This Week's Citation Classic®

Pardee A B. A restriction point for control of normal animal cell proliferation.
Proc. Nat. Acad. Sci. USA 71:1286-90, 1974.
[Moffett Laboratories, Princeton University, NJ]

This paper proposes a critical event located in the G_1 phase of the cell cycle that we named the restriction (R) point. External factors regulate cell proliferation prior to R; afterwards the cell is free to complete its duplication. Tumor cells are defective in R point control. [The *SCI*® indicates that this paper has been cited in more than 555 publications.]

A Growth Control Event Defective in Tumors

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This paper is the result of new insights I gained during my sabbatical with Michael Stoker at the Imperial Cancer Research Fund Laboratories, London, taken together with Ruth Sager and Henry Rozengurt. This year shaped research for all three of us for the next two decades. I cannot overemphasize the benefits of a sabbatical for creativity, a period free of the usual commitments and giving one time to work and think undisturbed. This was my third. Like the first with Jacques Monod during which we proposed the repressor model for control of gene expression, and the second by myself at Princeton when I discovered and characterized the first periplasmic binding protein, this sabbatical provided a concept that continues to be cited.

I came to London to continue our studies of membrane-transport changes during the cell cycle and as a consequence of transformation. This research plan resulted from my suggestion, made a decade earlier, that defective growth control of tumor cells is due to alterations in functional membrane properties. I soon learned the techniques of cell culture and synchronization and became aware that much needed to be understood about the conditions that determine whether or not a cell will continue to proliferate or go into a quiescent state and how this decision is changed in tumor cells. My experiments, summarized in this paper, led to the hypothesis that the choice between growth and quiescence is made during late G_1 phase, prior to a control point R. Remarkably, the same G_1 control event was discovered at this time in yeast by Hartwell, and named START. (See reference 1.)

The experiments were absorbing and they often required long sampling intervals. On one occasion I started a time-course experiment for which I took a sample at the end of the day, went to a restaurant for dinner and came back to obtain a time point, attended a play at nearby Covent Garden during which I took another point at intermission, and came back for the final point of the day after the play ended.

My laboratory at Princeton, and then at Harvard, continued along this line of work after my sabbatical. We wrote one of the first reviews on control of the mammalian cell cycle,[2] also frequently cited. We concluded from experiments with inhibitors that rapid protein synthesis is essential for normal but not tumor cells to pass R. From these data we postulated that an essential protein must be unstable in the normal but not the tumor cells, and we subsequently identified such a protein on 2D gels.[3] Very recently we have discovered a protein complex related to transcriptional control of thymidine kinase production that binds to the thymidine kinase promoter and which has the postulated properties.[4] Thus, our new experiments that identify nuclear binding factors active before the G_1/S boundary are a direct extension of both our repressor studies done 30 years ago and our R point hypothesis formulated 15 years ago.

Our early studies are now receiving increased attention because control of the cell cycle has become a hot topic.[5] Exciting discoveries have been made which link molecules such as cdc2 kinase, cyclins, p53, and the retinoblastoma gene product, to G_1 control.[1] Recently, I summarized my thoughts regarding the subject of cell proliferation control.[6] The varied clues surely will soon become integrated into a picture of how growth in both normal and tumor cells is regulated.

1. **Murray A W & Kirschner M W.** Dominos and clocks: the union of two views of the cell cycle. *Science* 246:614-21, 1989.
2. **Pardee A B, Dubrow R, Hamlin J L & Kletzien R L.** Animal cell cycle. *Annu. Rev. Biochem.* 47:715-50, 1978. (Cited 525 times.)
3. **Croy R G & Pardee A B.** Enhanced synthesis and stabilization of a Mr 68,000 protein in transformed Balb/c-3T3 cells: candidate for restriction point control of cell growth. *Proc. Nat. Acad. Sci. USA* 80:4699-703, 1983.
4. **Bradley D W, Dou Q-P, Fridovich-Keil J L & Pardee A B.** Transformed and nontransformed cells differ in stability and cell cycle regulation of a binding activity to the murine thymidine kinase promoter. *Proc. Nat. Acad. Sci. USA* 87:9310-4, 1990.
5. **Touchette N.** The cell cycle comes full cycle. *J. NIH Res.* 2:53-7, 1990.
6. **Pardee A B.** G_1 events and regulation of cell proliferation. *Science* 246:603-8, 1989.

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