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A rare eicosanoid precursor analogue, sciadonic acid (5Z,11Z,14Z–20:3), detected in vivo in hormone positive breast cancer tissue

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ABSTRACT

Numerous genetic alterations of HSA 11q13 are found frequently in several cancer types, including breast cancer (BC). The 11q13 locus harbors FADS2 encoding Δ6 desaturation which is not functional in several cancer cell lines, including hormone positive MCF7 BC cells. In vitro, the non-functional FADS2 activity unmasks 18:2n−6 elongation to 20:2n−6 and Δ5 desaturation by FADS1 to yield 5Z,11Z,14Z–20:3 (sciadonic acid) rather than 5Z,8Z,11Z,14Z–20:4 (arachidonic acid). In this pilot study we aimed to determine whether 5,11,14–20:3 appears *in vivo* in hormone positive human BC tissue. Fatty acids were profiled in surgically removed human breast tumor and adjacent normal tissue (n = 9). Sciadonic acid was detected in three of nine breast tumor samples and was below detect limits in normal breast tissue. The internal Δ8 double bond of arachidonic acid is required for normal eicosanoid synthesis but is missing in sciadonic acid. This pilot study demonstrates for the first time *in vivo* sciadonic acid in hormone positive BC tissue, warranting a larger survey study to further evaluate its appearance and the functional implications.

1. Introduction

Human breast cancer (BC) is the most common cancer among women in US and worldwide, with 2.4 million new cases diagnosed in 2015 [1,2]. It is the second most common cause of death from cancer in women in US, with estimated deaths of 40,610 in 2017 [2]. The large percentage (~70%) of BC are endocrine-related and ovarian sex hormone estrogen is regarded as both initiator and promoter of BC [3–6]. Another ovarian sex hormone progesterone and its metabolites are also considered to promote BC [7,8]. The BC expressing estrogen receptors (ER) and/or progesterone receptors (PR) responds to hormone therapy [9].

The human chromosome 11q13 (HSA 11q13) region is well known to be a major cancer hotspot, harboring potential oncogenic driver(s) [10–12]. Various genetic alterations of 11q13 (amplifications, deletions, insertions and translocations) are frequently found events in several cancer types, such as BC, ovarian cancer, cervical cancer, numerous types of squamous cell carcinoma, endocrine tumors, lymphomas and myelomas [13–20]. The biologically active eicosanoids and their metabolites are linked to tumor progression via several mechanisms including dysregulation of cell signaling [21–24]. In humans fatty acid desaturases, FADS1, FADS2, and FADS3 are three enzyme-coding genes localized to human chromosome 11q13 [25] and are required for the biosynthesis of 20 and 22 carbon polyunsaturated fatty acids (PUFA) that are direct cell signaling eicosanoid and docosanoid precursors [26–28]. In several cancer cell lines, including hormone positive MCF7 BC cells, FADS2 encoded Δ6 desaturation is not functional [29–31].

As FADS2 catalyzes the first critical step for the eicosanoid and docosanoid precursor biosynthesis, we hypothesized the depletion/dysregulation of normal eicosanoid and/or docosanoid cell signaling precursor milieu is a potential oncogenic driving event in certain cancer types, including BC. Wild type MCF7 cells have no bioactivity towards the polyunsaturated fatty acids 18:2n−6 and 18:3n−3, whereas transient transfection with FADS2 restores activity [29]. In normal cells, Δ6 desaturation catalyzing 18:2n−6 → 18:3n−6 masks the lower activity competing elongation pathway 18:2n−6 → 20:2n−6. In MCF7 cells, the absence of Δ6 desaturation activity unmasks elongation to 20:2n−6

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(11,14–20:2), which then accumulates at modest levels. FADS1 coded Δ5 desaturation then operates on 11,14–20:2 → 5,11,14–20:3, sciadonic acid, which is otherwise below detection limits in normal tissue [29,32,33]. The main purpose of the present pilot study is to test for the appearance of the rare (all cis double bonds) 5Z,11Z,14Z–20:3 fatty acid in hormone positive BC tissue *in vivo*, thereby replicating our *in vitro* cell culture findings to provide insight to possible metabolic derangement in fatty acids of hormone positive BC.

2. Materials and methods

2.1. Study approvals

The study was approved by The Cornell University Institutional Review Board and The Cayuga Medical Center at Ithaca Institutional Review Board for human participants. A written informed consent was obtained from all nine women participants in this pilot study. All the nine participants were diagnosed with estrogen receptor (ER) and progesterone receptor (PR) positive breast tumors. From each participant surgically removed fresh 50 mg of the breast tumor and 50 mg of the adjacent noncancerous breast tissues were used for fatty acid analysis.

2.2. Fatty acid analysis

Breast tumor and adjacent normal breast tissues (Fig. 1) were used for fatty acid extraction and analysis. Fatty acid methyl esters (FAME) were prepared using modified one-step method of Garces and Mancha [34] and were analyzed quantitatively using a Hewlett Packard 5890 series II gas chromatograph-flame ionization detector (GC-FID) equipped with a BPX 70 column (25 m, 0.22-mm inner diameter, 0.25 μm film; SGE, Austin, TX) using an equal weight mixture for response factor calibration. The peak structures were positively identified by GC-covalent adduct chemical ionization tandem mass spectrometry (GC-CACI-MS/MS) as previously described [35,36].

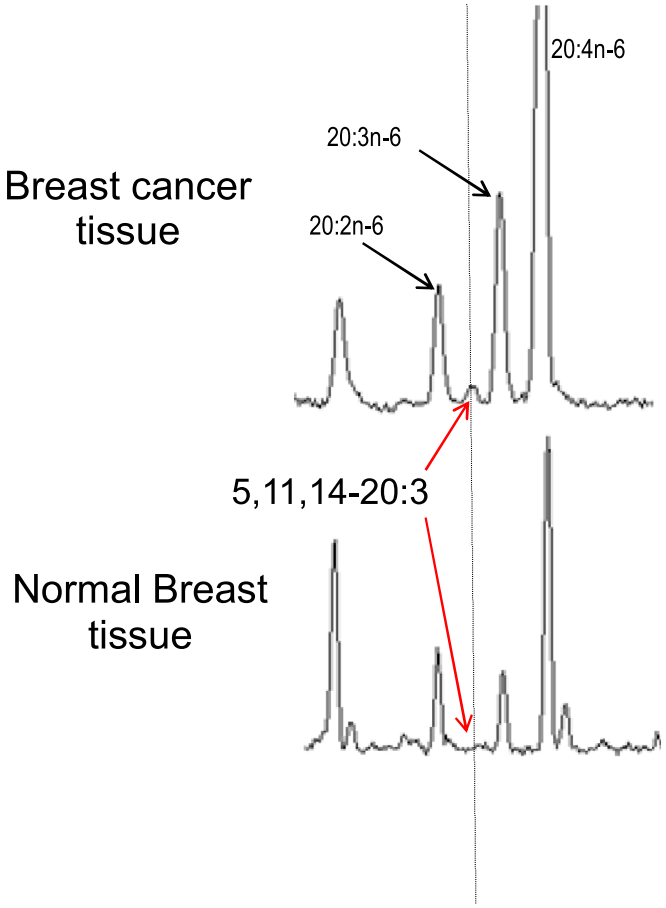

Fig. 2. Gas chromatography results, normalized to the peak for 20:2n − 6, from breast cancer and normal breast tissues. Top) Breast cancer tissue. Unusual 5,11,14–20:3 (sciadonic acid) detected in BC tissue at about 10% (area percent) of the precursor 20:2n − 6. 5,11,14–20:3 was found in three of nine samples. Bottom) Normal breast tissue. 5,11,14–20:3 is below detection limits.

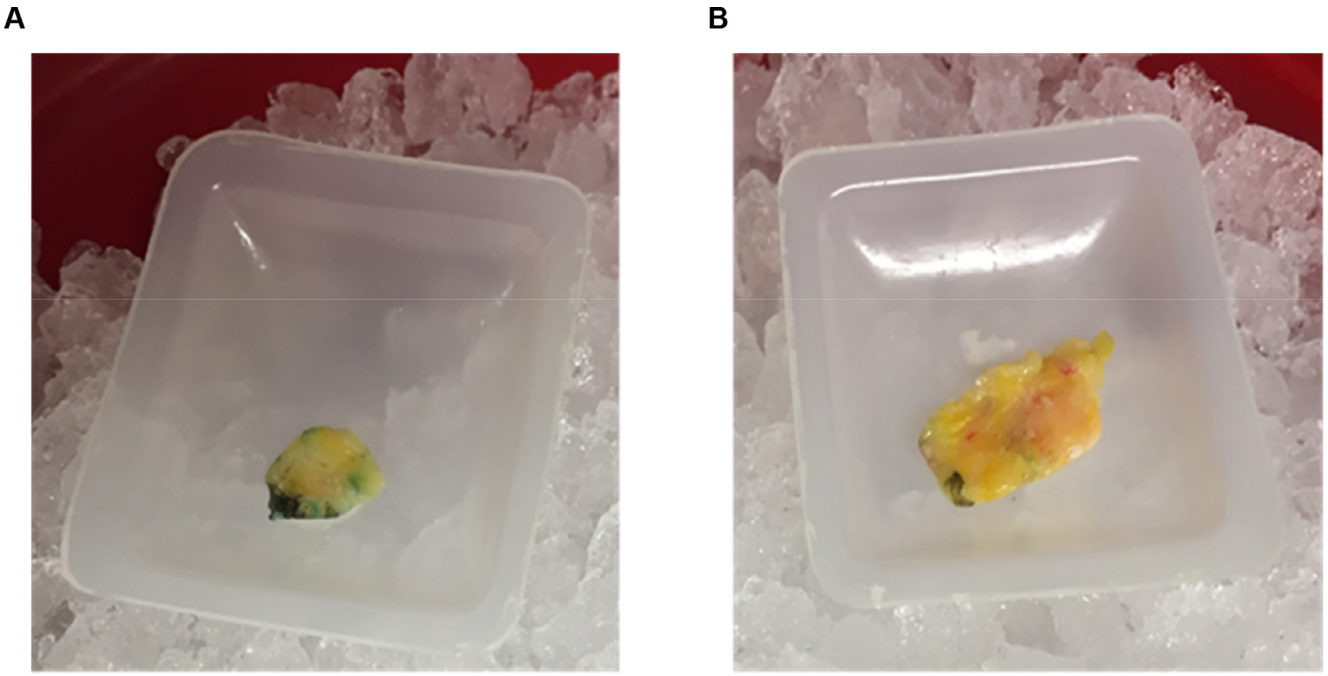

Fig. 1. Surgically removed human breast tissue samples. A) Normal breast tissue B) Breast cancer tissue. Residual blue dye is present in some samples. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)