Therapeutic potential of estradiol in treating breast cancer

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Breast cancer is the most common cancer among women worldwide and was first shown to be estrogen-dependent by Beatson in 1896 [1]. Estrogen receptors (ERs) are involved in the development of breast cancer and have also been shown to play a vital role in its prognosis and occurrence. These classified hormone positive breast cancer cells contain either ER, progesterone receptors (PR) or both [2]. Two such receptors, ER α and ER β , are used by the female hormone estradiol (E2) to elucidate the downstream signaling pathways.

ER α is the most frequently detected receptor in the breast cancer cells and, upon activation by ligand binding or phosphorylation, regulates its target genes by binding to specific elements or interaction with other transcription factors [3]. The other ER subtype, ER β , has also been reported to be involved in other types of cancers aside from breast cancer [4]. There are two ER β subtypes, ER β 1 and ER β 2, which can only activate transcription after the formation of heterodimer (ER β subtypes with ER β 1) [5]. Interestingly, ER β 2 forms the dimer with ER α preferentially, thus inhibiting its transcriptional activation [5]. In agreement with this, it has been shown that ER β can antagonize ER α dependent transcription [6,7] and that ER α proteolytic degradation is enhanced by an increase in expression of ER β [7].

Treatment and diagnosis of breast cancer have developed a lot in recent years. Treatment of the most prolific hormone receptor positive breast cancers (~70% of breast cancer cases) mainly involves endocrine therapy and chemotherapy [8]. Nonmetastatic breast cancers are eliminated by surgical removal from the breast and regional lymph nodes followed by postoperative radiation. In contrast, metastatic breast cancers are treated with a primary goal of prolonging life and reducing symptoms and there is a poor chance of the treatment being curative. The systematic therapeutic interventions in various breast cancers involve mild to severe side effects, as listed in detail in a review by Waks and Winer [8]. Moreover, most of the systematic therapies are very expensive and inaccessible to people living in developing nations. Given the adverse side effects and high cost of the current effective therapies, scientists have been looking for more effective and natural solutions to this deadly problem for decades. Here, we discuss our recent findings which might give momentum to the understanding of how to use our own hormone against the cells of the body, an old remedy discovered many years ago.

In a recent study, our group [9] analyzed the possible therapeutic potential of the endogenous female hormone E2 in treating breast cancer cells. It has been reported earlier that E2 promotes cell proliferation in a dose dependent manner [10]. In contrast, other studies have shown that low concentration of E2 can cause apoptosis in long-term estrogen-deprived breast cancer cells [11,12]. In this study, we demonstrated the impact of high E2 exposure on cell proliferation and receptor expression which uncovered a novel therapeutic potential and broadened our understanding on the transcriptional regulation of these two well-studied receptors. Here, we have shown that high E2 concentration increases cell proliferation in a time dependent manner and even higher E2 concentration can cause a decline in cell number by inducing apoptosis [9]. Although the potential to induce apoptosis in several

different cell types by E2 has been previously shown by various groups [11–16]; we also reported a differential expression of the receptors ER α , ER β 1 and ER β 2 after E2 treatment.

Another aspect of the research focused on the effect of subculturing both the proliferative capacity and receptor expression of the cell line MCF-7. There has been a growing awareness among the scientific community that the passage number (the number of times cells were transferred onto a new vessel with 80% confluence) affects the properties of the cells under investigation and can lead to misinterpretation of data [17,18]. Our data, consistent with the current understanding, revealed that a higher passage number leads to changes in expression of the receptors ER α , ER β 1 and ER β 2 as well as higher cell proliferation rates after E2 administration [9].

In conclusion, our data suggest that E2 can be used as a therapeutic intervention to treat breast cancer cells though further investigation is required. Furthermore, the side effect or secondary effect on the neighboring cells is an important issue which needs more analysis. Overall, this opens a new window and strengthens an old discovery of the beneficial effect of E2 on cancer cells.

In terms of the future perspective for the evolution of E2 as an effective first line of treatment for ER positive breast cancer patients, there are several factors that would remain vital. First and foremost, it will be very important to analyze similar observations in other established animal model systems, especially in mice cancer model. Subsequently, the optimum concentration of E2 that can serve the purpose without causing much side effects needs to be determined. Second, the underlying mechanism of action remains to be elucidated, once understood this will allow scientists to better design the treatment for breast cancer patients. Next, we also have to examine the options available for administering E2 in a tissue specific (breast) manner so that other tissue types can retain normal function. Finally, inducing more endogenous E2 production would ensure significant benefits rather than administering synthesized E2 externally. Taken together with the already observed effectiveness of this naturally occurring hormone, scientists may not be surprised to see it in the clinical trials for breast cancer treatment in the next 5–10 years.

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