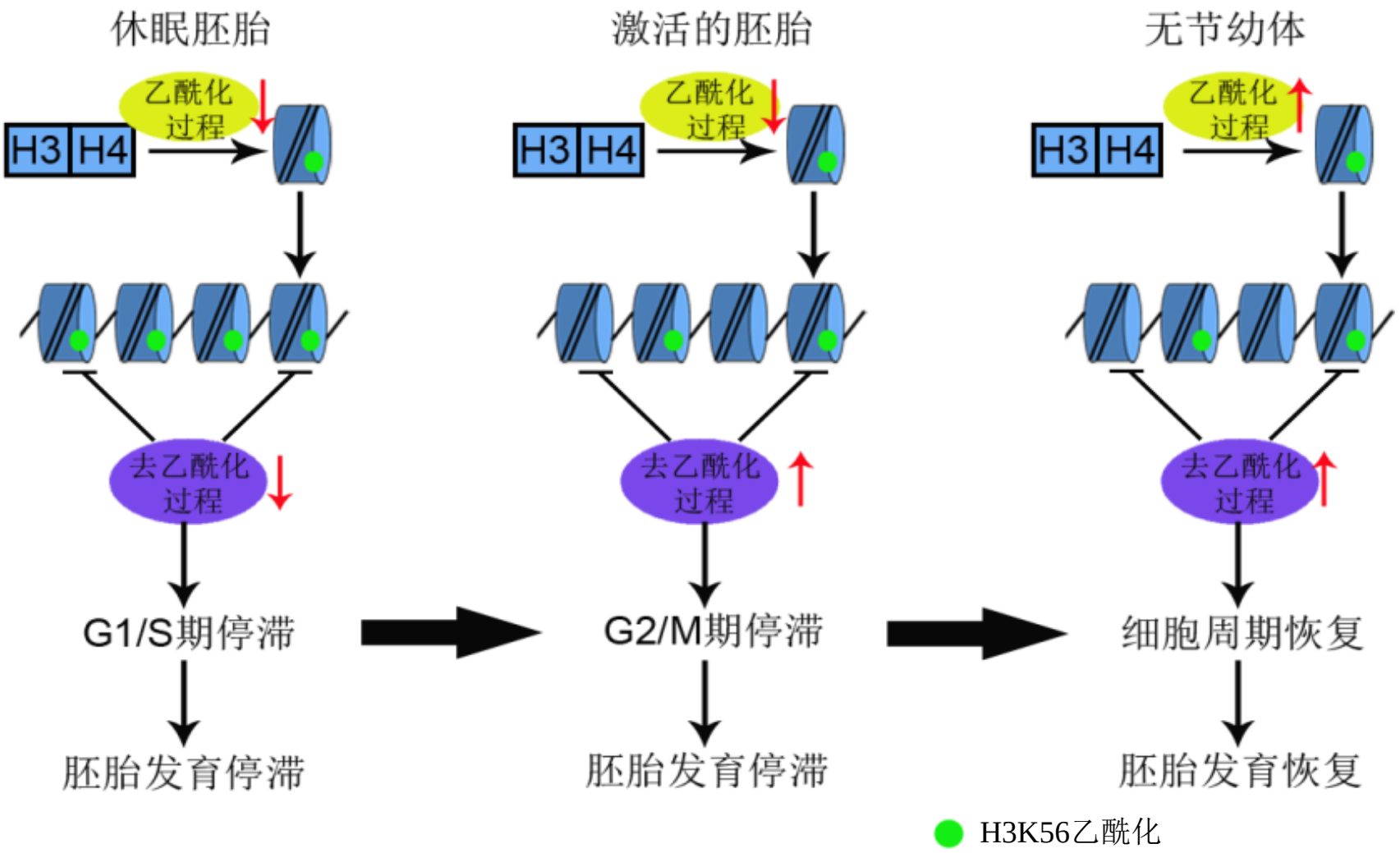
45μm
60μm

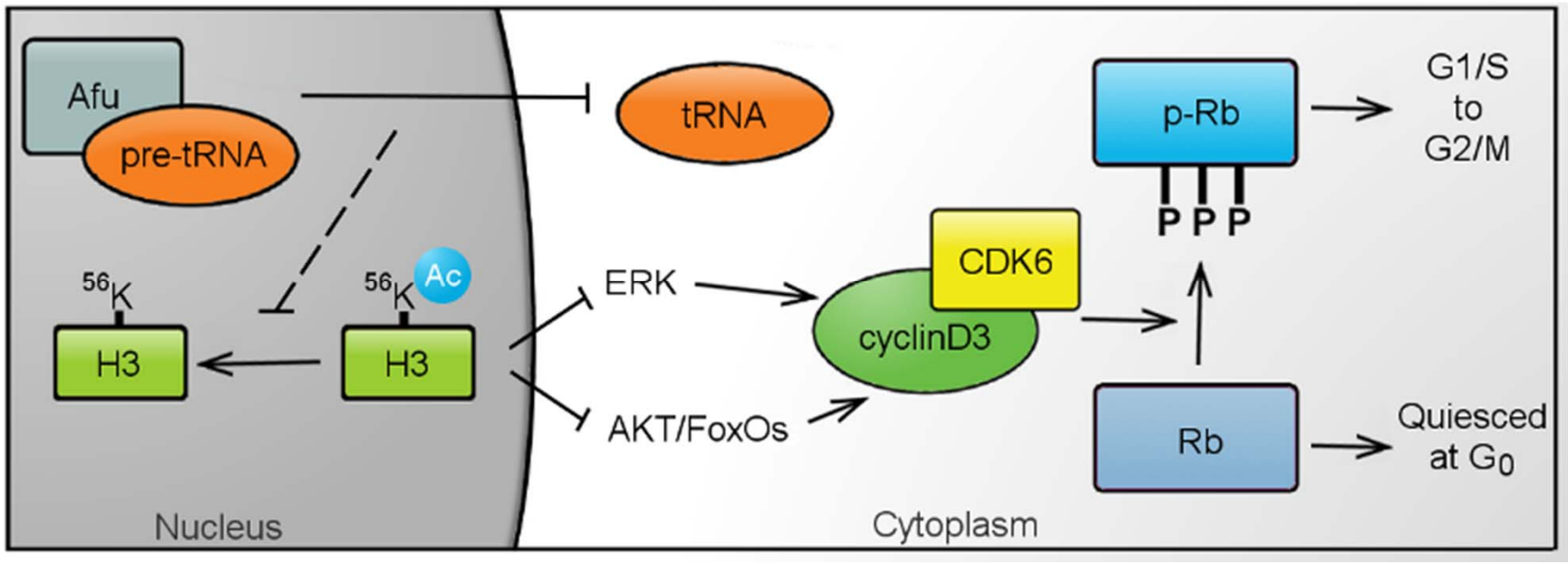
NM artificially arrests the cell cycle and development in post-diapause embryos






休眠胚胎
乙酰化过程
H3
H4
去乙酰化过程
G1/S期停滞
胚胎发育停滞
激活的胚胎
乙酰化过程
H3
H4
去乙酰化过程
G2/M期停滞
胚胎发育停滞
无节幼体
乙酰化过程
H3
H4
去乙酰化过程
细胞周期恢复
胚胎发育恢复
H3K56乙酰化

A working model for G1/S arrest regulation by Afu-induced suppression of tRNA trafficking



Summary

1. A tRNA binding protein, named Afu, accumulated in nuclei, controlling the cell quiescence to cease the cell division at onset of *Artemia* diapause.
2. Afu can also cause the quiescence and inhibit cancer cell dividing and tumour growth in xenograft mouse model.
3. Afu mediates the suppression of tRNA trafficking by binding to tRNA in the nucleus, thereby controls cell quiescence.
4. These findings may provide insight into regulation of the cellular quiescence and further description of this novel model for studying tumor dormancy and cancer stem cell quiescence.