1. **No.**

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2. **Title**

   Effect of Tobacco Smoke Condensate in Breast Cancer and its Molecular Target Therapy via Membrane-type Estrogen Receptor

3. **Period**

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4. **Summary**

Many previous studies showed that tobacco smoking can be a possible risk factor for breast cancer in Japanese women. On the other hand, the effect of tobacco smoke on breast cancer, especially patients who are treated with hormonal therapy, has not been clarified yet. We found tobacco smoke condensate (TSC) showed estrogen-like activity on ER-positive breast cancer cells. Especially ER activity of hormonal therapy resistant cells was strongly activated by TSC, and it was ligand-dependent and –independent manner. The ER activity of the cells obtained from tissue specimens was analyzed, and most of them were significantly activated by TSC, but the level was varied among individuals. Recently, membrane-associated ER (mER) has been reported, and suggested it involve with activation of intra-cellar phosphorylation signaling. We synthesized the specific ligand (Qdot-E2) for mER and analyzed its cellar localization by fractionation and laser-confocal microscope, and confirmed that ER was also localized in plasma membrane. The cell growth and ER activity were up-regulated by addition of Qdot-E2. One-hybrid assay using Qdot-E2 confirmed that mER was localized in plasma membrane. The western blot analysis revealed mER possibly activate nuclear ER and cell proliferation through intracellular phosphorylation signaling pathway, such as MAPK pathway and PI3K/Akt pathway. The effect of Qdot-E2 on cell growth and ER activity were more remarkable in hormonal therapy resistant cells than parental MCF-7 cells. Furthermore, it has been shown that palmitoylation of ER is important for membrane-association of ER. These observations suggest that TSC might be mediated by mER induced by its palmitoylation, and stimulate the phosphorylation signaling pathway, and enhanced growth of breast cancer cells. Tobacco smoking may interfere with hormonal therapy in breast cancer patient and involve with the recurrence of cancer..