Reviewer's report

Title: Glycogen Synthesis correlates with androgen-dependent growth arrest In Prostate Cancer

Version: 1 Date: 31 January 2005

Reviewer: Anna M. Gómez Foix

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The study "Glycogen synthesis correlates with androgen-dependent growth arrest in prostate cancer" by Schnier et al. examines glycogen content and cell growth in androgen-receptor reconstituted prostate cancer cells PC3 (PC3-AR) upon stimulation with the androgen R1881, the glycogen phosphorylase inhibitor CP-91149 or co-expression of papilloma virus E7 protein, which is known to bind and inactive tumor suppressor pRb. Regulation of the activity of glycogen metabolizing enzymes, glycogen synthase and phosphorylase and accumulation of glucose 6-P is also examined upon androgen stimulation. The major conclusion is that inhibition of glycogen phosphorylase by CP-91149 suppresses cell growth while enhancing glycogen accumulation in PC3-AR cells as well as in the androgen-dependent prostate cancer cell line LNCaP. The authors hypothesize that inhibitor CP-91149 could be a therapeutic aid for decreasing survival of prostate cancer cells.

While the description of CP-91149 effects on prostate cancer cells is interesting, data on the mechanism of the glycogenic effect of androgen on PC3-AR cells are presented in an appropriate manner that invalidates the corresponding conclusions.

Major comments:

1. Data on glycogen synthase, shown in figure 3A and B, are not presented in an appropriate manner. Units 14C-UDP-Glucose incorp/10-3 cpm have no meaning in terms of levels of enzymatic activity in cells. Furthermore, in the footnote of figure 3, it is not clearly explained what type of GS activity (- G6P, + G6P or the ratio) is shown in panel A.
2. Data on glucose 6-P, in figure 3 C, are not shown in a standard manner. Data are expressed as micromolar, which are probably the concentrations measured in cell extracts. G6P levels (mol or nmol) should be referred to the either the cell count or the total cell protein.
3. Data on glycogen phosphorylase, in figure 4, are expressed as units per min per mg of protein. An international unit of enzyme activity is the amount of enzyme that catalyzes the reaction of a micromol of substance per minute. Therefore, enzyme activity should be either U/mg protein or mol substrate/min/mg protein.
4. The identity of PC3-AR2-V1 and PC3-AR2-V2, PCR-AR2-E72 and PCR-AR2-E73 should be defined somewhere.
5. In discussion, the sentence "these two cell lines demonstrated a response to androgen leading to G1 arrest with a corresponding increase in glycogen content" should be clarified. Since on PCR3-AR the effect is due to androgen stimulation while in LNCaP cells it is androgen withdrawal. Indeed, the authors should comment on the possible basis of this contradictory effect.

Minor comments

1. In the abstract, methods section, the origin of PC3 cells, prostate cancer cells, should be specified.
2. In the background, on page 2, line 8, the fact that only muscle and brain isoforms of GP are allosterically activated by AMP should be acknowledged.
3. In methods, in section "glycogen synthase (GS), phosphorylase …", the composition of the lysis buffer is not stated nor are the methods used to homogenize cell extracts.
4. In methods, in the section mentioned above, in line 11, the sentence Cells from 9, makes no sense
5. In methods the composition of PCA should be defined.
6. In methods the nomenclature of cells used in the figures (PC3-AR-E73 and PC3-AR-V1) should be specified.

**What next?:** Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No

**Declaration of competing interests:**

I have non-financial non-competing interests in relation to this paper.