



# CDB SEMINAR

## Joel D. Richter

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Thursday, November 13, 2008

16:00~17:00 C1F CDB Auditorium

## Translational Control of Cellular Senescence

### Summary

In early development, translational control of many mRNAs is regulated by cytoplasmic polyadenylation. In *Xenopus*, where it has been studied most intensively, polyadenylation-induced translation is essential for meiotic progression of germ cells as well as the early mitotic events in the embryo. CPEB, a sequence-specific RNA binding protein, is the key factor that regulates polyadenylation. CPEB knockout mice have been generated and while they are overtly normal, they have defects in germ cell development that cause sterility. To investigate the involvement of CPEB in mammalian mitosis, mouse embryo fibroblasts (MEFs) were prepared. Wild type MEFs divide several times before they exit the cell cycle and become senescent, an expected result. Senescence, like apoptosis, is a process that inhibits malignant transformation both in vitro and in vivo. The CPEB KO MEFs, however, did not senesce, but indeed were immortal. In MEFs, CPEB-regulated translation of myc mRNA is essential for senescence. In primary human skin fibroblasts, as in MEFs, shRNA-directed knockdown of CPEB causes senescence bypass. In these cells, CPEB is essential for maintaining the long poly(A) tail and robust translation of p53 mRNA. When CPEB is reduced by the shRNA, p53 translation is inefficient and as a result, the cells bypass senescence. Interestingly, in the CPEB knockdown human cells, there is a large change in bioenergetics. That is, there is reduced mitochondrial mass and reduced respiration. However, normal ATP levels are maintained by a very large increase in glycolysis. This change in bioenergetics, known as the Warburg Effect, is a characteristic of cancer cells. The possibility that CPEB acts as a tumor suppressor will be discussed.

### Host:

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- Groisman, I., Ivshina, M., Marin, V., Kennedy, N., Davis, R., and Richter, J.D. (2006). Control of cellular senescence by CPEB. **Genes & Development** 20, 2701-2712.
- Richter, J.D. (2007). CPEB: A life in translation. **Trends in Biochem. Sci.** 32, 279-285.
- Burns, D., and Richter, J.D. (2008). CPEB regulation of human cellular senescence, energy metabolism, and p53 mRNA translation. **Genes & Development** in press.

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