ABSTRACT

FRA-1 LEVEL IN AGGRESSIVE CANCER CELL LINES UNDER SERUM STARVED STATE AND ITS IMPACT ON AN AUTOCRINE LOOP

By

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Fos related antigen 1 (Fra-1) is a component of the dimeric AP-1 transcription factor that plays an important role in both cell cycle regulation and cancer initiation and progression. Fra-1 is highly increased in invasive types of breast cancer, e.g. MDA-MB-231 cells, when compared to the noninvasive types. Furthermore, Fra-1 in normal fibroblasts show a strictly regulated pattern of expression during G0 to G1 transition in response to growth factors.

My thesis research focused on the significance of the excessively high levels of Fra-1 in serum starved MDA-MB-231 cells, and how this phenomenon is maintained in absence of any external stimuli? To answer this question, we characterized the pattern of expression of Fra-1 and other AP-1 family members as a function of cell cycle in invasive breast cancer cell lines, and compared them to non-invasive and normal cells. One of the major results we observed was the excessive levels of Fra-1 produced by MDA-MB-231 under serum starvation and its maintenance all-through the cell cycle. Also, we identified a role for Fra-1 in keeping MDA-MB -231 cells growing, albeit very slowly.

Additionally, we explored different properties of Fra-1 in MDA-MB-231. Our work showed that Fra-1 is increased in this cell line due to both increased expression and stability. In addition, we found Fra-1 in MDA-MB-231 cells to be both nuclear and cytoplasmic in distribution which was contrary to what was found before in normal cells where Fra-1 is solely nuclear.

Furthermore, we utilized A-Fos, a dominant negative form of Fra-1, to test the role of AP-1 in maintaining the oncogenic and metastatic properties of MDAMB-231 cells. We found that A-Fos completely suppressed the ability of MDA-MB231 cells to grow on agar.

In addition, it attenuated the migration of these cells.

A further major finding of our work demonstrated an ability of MDA-MB-231 cells to secrete in their medium some factors(s) that can induceFra-1, as tested in MCF10A maintained in serum free medium. We found that both the MEK/ERK and MLK mediated pathways are involved in this process. These secreted factors were found to have a significant role in controlling migration and proliferation of neighboring cells, an effect that was mediated through Fra-1. Furthermore, by inserting A-Fos in MDA-MB-231 cells we were able to show that the control of such secretion of these substances is mediated through Fra-1. The ability of these factors to self-control MDA-MB-231 cells is yet to be tested.

Lastly, we extended these results to invasive cancers from other tissue origins, e.g. prostate and colon cancers, suggesting a universal role of Fra-1 in invasive cancers.