 doi:10.20944/preprints202210.0206.v1

FADS2 Function at the Major Cancer Hotspot 11q13 Locus Alters Fatty Acid Metabolism in Cancer

Kumar S. D. Kothapalli[1]*, Hui Gyu Park[1], J. Thomas Brenna[1]*

[1]Dell Pediatric Research Institute, Dell Medical School, The University of Texas at Austin, 1400 Barbara Jordan Blvd, Austin, Tx 78723

Running Title: FADS2 function in Cancer

* Corresponding authors.
Kumar Kothapalli, Dell Pediatric Research Institute, Dell Medical School, The University of Texas at Austin, 1400 Barbara Jordan Blvd, Austin, Tx 78723, USA; v. 512-495-5950; kkothapalli@utexas.edu ORCID 0000-0003-0854-1023

J. Thomas Brenna, Dell Pediatric Research Institute, Dell Medical School, The University of Texas at Austin, 1400 Barbara Jordan Blvd, Austin, Tx 78723, USA; v. 512-495-5249; tbrenna@utexas.edu ORCID 0000-0001-9494-4245

Key words. fatty acid desaturases, highly unsaturated fatty acids, unusual unsaturated fatty acids, sciadonic acid, sapienic acid, mead acid

Abstract. The human chromosome 11q13 (HSA 11q13) genomic locus is a major cancer hotspot and has been established as the most frequently altered by amplification in a variety of human cancers. The fatty acid desaturase genes (FADS1, FADS2 and FADS3) localize to the 11q12-13.1 region. FADS2 activity is promiscuous, catalyzing biosynthesis of polyunsaturated and monounsaturated fatty acids, including unsaturated branched chain fatty acids (BCFA) by Δ6, Δ8, and Δ4 desaturation toward at least 16 substrates. Our main aim here is to review known and putative consequences of FADS2 dysregulation due to effects on the 11q13 locus in various cancer types. We searched PubMed and Google Scholar databases for articles that showed 11q13 amplification and studies reporting FADS2 function in various cancer types. FADS2 silencing causes synthesis of sciadonic acid (ScA, 5Z,11Z,14Z-20:3) in MCF7 cells and breast cancer in vivo. 5Z,11Z,14Z-20:3 is structurally identical to the eicosanoid precursor arachidonic acid (5Z,8Z,11Z,14Z–20:4) except it lacks the internal Δ8 double bond required for prostaglandin and leukotriene synthesis, among other eicosanoids. Melanoma, prostate, liver and lung cancer cells insensitive to SCD inhibition show increased FADS2 activity leading to sapienic acid (16:1n-10) biosynthesis from 16:0. Elevated serum mead acid (20:3n-9) levels were found in more than a third of hepatocellular carcinoma patients, indicative of an unsatisfied demand for arachidonic acid, likely as a substrate for eicosanoids. A highly expressed circular RNA (hsa_circ_022382) within an exonic region of FADS2 is associated with shorter overall survival in colorectal cancer patients. Similarly, in lung cancer tissues circFADS2 RNA is highly expressed. Palmitic acid (16:0) is a common substrate for SCD and FADS2. FADS2 circular RNAs are at high levels in colorectal and lung cancer tissues. The evidence thusfar supports an effort for future research on the role of FADS2 as a tumor suppressor in a range of neoplastic disorders.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 14 October 2022 doi:10.20944/preprints202210.0206.v1

Introduction

Cancer is the second leading cause of death in the United States and worldwide estimates show cancer deaths rising to 10 million deaths in 2020 (2, 3). Large-scale cancer genome sequencing efforts have identified both inherited and acquired somatic mutation events as contributors to cancer development (4, 5). The acquired somatic mutations (ASM) include point mutations (e.g. G>T substitution that causes a glycine to valine substitution in codon 12 of the HRAS gene), small insertions and deletions (e.g. EGFR Exon 19 Indel), gene fusions (e.g. C11orf95-RELA at 11q12.1-11q13.3), translocations (e.g. BCR-ABL1 translocation in chronic myeloid leukemia; t(11;14)(q13;q32) in mantle cell lymphoma), structural variations involving deletions or amplifications of genomic material as low as few kilobases of DNA up to loss of partial or entire chromosome (e.g. 11q13 amplification in breast cancer, 11q13 loss in cervical cancer) and epigenetic changes (e.g. *COX2* methylation) (4, 6-13). Several oncogenes map to the 11q13 region which has been established as the most frequently amplified genomic locus in a number of human cancers, including breast, ovarian, head and neck, oral, and esophageal cancer (14-19) and has prognostic significance (20). 11q13 amplification is associated with poor response to cancer immunotherapy and to hyper-progressive disease, highlighting the potential importance of this locus for therapy (21-24). The 11q13 region hosts specialized enzyme-encoding genes required for endogenous biosynthesis of fatty acids that are precursors for signaling molecules known to be critical for progression of many cancers. Our purpose here is to review on a cancer-by-cancer basis the association of the 11q12.1-11q13 region as it may relate to fatty acid metabolism.

Highly Unsaturated Fatty Acids (HUFA) and Desaturases

Omega-3 (ω3 or n-3) and omega-6 (ω6 or n-6), highly unsaturated fatty acids (HUFA), especially n-3 eicosapentaenoic acid (EPA, 20:5n-3), n-3 docosahexaenoic acid (DHA, 22:6n-3) and n-6 arachidonic acid (AA, 20:4n-6, 5Z,8Z,11Z,14Z–20:4) are ubiquitous in mammalian tissue, are metabolically required for human and animal health, especially vision and cognition during various stages of development and aging (25). They are bioactive components of cell membrane phospholipids, natural ligands for nuclear transcription factors, regulate gene expression, and anchor proteins in cell membranes. DHA and AA together constitute more than 25% of CNS fatty acids, serving primarily as membrane structural components, where they can be liberated as precursors to signaling molecules, for instance, eicosanoids and docosanoids. Inhibition of the biosynthesis or receptor-mediated actions remains a prevailing strategy for developing valuable drug targets used over-the-counter, on the model of drugs such as aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs, ibuprofen and naproxen) and leukotriene receptor inhibitors (zafirlukast, montelukast, and zileuton) (25-30).

The nonheme, iron-containing, oxygen-dependent fatty acid desaturase(s) FADS1 and FADS2 are the only means to introduce double bonds into polyunsaturated fatty acids (PUFA) (Figure 1). FADS2 but not FADS1 operates on several saturated and monounsaturated FA (MUFA) as well. In each case, FADS2 and FADS1 catalyzes the introduction of *cis* double bonds at specific positions in a fatty acid chain (Table 1) (31-34). FADS2 also catalyzes biosynthesis of branched chain fatty acids (BCFA) and normal odd chain fatty acid (Table 1) (35). FADS3 is the third member of the FADS gene cluster, positioned tail to tail at a distance of 6.0 kb telomeric to FADS2 (36). Because of its sequence and genomic similarity (12 exons, 11 introns) it was long assumed to be a fatty acid desaturase, however extensive searching revealed activity only toward 11E-18:1→11E,13Z-18:2, a rare fatty acid in mammals (37). Recently we showed FADS3 to be a sphingolipid back-end desaturase (38). Compelling, accumulated data now indicate that all PUFA desaturation is mediated entirely by FADS1 and FADS2 (39).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 14 October 2022 doi:10.20944/preprints202210.0206.v1

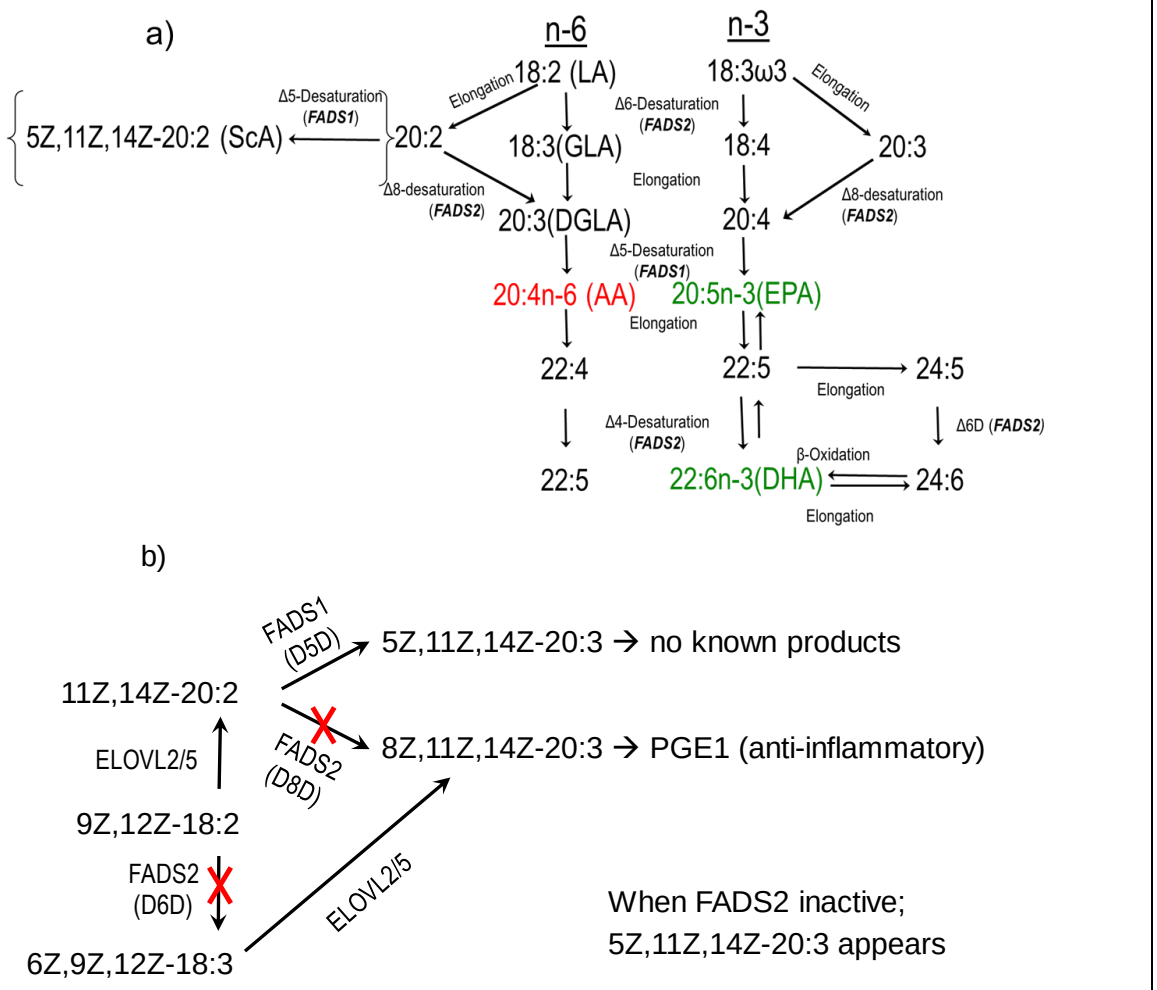

Figure 1. Molecular/biochemical pathway for synthesis of HUFA showing only steps related to 11q12-13.1 resident *FADS1* and *FADS2* coded enzymatic activities. a) Canonical HUFA synthetic pathway in genetically-intact cells. The bracketed step occurs only when FADS2 but not FADS1 is silenced. The major route of synthesis from the dietary essential fatty acid 9Z,12Z-18:2 (linoleic acid, LA) is conversion to 6Z,9Z,12Z-18:3 (GLA) via FADS2-mediated Δ6-desaturation (D6D). A minor route is 9Z,12Z-18:2 elongation to 11Z,14Z-20:2 (20:2n-6) initiated by the action of ELOVL2 or ELOVL5. 20:2n-6 is uniquely a substrate for both FADS1 and FADS2. 11Z,14Z-20:2 via FADS1 mediated Δ5-desaturation (D5D) is converted to 5Z,11Z,14Z-20:3 which has no known downstream products. FADS2 Δ8-desaturases (D8D) 11Z,14Z-20:2 to produce 8Z,11Z,14Z-20:3 (20:3n-6, DGLA) a precursor of the anti-inflammatory PGE1. b) When FADS2 is inactive, for example in certain cancer tissues or cells, 5Z,11Z,14Z-20:3 (ScA) appears, catalyzed by FADS1.

Dysfunctional endogenous and de novo fatty acid synthesis has long been recognized as a characteristic of human cancer(s). Fatty acid products, the biologically active eicosanoids and their metabolites, are linked to tumor progression via several mechanisms including dysregulation of cell signaling and apoptosis (40-42). Eicosanoids are locally acting (paracrine) bioactive signaling lipids derived from AA and EPA (43) and lesser amounts from a few other HUFA. In human and rodents, the products of 3 genes (FADS1, FADS2, and SCD (10q24.31)) introduce double bonds (desaturate) at specific positions within a fatty acid chain (44). FADS2 [EC

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 14 October 2022 doi:10.20944/preprints202210.0206.v1

1.14.19.-] catalyzes the first step in the biosynthesis of HUFA and is a multifunctional even numbered desaturase (31, 34, 35). In several cancer cell lines, the FADS2-mediated first step required for the biosynthesis of eicosanoid precursors is not functional (29, 45, 46).

FADS2 and *FADS1*, the genes mediating synthesis of all HUFA are very different in their substrate specificities and their regulation (39). FADS1 is highly specific, limited to desaturation of 20 carbon PUFA, with its most active product AA. Several lines of evidence indicate that it is primarily

	Substrate	**Activity**
FADS2		
Δ4-desaturation	*22:5n-3 → 22:6n-3*	*Minor*
	22:4n-6 → 22:5n-6	*Minor*
Δ6-desaturation	*18:3n-3 → 18:4n-3*	*Most preferred substrate in normal metabolism*
	18:2n-6 → 18:3n-6	*Preferred substrate in normal metabolism*
	18:1n-9 → 18:2n-9	*Activity unmasked in essential fatty acid deficiency*
	24:5n-3 → 24:6n-3	*Minor, Rodent LCPUFA pathway*
	24:4n-6 → 24:5n-6	*Minor, Rodent LCPUFA pathway*
	16:0 → 16:1n-10	*Tissue specific preference, active in human skin or when SCD is inactive or reach saturation*
	17:0 → 17:1n-11	*Minor*
	iso-16:0 → iso-6Z-16:1	*Minor*
	iso-18:0 → iso-6Z-18:1	*Minor*
	iso-17:0 → iso-6Z-17:1	*Minor*
	anteiso-17:0 → anteiso-6Z-17:1	*Minor*
Δ8-desaturation	*20:1n-9 → 20:2n-9*	*Activity unmasked in essential fatty acid deficiency*
	20:3n-3 → 20:4n-3	*Minor*
	20:2n-6 → 20:3n-6	*Minor*
FADS1		
Δ5-desaturation	*20:3n-6 → 20:4n-6*	*Key activity in normal metabolism*
	20:4n-3 → 20:5n-3	*Preferred substrate in normal metabolism*
	20:2n-6 → 5,11,14-20:3	*Preferred when FADS2 is inactive*
	20:3n-3 → 5,11,14,17-20:4	*Preferred when FADS2 is inactive*
	20:2n-9 → 20:3n-9	*Tissue specific preference, active in human cartilage or during EFA deficiency*
Δ7-desaturation	*20:1n-9 → 7,11-20:2*	*Novel function, minor activity*

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 14 October 2022 doi:10.20944/preprints202210.0206.v1

regulated at the transcriptional level: human cells increase FADS1 expression when treated with statins (47); statin treatment increases AA and decreases upstream precursor LA; circulating AA levels in free-living adults are strongly related to a specific genetic polymorphism, rs66698963 (48, 49), 137 bp downstream of a sterol response element in FADS2 intron 1 (47). Polymorphism status controlling the FADS1-meditated step 20:3→20:4 (AA) also causes all upstream precursors to be depleted and downstream products to be enriched, fully consistent with FADS1 as the pivotal control point in HUFA biosynthesis (39). The FADS1 expression is significantly increased in several primary tumors and even at a higher level in the metastatic and recurrent tumors (50).

FADS2 is a promiscuous enzyme with at least 10 PUFA and 6 saturated fatty acid substrates (Table 1). Its regulation is likely to be tissue specific and far more complex than FADS1. FADS2 mediated desaturation is well recognized as required for synthesis of all HUFA and especially the key neural HUFA docosahexaenoic acid (DHA) where it operates twice in the biochemical pathway. It is also the key desaturase in human skin, where it has long been known to mediate synthesis of 16:1n-10, with trivial name sapienic acid because this fatty acid is rare in the skin of animal models, such as rodents. More recently, FADS2 was demonstrated unequivocally to mediate synthesis of monounsaturated, monomethyl branched chain fatty acids, and one odd chain fatty acid (17:0→17:1) (35). The action of FADS2 is related to the mixture of fatty acid substrates available in the cellular pool at any one time, all competing for the active site (32). As a result, FADS2 action may be dysfunctional when the mixture of substrate fatty acids, originating from diet or de novo synthesis, is abnormal.

11q13 Genomic Region

The genetic composition of human chromosome 11q13 is known to contain hotspots for viral integration, harbor fragile sites, copy number variations (CNV) (Figure 2), and various disease phenotypes, including several types of cancers (51-54). The 11q13 locus is well known to contain fragile sites that are prone to breakage (55). This region has a high frequency of repeats, low GC content, two folate-sensitive fragile sites, potential secondary structures, and a high incidence of cytogenetic and molecular alterations in several cancers (51, 54-57). Structural variations (SV) that alter chromosomal structure and the DNA copy number are increasingly recognized as major contributors to genome variability (58). Copy number changes in the 11q13 region are associated with several cancers such as breast cancer (BC) (59), ovarian cancer (16), melanoma (60), head and neck cancers (61-63), bladder, colorectal, lung, liver and esophageal cancers (16, 53, 64), endocrine tumors of pancreas and duodenum (65), and prostate cancer (66). Chromosomal translocations involving 11q12-13 are seen in mantle cell lymphoma (9), multiple myeloma (67) and renal cell carcinoma (68). A 300 kb deletion within 11q13 region is reported in cervical cancer (12, 57). A breakpoint-rich region on 11q13 was found in neuroblastoma (NB) (69). The 11q13 deletion was increasingly found in relapse and 4S stage NB patients, associated with the development of an aggressive NB phenotype and higher sensitivity to PARP (poly ADP ribose polymerase) inhibitors (69-71). Gene fusions involving C11orf95-RELA at 11q12.1-11q13.3 as a result of chromothripsis is seen in supratentorial ependymomas brain tumors (8). In certain disease conditions, the 11q13 CNV span several mega bases (Mb) of DNA (72, 73).

These and many related observations indicate that the 11q13 region is of particular importance in the etiology of cancer. Despite strong underlying evidence of the involvement of AA and other HUFA in cancer incidence and aggressiveness, silencing of their biosynthetic genes by genetic abnormalities in the 11q13 region have seldom focused on the downstream effects on HUFA composition and the implications for cell-cell signaling. Our purpose here is to collect key references that implicate 11q13 in human cancers, organized according to tissue.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 14 October 2022 doi:10.20944/preprints202210.0206.v1

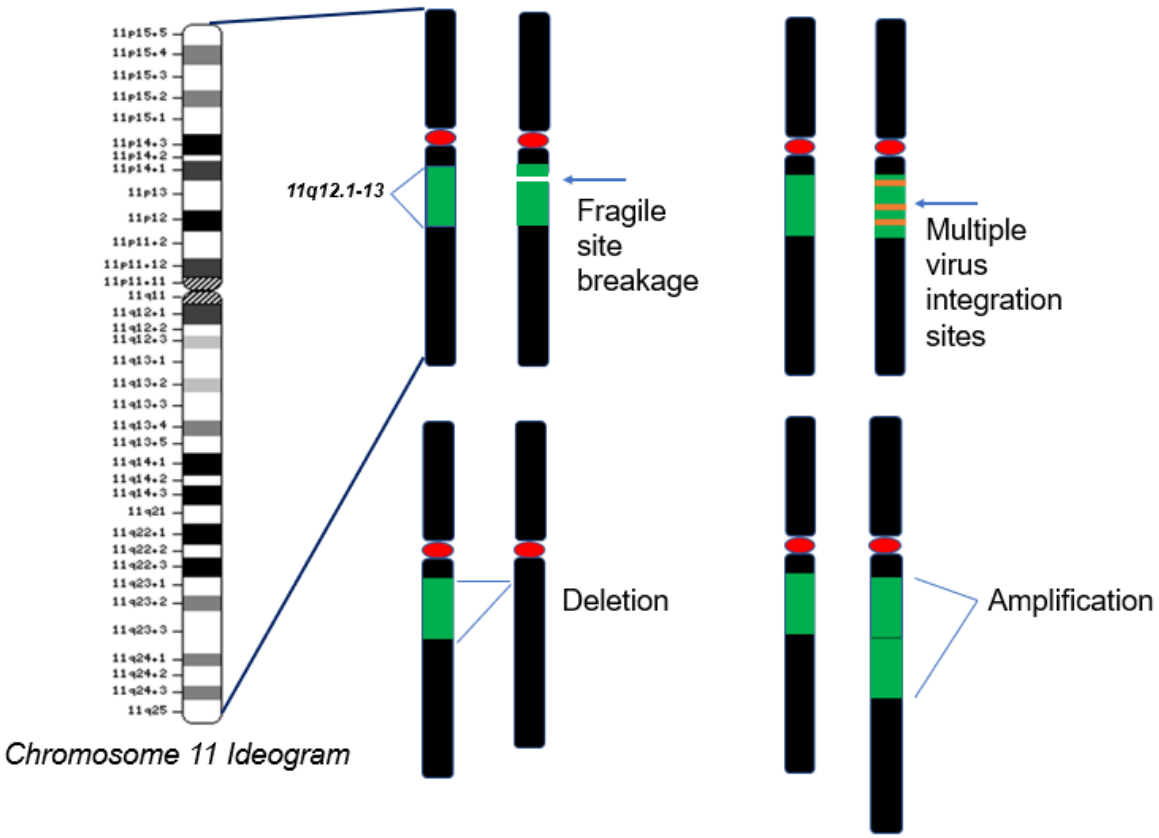

Figure 2. Human chromosome 11 ideogram (1), simplified to illustrate cancer-related genetic events at the 11q12.1-11q13 (green box) cancer hot spot region. Chromosomal breakage at fragile sites, sites for multiple virus integration, deletion and amplification of the region have been described in a wide range of cancers as discussed in the text.

Review method

Our main focus is on FADS2, and to a lesser extent FADS1, in major cancer types showing 11q12-13 amplification. We searched PubMed and Google Scholar databases for peer-reviewed research articles using keywords such as 11q13 cancer, 11q12 cancer, 11q13 specific cancer type (for example 11q13 breast cancer) and 11q12 specific cancer type (for example 11q12 breast cancer). Subsequently, articles that matched our search criteria were fully reviewed and the findings in the articles that showed 11q12-13 amplification are recorded. We also searched PubMed and Google Scholar databases for studies reporting FADS2 or Δ6-desaturase and FADS1 or Δ5-desaturase in various cancer types.

Breast Cancer

Human BC is the most common cancer among women in US and worldwide, with 24% of new cancer cases and 15% of cancer deaths in 2018 (74-76). The 11q13 region is amplified in 15–20% of BC and comprises multiple amplicons highly variable in size, spanning several Mb of DNA from 11q12.2 to 11q14.1 (11, 77-81). Detailed investigation of 11q13 amplification in BC has revealed four core regions within 11q13 that can be amplified independently or together in various combinations (82). A 2010 genome wide association study (GWAS) identified an ER positive BC susceptibility locus on 11q13 (83). A GWAS replication study involving a total of 44,662 cases and 45,502 controls of European descent and 4,076 cases and 2,573 controls of Asian descent identified 11q13 as the strongest susceptibility locus for ER positive BC (84). Comprehensive

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 14 October 2022 doi:10.20944/preprints202210.0206.v1

genomic profiling (CGP) of tumor samples from 255,117 patients of multiple types of advanced cancers showed that 11q13 amplicon is associated with HPV status, and ESR1 and AR alterations (85). A GWAS of hormone related cancers, namely breast, ovarian, and prostate identified 11q12 as a major susceptibility locus for all three cancers (86). A recent study showed amplification of 11q12.3 locus which includes candidate genes *FADS* gene cluster, *MYRF*, *FEN1* and *FTH1* in mucinous BC (87). A GWAS study identified two functional SNPs rs633800 and rs11227311 within the 11q13 region to be associated with human triple negative breast cancer (TNBC) (88). Zhuang, et al. reported identical allelic loss of 11q13 in 15 of 15 microdissected *in situ* and invasive BC (89). A long-range PCR analysis showed a heterozygous 5.5 kb deletion at 11q13 in 28% of African-Americans, but only 5% among Caucasians (55). African-American women have a higher incidence of BC before the age of 40 years, more severe disease phenotype and approximately 40% higher mortality rate compared with Caucasian women (90, 91). Comparative genomic hybridization, fluorescence in situ hybridization (FISH), GWAS and fine mapping studies identified significant 11q13 genetic associations with BC in Chinese, European and African-American women (92-94). 11q13 amplification in BC is associated with estrogen receptor (ER) expression, resistance to endocrine therapy and poor prognosis (15, 81, 95-98). Rosa-Rosa et al. (79) conducted a familial genetic study and identified a candidate region on 11q13 spanning several Mb of DNA to contain a highly penetrant BC gene. Despite all these data, the gene(s) responsible for the emergence of 11q13 amplicon has not been identified. The FADS gene cluster in this region is rarely considered with respect to BC or any other cancers. The loss of FADS2-encoded activities in cancer cells shuts down the HUFA biosynthetic pathway, limiting cell-cell signaling due to elimination of eicosanoid and docosanoid precursor biosynthesis (29, 46).

Cell culture studies in the 1980s and 90s showed anomalous loss of polyunsaturated FA (PUFA) desaturase activity in several cancer cells, including BC MCF7, HeLa and K562 (29, 45, 46). By using unique molecular and lipidomic methodologies, we extended that work to show that *FADS2* is the specific gene that is silenced (29, 99). This metabolic defect was corrected *in vitro* by the transfection of functional FADS2 into MCF7 BC cells (29). Reduced FADS2 expression is seen in BC tissues of patients with poor prognosis (100). Despite the key importance of FADS2 and the loss of its function in several cancer cells, the consequences of FADS2 loss has not been investigated in detail.

Absence of the first required step in the endogenous biosynthesis of omega-6 and omega-3 HUFA, Δ6-desaturation catalyzed by FADS2 (31), leads to synthesis of the unusual unsaturated fatty acid (uUFA) sciadonic acid (ScA; 5Z,11Z,14Z-20:3). ScA is synthesized via an alternative unmasked Δ5-desaturation catalyzed by FADS1 in MCF7 BC cells (Figure 1) (29). ScA replaces much of the normal signaling precursor AA. Importantly, this pathway eliminates synthesis of the anti-inflammatory prostaglandin E1 (PGE1) precursor dihomogamma linolenic acid (DGLA; 20:3n-6) *in vitro* (29). A small pilot study showed 3 out of 9 ER positive breast cancer surgical samples, but not the adjacent noncancerous tissue had ScA (99). ScA was detected in BC tissue at about 10% of the precursor 20:2n-6 FA (99). MCF7 cells also make another uUFA dihomotaxoleic acid (7,11-20:2) via FADS1 when supplemented with 20:1n-9 (33). ScA has been the subject of scattered reports relevant to humans over the years (101-103), whereas we know of no reports of 7,11-20:2 in humans, though it has been reported in nature, in seed lipids of *Taxus chinensis* and *T. baccata* and hardshell clam (104, 105). The 7,11-20:2 molecule is unstudied in normal metabolism but FA with similar structures are known to inhibit topoisomerases required for DNA replication (106).

ScA has structural similarity to AA, but lacks the internal Δ8 double bond (Figure 3). The double bond at position 8 is required for the biosynthesis of eicosanoids, and thus its absence at position

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 14 October 2022 doi:10.20944/preprints202210.0206.v1

8 renders ScA inactive as substrate for biosynthesis of most eicosanoids (107-109). Moreover, the possible action of the ScA as competitive inhibitors of eicosanoid biosynthetic enzymes is unknown, as is the activity of other key eicosanoid synthetic enzymes (e.g. cytochrome P450) whose actions on the uUFA would result in products with unknown activit(ies).

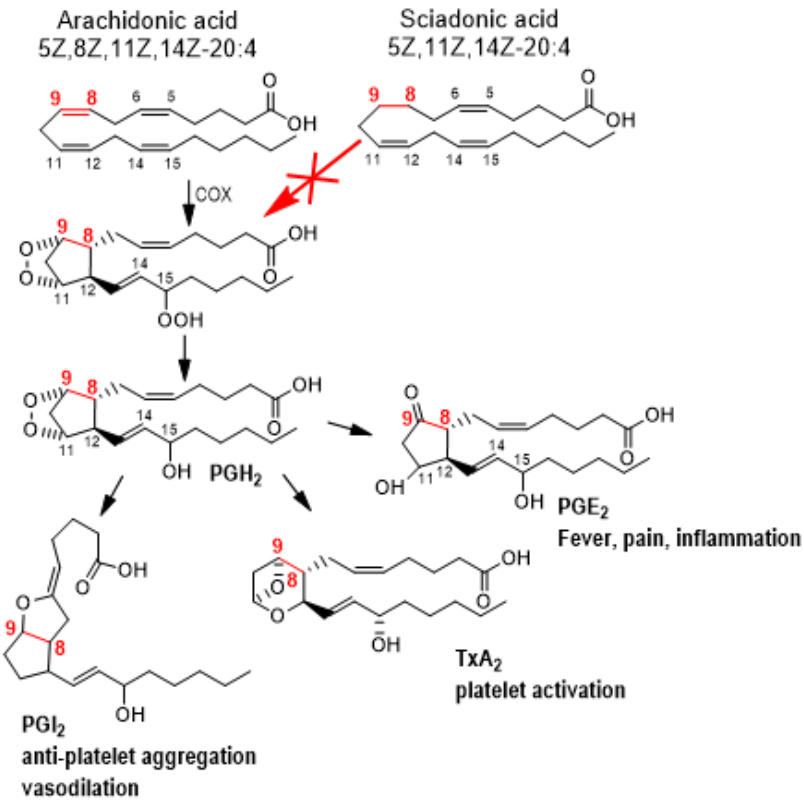

Figure 3. Arachidonic acid (AA) conversion to classical eicosanoids catalyzed by cyclooxygenase (COX) through PGH2 requires the 8-9 double bond. PGH2 is further metabolized into biologically active PGE2, TXA2 and PGI2. Sciadonic acid, missing the 8-9 double bond, cannot be converted to PGH2 or downstream active signaling products.

ScA replaces the eicosanoid precursor AA in the phosphatidylinositol (PI) fraction when ScA is fed in small quantities (101). One of the key features of BC is its dependence on the phosphatidylinositol-3-kinase (PI3K) pathway (110). As the acyl composition of PI is normally highly resistant to dietary modifications. Replacement of normal AA in PI pools by ScA may lead to the production of novel secondary messengers (101). Feeding ScA for 2-weeks resulted in a 50% reduction in the levels of AA in hepatic PI fractions. In the same study ScA was extensively incorporated into hepatic phosphatidylinositol bisphosphate (PIP2), a precursor of second messengers. The PI signaling pathway is frequently altered in BC and alterations in this pathway are associated with resistance to hormone therapy (111, 112). PhospholipaseA2 has poor affinity for ScA which can accumulate in membrane phospholipid (PL) pools even at low doses (113). ScA was shown to reduce ear edema in mice demonstrating epidermal anti-inflammatory properties (102). Apart from this and scattered reports, the effects of ScA substitution for DGLA and AA are unknown. Circulating levels of estrogens and androgens in pre- and postmenopausal women are positively associated with BC risk (114). 17-β-estradiol (E2) significantly inhibits Δ5-desaturation activity and AA levels in a dose dependent manner in isolated normal hepatocytes (115). Letrozole causes a decrease in ScA with concomitant increase in DGLA levels in a dose-dependent manner (116). These changes in metabolite levels demonstrate that restoration of FADS2 mediated Δ8-desaturase function restores normal PUFA levels, pointing to high ScA levels as pathological. Earlier we have shown *in vitro* restoration of normal FADS2 mediated Δ6-desaturase function also eliminates ScA and restores normal GLA/PUFA synthesis (29).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 14 October 2022 doi:10.20944/preprints202210.0206.v1

In normal HUFA biosynthesis (Figure 1a), omega-6 gamma linolenic acid (GLA; 18:3n-6) is the immediate product of linoleic acid (LA; 18:2n-6) desaturation catalyzed by FADS2, exerting cytotoxic actions and modulation of steroid hormone receptors in cancer cells (117, 118). In BC MCF7 cells GLA biosynthesis is hindered due to non-functional FADS2 (Figure 1b). GLA improved the effectiveness of BC chemotherapy by enhancing chemotherapeutic drug cytotoxicity in cell culture experiments (119). Lower GLA and EPA levels in the breast adipose tissue of BC patients are found to be associated with inflammatory BC (120). In human BC studies GLA administration was found to be effective in treating cyclical mastalgia and caused a faster clinical response (117, 118, 121). GLA supplementation along with tamoxifen as primary therapy reduced ER expression in hormone positive BC patients (117). The putative mechanism for this positive response is likely to be preformed GLA bypass the metabolic block created by non-functional FADS2 in certain cancer cells like hormone positive BC MCF7, correcting local deficiency and serving as precursor for downstream HUFA DGLA and AA.

The AA-based eicosanoid signaling pathway has been implicated in the development and progression of BC (122). Elevated AA is associated with increased risk of certain cancers, based on genetic prediction and metabolite studies (123-125). Increased levels of prostaglandins (PG) are seen in BC due to upregulation of cyclooxygenase-2 (COX2), the initial enzyme in eicosanoid biosynthesis (126). COX2 is upregulated in approximately 40% of BC (126). AA release is an important initiating event leading to cellular proliferation, inflammation and eicosanoid biosynthesis (125, 127), whereas omega-3 EPA, the precursor for PGE3, has anti-proliferative effects (128). The cytosolic phospholipase A2 (cPLA2α) catalyzes the hydrolysis of the sn-2 linkage to release AA, leading to the production of prostaglandin E2 (PGE2) via COX2 (129). Activation of COX2 and PGE2 production are linked with BC progression. IHC analysis showed PGE2 was produced by the cells located in close proximity to the tumor cells and not by the tumor cells (130). We speculate that the replacement of AA by ScA in the tumor tissue will increase demand for AA and this could be the reason for enhanced production of PGE2 in the cells located in close proximity to the tumor cells. AA metabolite 20-hydroxyeicosatetraenoic acid (20-HETE) derived via cytochrome *P*-450A (CYP4A) was found to regulate the growth of new blood vessels (131). cPLA2α can be rapidly activated by physiological concentrations of E2 via trans-activation of EGFR/HER2 heterodimers signaling, causing proliferative signals in both ER-positive and ER-negative BC cells (132).

Ovarian Cancer

Ovarian cancer is the second most common cancer in women over the age of 40 and is broadly classified into three main types (epithelial (most common), germ cell, and sex-cord-stromal) (133, 134). A 6-Mb region encompassing several oncogenes within the 11q13 region was amplified in 12 to 25% of ovarian carcinomas (16, 135). A 62-69 Mb region on 11q12–q13 commonly known as malignancy-associated regions of transcriptional activation (MARTA) is amplified in ovarian, breast, colon and prostate cancers (11).

Microsomes prepared from ovarian cancer tissue sample upon incubation with 20:2n-6 showed appearance of ScA (136). The presence of ScA shows that it is synthesized via an alternative, unmasked, Δ5-desaturation catalyzed by FADS1 as seen in BC (29, 99). In the tumor microenvironment substrate specificity between stearoyl CoA desaturase (SCD) and FADS2 is gaining acceptance after we showed first molecular evidence of FADS2 mediated biosynthesis of 16:1n-10 (Figure 4) (32, 137, 138). SCD is highly expressed in various ovarian cancer types and regulates ferroptosis (139). Blocking of SCD by MF-438 or CAY10566 inhibitors induced both ferroptosis and apoptosis (140). *FTH1*, a major intracellular iron storage protein localizes to 11q13 locus adjacent to FADS gene cluster and its expression increased during ferroptosis (141, 142). To the best of our knowledge SCD inhibition in ovarian cancer cells leading to the FADS2

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 14 October 2022 doi:10.20944/preprints202210.0206.v1

mediated biosynthesis of 16:1n-10 has not been reported to date. We speculate ovarian cancer cells can utilize FADS2 mediated 16:1n-10 metabolic pathway to survive, and on that basis ovarian cancer cells would be expected to contain 16:1n-10.

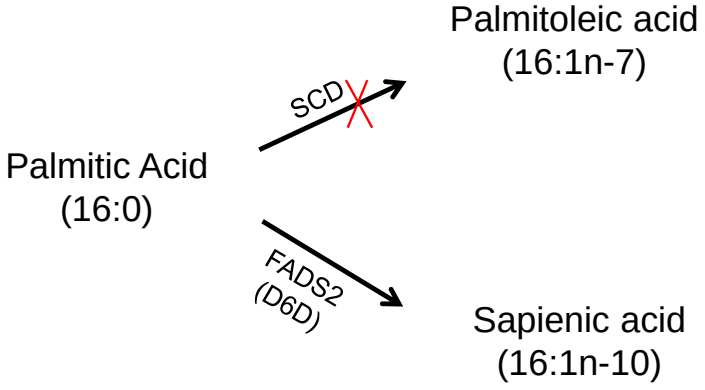

Figure 4. Biosynthesis of monounsaturated fatty acids (MUFA) mediated by SCD and FADS2. SCD mediates 16:0 conversion to 16:1n-7. In cancer cells 16:1n-10 is formed via FADS2 mediated Δ6-desaturation (D6D) when 16:0 is in excess of SCD capacity (or) when SCD is inactive.

Skin Cancer

Skin cancer is the most common cancer in the United States (US) with 1 in 5 Americans developing it by the age of 70 (143). Human skin fatty acid metabolism is unique compared to rodents. In mice, Scd1 and Scd3 are expressed and Scd1 catalyze the conversion of 18:0→18:1n-9 and 16:0→16:1n-7 which are the major unsaturates in mouse skin (144, 145). No human tissue expresses Scd3/SCD3, and human skin does not express SCD1. Rather, FADS2 is highly expressed in human skin where it catalyzes Δ6-desaturation of several saturated fatty acids, most prominently 16:0→16:1n-10, known as sapienic acid because of its rare occurrence in nature apart from human skin. Sapienic acid is the most abundant unsaturated fatty acid in human skin where it function as a component of the innate immune system as an antimicrobial agent (146). FADS2 action is unmasked because of the absence of SCD1. FADS2 recently has been shown to catalyze unsaturation of sebum-resident branched and odd chain fatty acids iso-16:0 →iso-6Z-16:1, iso-17:0 → iso-6Z-17:1, anteiso-17:0 → anteiso-6Z-l7:1 and iso-18:0 → iso-6Z-18:1 (35). Branched chain fatty acids (BCFA) antitumorigenic activity has been described for BC in an isolated report (147), but the significance in skin cancer is unstudied to our knowledge.

Increased copy number changes and amplification of 11q13 are more commonly seen in mucosal, acral and chronic sun-induced damage melanomas (148, 149). Increased copy number gains at 11q13 is associated with poor prognosis in melanoma (60). Anomalous loss of delta-6-desaturation activity was reported in mouse melanoma BL6 cells (150). The two circRNAs derived from the FADS2 gene are the most significantly downregulated in basal cell carcinoma and cutaneous squamous cell carcinoma compared to control non-lesional skin biopsies (151). Mathieu et al. 2012 also reported overexpression of several genes within the 11q12-14 region in melanoma (152). In a 2020 preprint, Lee et al. showed increased FADS2 expression and increased synthesis of 16:1n-10 in metastatic melanoma (153). The liver (HUH7) and lung (A549) cancer cells insensitive to SCD inhibition showed increased FADS2 activity leading to 16:1n-10 biosynthesis (137).

Recently, Lee et al. has proposed blocking FADS2 mediated desaturation as a potential therapy for metastatic melanoma (153). Any strategy to inhibit FADS2 in cancer should be carefully thought as it catalyzes wide range of fatty acid substrates. FADS2 is promiscuous and a multifunctional enzyme which catalyzes even numbered Δ4-, Δ6- and Δ8-desaturation towards normal even chain fatty acids (n-ECFA), normal odd chain fatty acid (n-OCFA) and monomethyl BCFA substrates including eight polyunsaturates, two monounsaturates, one saturate, one n-OCFA, and four BCFA (25, 35). FADS2 loss can affect saturated, monounsaturated,

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 14 October 2022 doi:10.20944/preprints202210.0206.v1

polyunsaturated and branched chain FA levels *in vitro* and *in vivo* (25, 32, 46, 99). If FADS2 has to be inhibited we suggest that it should be targeted to the specific tumor area not disturbing the normal tissue fatty acid composition. Understanding the tumor microenvironment is very important.

Head and Neck Cancers

11q13 amplification is reported in 30 to 62% of the Head and Neck cancers (HNC) (17, 154). HNC usually originate in the squamous cells and is the seventh most common cancer worldwide in 2018 (155). Major anatomical sites of HNC include oral cavity, pharynx, larynx, paranasal sinuses and nasal cavity (155). In recent years tobacco-related HNC decreased worldwide, however, human papillomavirus (HPV)–associated HNC rose from 16.3% in the 1980s to more than 72.7% in the 2000s in the United States (155).

The Cancer Genome Atlas Network identified somatic genetic changes in several HNC (156). Somatic mutations within AA metabolism genes are reported in oral cancer (157) downstream of AA pathway and thus implying that eicosanoid signaling is a contributory factor. Several studies have shown 11q13 amplification is more common in HPV negative HNC (20, 158, 159). A 1.8 Mb critical region on 11q13 was responsible for tumor suppression in nasopharyngeal carcinoma (160). FADS2 was the most downregulated among 20 differentially expressed genes in oral cavity cancer samples (161). FADS1 was differentially expressed in lymph node positive versus lymph node negative primary larynx squamous cell carcinoma (162) and a GWAS identified susceptibility loci for larynx squamous cell carcinoma (rs174549) within FADS1 in Chinese population (163). A genome-wide array comparative genomic hybridization revealed FADS1 presence along with CCND1 in the 11q13 amplicon in HNC (164). The presence of FADS1 in the 11q13 amplicon shows its activity during cell transformation in HNC. Earlier we demonstrated “during cell transformation FADS1 activity would persist when FADS2 is inactive. However, the preferred substrates for FADS1 are not essential fatty acids (18:2n−6 and 18:3n−3), but their elongation products 20:2n−6 and 20:3n−3” leading to the production of uUFA 5,11,14–20:3 and 5,11,14,17–20:4, respectively with unpredictable consequences for cellular communication and signaling (29). In HNC patient’s omega-3 fatty acids supplementation improved immune function, increased body weight and reduced postoperative complications (165, 166). These results imply endogenous synthesis of HUFA is limited in HNC patients.

Bladder Cancer

Bladder cancer (BLC) accounts for over 550,000 cases diagnosed and 20,000 deaths worldwide in 2018 (167, 168). Most cases of BLC are of non-muscle invasive (80%) and the remaining 20% are muscle-invasive (168). 11q13 amplification is reported in up to 10 to 20% of BLC (169, 170). Increased FADS1 expression was found to be associated with high grade, lymphatic, distant metastasis and decreased survival in BLC patients (167). FADS1 expression is also considered as a prognostic biomarker for BLC survival (167, 171). Liu et al. (172) reported higher expression of FADS2 was associated with poor survival in BLC and they have also shown that FADS2 acted as a suppressor factor for ferroptosis. Microsomes extracted from BLC tissue samples upon incubation with 20:2n-6 showed appearance of unusual ScA based on the retention time peak of ScA standard (136). FADS2 encoded Δ6-desaturase activity was decreased in BLC tissues when compared to the normal surrounding tissues (136). Presence of ScA and decreased Δ6-desaturase activity shows compromised FADS2 function as seen in BC (29, 99). Plasma fatty acid levels of anti-inflammatory omega-3 EPA and docosahexaenoic acid (DHA) were found to be significantly reduced in BLC patients from Tunisia (173). DHA significantly inhibited viability of T24 BLC cell line by 22% compared to vehicle control (174). Omega-3 fatty acids inhibited malignant lesions development in a rat model of BLC (175). These results show omega-3 supplementation can correct local omega-3 deficiency in BLC patients.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 14 October 2022 doi:10.20944/preprints202210.0206.v1

Gastroesophageal and Pancreatic Cancers

Gastroesophageal cancers account for 26,650 deaths in the US in 2017 (176). The majority of gastric cancers are adenocarcinomas (GAC), whereas two histological types comprise esophageal cancers, namely esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinomas (EAC) (176). Copy number analysis identified 11q13 amplification in 25% to 48% of ESCC patients (21, 177). 11q13 amplicon in ESCC was found to span 3 to 5 Mb comprising many potential genes (178). Salem et al. reported 11q13 amplification is more common in ESCC when compared to EAC and GAC (176). FADS1 is silenced by methylation in gastric cancer, whereas, it is not methylated in normal gastric mucosa (179). Increased expression levels of *FADS1* and *ELOVL5*, are found in all mesenchymal-type gastric cancer cells, which lead to ferroptosis sensitization (180). Immunohistochemical staining of 251 ESCC patient tissue samples showed higher FADS1 expression in 41.8% (105/251) and lower FADS1 expression in 58.2% (146/251) (181). High levels of inter- and intratumor heterogeneity is commonly seen in ESCC (182). A Mendelian randomization genetically predicted (rs174547 in *FADS1*) model showed higher plasma phospholipid AA concentrations is positively associated with esophageal cancer (odds ratio 1.09; 95% CI 1.02-1.17; P = 0.016) (124). Peri-operative enteral nutrition enriched with 2.2 g EPA/d was found to prevent loss of lean body mass (LBM) in the first 3 weeks after esophageal cancer surgery (183). Fish oil enriched supplementation significantly improved skeletal muscle mass and lean body mass in gastrointestinal cancer patients (184). Higher incidence of 11q13 amplification is seen in pancreatic cancer cells and tumor tissues (185). Several studies in pancreatic cancer patients reviewed by Gorjao et al. 2019 showed oral fish oil supplementation, especially EPA improved body weight, LBM, quality of life and decreased plasma IL-6 levels (186). In the Korean population, the risk of gastric cancer decreased significantly in individuals on higher intakes of omega-3 DHA (187).

Colorectal Cancer

Colorectal cancer (CRC) is the second leading cause of cancer death in the US and third leading cause of cancer death worldwide (188). A 62-69 Mb MARTA region on 11q12–q13 was amplified in CRC (11). A GWAS study involving a total of 14,963 cases and 31,945 controls of East Asian descent identified SNPs within a nearby FADS gene locus to be associated with sporadic CRC risk (189). A study integrating functional genomic/epigenomic and eQTL analyses consisting of 6,024 cases and 10,022 controls, identified G allele of rs174575 within FADS2 intron 1 to be associated with an increased CRC risk (190). The rs174575 acted as an allele specific enhancer to facilitate long-range enhancer–promoter interactions mediated by E2F1 to promote the expression of FADS2 and long noncoding RNA (lncRNA) AP002754.2, showing a novel mechanism by which a functional noncoding variant can modulate expression of multiple genes including lncRNA by long-range genome interactions (190). A circular RNA (circRNAs; hsa_circ_022382) derived from the exonic region of FADS2 gene was highly expressed in CRC patients (191). In CRC patients higher circFADS2 expression levels are associated with distant metastasis and shorter overall survival (191). Circular RNAs are generated by pre-mRNA back splicing (192). We reported in a series of papers that all three FADS are extensively spliced, that splice variants are evolutionarily conserved, and have found functions for two of the four alternative transcripts discovered for FADS2 and FADS1 thusfar (23-27). We speculate some of the FADS splice variants may be expressed differentially in cancer. Earlier we proposed that FADS splice variants can remove omega-3 fatty acids from availability for enzymatic reactions by preferentially binding and sequestering omega-3 fatty acid substrates. This will create a greater demand for omega-3 fatty acids (193). RBC membrane phospholipid fatty acids and rs174537 genotypes data collected from 1,733 individuals who participated in the Tennessee Colorectal Polyp Study showed higher prevalence of the homozygous rs174537 GG genotype and higher AA levels in African Americans compared to European Americans (194).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 14 October 2022 doi:10.20944/preprints202210.0206.v1

Prostate Cancer

Prostate cancer (PCa) affects one in nine men in the USA and is estimated to account for 191,930 new cases and 33,330 deaths in 2020 (195). A 62-69 Mb MARTA region on 11q12–q13 was amplified in PCa (11). Several GWAS found two SNPs rs10896449 and rs7931342 at 11q13 locus to be strongly associated with PCa risk (66, 196, 197), whereas a Japanese GWAS with 7,141 prostate cancer cases and 11,804 controls found rs1938781 at 11q12 to be associated with PCa susceptibility (198). A study in families with both PCa and kidney cancer (KC) showed evidence for a suggestive linkage at 11q12.2 (199). Increased FADS2 gene expression, protein expression and 16:1n-10 biosynthesis was found in the DU145 prostate carcinoma cell line compared to RWPE-1 prostate benign cells (137). In a recent study significantly higher FADS2 expression and increased 16:1n-10 biosynthesis was seen in three prostate cancer cell lines (PC-3, LNCaP, DU145) (200). The cancer cells insensitive to SCD inhibition show increased FADS2 activity and 16:1n-10 biosynthesis (137).

Lung Cancer

Lung cancer is the second most common cancer and is estimated to account for 235,760 new cases and 131,880 deaths in 2021 in the United States (2). 11q13 amplification is seen in up to 13% of lung cancers and chromosomal micro-dissection analysis showed that 11q13 amplification occurs first and other types of structural rearrangements will be followed later (201). A systematic study generated by evaluating GWAS identified variants for lung cancer risk showed rs174549 within FADS1 to be positively associated with lung cancer after multiple correction (202). Increased FADS2 expression was found in 8 out of 10 lung cancer tissue samples compared to adjacent non-cancer tissue (137). The expression of circFADS2 RNA was elevated in lung cancer tissue samples. circFADS2 by acting like a sponge of miR-498 promoted cell proliferation and invasion of lung cancer cells (203). Cachexia is common in the lung cancer patients. Oral omega-3 supplementation preserved body weight in lung cancer patients undergoing chemoradiotherapy (204). Lung cancer patients with higher plasma phospholipid EPA concentrations showed better preservation of body weight (204). These results imply endogenous synthesis of HUFA is limited in lung cancer.

Liver Cancer

Liver cancer is the fourth leading cause of cancer death, with about 841,000 new cases and 782,000 annual deaths worldwide in 2018 (76). Hepatocellular carcinoma (HCC) is the most common type of liver cancer and occurs in patients with chronic liver diseases, such as cirrhosis caused by hepatitis B virus (HBV) or hepatitis C virus (HCV) infections (205). As HBV is a DNA virus it can integrate into host DNA and three out of four HBV positive tumors found to have integration sites at 11q12-13 region (206). At the 11q13 region, HBV is integrated with the protein coding genes (206) and this region was preferentially amplified in HBV positive liver cancers (207). Several transformed cell lines via chemical or viral exposures lost FADS2 mediated Δ6-desaturase activity, however, FADS1 mediated Δ5-desaturase activity was intact (208, 209). Elevated serum Mead acid (20:3n-9) levels were found in 37.5% (9 out of 24) of HCC patients, whereas, Mead acid is undetected in controls (210). Mead acid is generally considered as a marker for essential fatty acids (EFA), namely linoleic acid (LA; 18:2n-6) and α-linolenic acid (ALA; 18:3n-3) deficiency, however, in the 9 HCC patients EFA levels were elevated (210). Figure 5 shows normal Mead acid biosynthesis and Mead acid biosynthesis when FADS2 mediated Δ6-desaturase activity is lost (as seen in 9 out of 24 of HCC patients). Horrobin, 1980 pointed out that EFA accumulation in HCC patients is due to the failure of LA conversion to gamma-linoleic acid (GLA; 18:3n-6) because of the loss of FADS2 mediated Δ6-desaturase activity (209). Due to the loss of Δ6-desaturase activity the metabolic demand for the supply of GLA and DGLA increases and the ability to make anti-inflammatory PGE1 decreases (209). Elongation enzymes

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 14 October 2022 doi:10.20944/preprints202210.0206.v1

are active in several cancer cell lines that lost Δ6-desaturase function and in these cell lines LA is elongated to eicosadienoic acid (20:2n-6) (29, 208). FADS1 action on 20:2n-6 leads to the synthesis of ScA. In liver cancer HepG2 cells, ScA reduced the AA content of the PI fraction which may have influence on PI-originating bioactive lipids (103, 211). An array-based comparative genomic hybridization showed upregulation of both FADS1 and FADS2 in hepatocellular adenomas (212). FADS2 expression levels were increased in the HUH7 liver cancer cell line and tumor samples from the primary liver cancer patients (137).

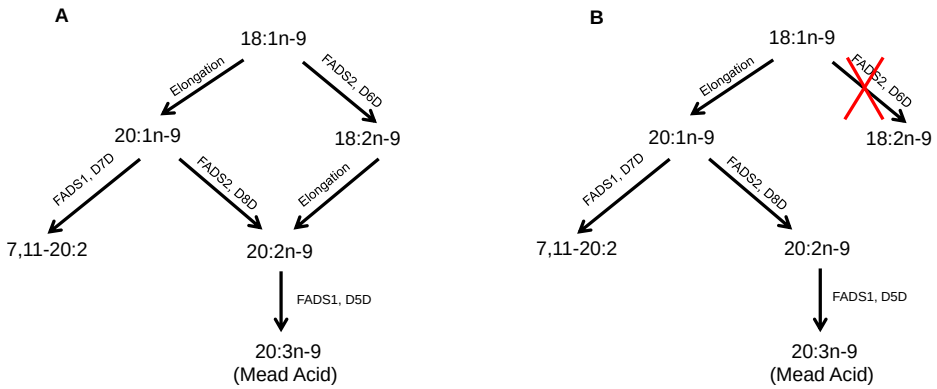

Figure 5. The oleic acid (18:1n-9) metabolic fate. A) Normal metabolism oleic acid gets metabolized to mead acid via two routes 1) Δ6-pathway (FADS2, Δ6-desaturation, D6D) → elongation → Δ5-desaturation (FADS1, D5D) (or) elongation → Δ8-desaturation (FADS2, D8D) → Δ5-desaturation (FADS1, D5D) to biosynthesize Mead acid (20:3n-9). 7,11-20:2 (via Δ7-desaturation, FADS1, D7D) is biosynthesized when 20:1n-9 is in excess of FADS2 (Δ8-desaturase) capacity (or) when FADS2 (Δ8-desaturase) is inactive/residual. B) when FADS2 mediated Δ6-desaturase activity is lost as seen in 9 out of 24 of HCC patients, mead acid seems to be biosynthesized via FADS2 mediated Δ8-desaturation pathway (elongation → Δ8-desaturation (FADS2, D8D) → Δ5-desaturation (FADS1, D5D)).

Brain Cancer

Brain cancer accounts for 296,851 new cases and 241,037 number of deaths worldwide in 2018 (76). Glioma is a common type of brain tumor which accounts for 33 percent of all brain cancers (213). The amplification of 11q12-q22 region has been seen in low-grade and high-grade areas of glioblastoma resection specimen and malignant gliomas (214, 215). Korbecki et al. in peritumoral area of glioblastoma multiforme (GBM) tumor tissues showed decreased FADS2 expression (216). DHA levels were significantly reduced in glioma patients tissue samples (4.8±2.9) compared to normal brain samples (9.2±1.0) (217). The ω-3:ω-6 ratio was found to be significantly altered in malignant glioma tumors due to decreased DHA and increased linoleic acid contents (218). A meta-analysis showed that consumption of fish rich in ω-3 HUFA is associated with a lower risk of brain cancer (219).

11q13 genetic abnormalities and fatty acid changes in different cancer types are presented in Supplementary Table 1.

Conclusions. The human chromosome 11q13 region is one of the most frequently amplified genomic loci in a number of human cancers and in some cancer types, may carry prognostic significance. Several candidate genes have been proposed as drivers of 11q13 amplicon. Despite key importance of FADS2, the consequences of FADS2 dysregulation in several cancers has not been investigated in detail. Several transformed cell lines via chemical or viral exposures lose FADS2 mediated Δ6-desaturase activity, however, FADS1 mediated Δ5-desaturase activity seems to be intact. Due to the loss of FADS2 mediated Δ6-desaturase function EFA cannot be converted to HUFA. The non-functional Δ6-desaturase activity unmasks 18:2n-6 elongation to 20:2n-6. The 20:2n-6 is a unique substrate that possess specificity for FADS2 and FADS1,

similarly, 16:0 possess specificity for SCD and FADS2. Under normal metabolism FADS2 acts on 20:2n-6 to make DGLA, when FADS2 is inactive FADS1 desaturates 20:2n-6 to 5Z,11Z,14Z-20:3. The 5Z,11Z,14Z-20:3 is structurally identical to the eicosanoid precursor arachidonic acid (5Z,8Z,11Z,14Z-20:4) except it lacks the internal Δ8 double bond required for prostaglandin and leukotriene synthesis, among other eicosanoids. In metastatic melanoma, liver and lung cancer tissues and cells when SCD is not active or SCD reach its saturation capacity, FADS2 desaturates 16:0 to 16:1n-10. In normal physiological conditions, higher bioavailability of 18:2n-6 or 18:3n-3 results in decreased bioconversion of 16:0 to 16:1n-10. This shows that FADS2 mediated Δ6-desaturase function is substrate dependent at least in cancer cells. However, in certain cancer types due to the functional loss of FADS2 to catalyze critical first step, 18:2n-6 or 18:3n-3 accumulates. Elevated Mead acid levels are seen in 37% of hepatocellular cancer patients. Interestingly in these patients EFA levels are also elevated, it is possible that 18:2n-6 to 18:3n-6 conversion mediated by FADS2 is defective. FADS2 circular RNAs are highly expressed in colorectal and lung cancer tissues. This review provides an impetus to better understanding the role of FADS2 as a tumor suppressor in neoplastic disorders.

Acknowledgments. This review was supported by NIH grant R01 AT007003 from the National Center for Complementary and Integrative Health (NCCIH). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. We thank Niharika Kothapalli, University of Texas at Dallas for helping with literature search.

Supplementary Table 1. 11q13 genetic abnormalities and fatty acid changes in different cancer types

Cancer Type	11q13 Genetic Abnormalities	Fatty Acid Anomalies
Breast	Amplification	Sciadonic acid (ScA; 5Z,11Z,14Z-20:3)
Ovarian	Amplification	Sciadonic acid (ScA; 5Z,11Z,14Z-20:3)
Skin	Increased copy number changes and amplification, circRNAs	Sapienic acid (16:1n-10)
Head and Neck	Amplification	Sciadonic acid (ScA; 5Z,11Z,14Z-20:3)?
Bladder	Amplification	Sciadonic acid (ScA; 5Z,11Z,14Z-20:3)
Gastroesophageal and Pancreatic	Amplification	Sciadonic acid (ScA; 5Z,11Z,14Z-20:3)?
Colorectal	Amplification, circRNAs	Sciadonic acid (ScA; 5Z,11Z,14Z-20:3)?
Prostate	Amplification	Sapienic acid (16:1n-10)
Lung	Amplification, circRNAs	Sciadonic acid (ScA; 5Z,11Z,14Z-20:3)?
Liver	Hepatitis B virus (HBV)	Mead acid (20:3n-9)
Brain	Amplification	Sciadonic acid (ScA; 5Z,11Z,14Z-20:3)?

 doi:10.20944/preprints202210.0206.v1

References.

1. N. M. viewer, Ideogram of human chromosome 11. G-banding pattern at the 850 band resolution. *https://commons.wikimedia.org/wiki/File:Human_chromosome_11_-_ideogram_from_NCBI_Map_viewer.png* (2015).
2. R. L. Siegel, K. D. Miller, H. E. Fuchs, A. Jemal, Cancer Statistics, 2021. *CA Cancer J Clin* **71**, 7-33 (2021).
3. H. Sung *et al.*, Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 10.3322/caac.21660 (2021).
4. J. G. Tate *et al.*, COSMIC: the Catalogue Of Somatic Mutations In Cancer. *Nucleic Acids Res* **47**, D941-D947 (2019).
5. T. Qing *et al.*, Germline variant burden in cancer genes correlates with age at diagnosis and somatic mutation burden. *Nat Commun* **11**, 2438 (2020).
6. I. A. Prior, P. D. Lewis, C. Mattos, A comprehensive survey of Ras mutations in cancer. *Cancer Res* **72**, 2457-2467 (2012).
7. J. Su *et al.*, Molecular characteristics and clinical outcomes of EGFR exon 19 indel subtypes to EGFR TKIs in NSCLC patients. *Oncotarget* **8**, 111246-111257 (2017).
8. M. Zhang *et al.*, Genomic Landscape of Intramedullary Spinal Cord Gliomas. *Sci Rep* **9**, 18722 (2019).
9. P. Jares, D. Colomer, E. Campo, Genetic and molecular pathogenesis of mantle cell lymphoma: perspectives for new targeted therapeutics. *Nat Rev Cancer* **7**, 750-762 (2007).
10. E. Jabbour, H. Kantarjian, Chronic myeloid leukemia: 2018 update on diagnosis, therapy and monitoring. *Am J Hematol* **93**, 442-459 (2018).
11. G. V. Glinsky, Y. A. Ivanova, A. B. Glinskii, Common malignancy-associated regions of transcriptional activation (MARTA) in human prostate, breast, ovarian, and colon cancers are targets for DNA amplification. *Cancer Lett* **201**, 67-77 (2003).
12. E. S. Srivatsan *et al.*, Localization of deletion to a 300 Kb interval of chromosome 11q13 in cervical cancer. *Oncogene* **21**, 5631-5642 (2002).
13. M. Toyota *et al.*, Aberrant methylation of the Cyclooxygenase 2 CpG island in colorectal tumors. *Cancer Res* **60**, 4044-4048 (2000).
14. P. Schraml *et al.*, Tissue microarrays for gene amplification surveys in many different tumor types. *Clin Cancer Res* **5**, 1966-1975 (1999).
15. C. J. Ormandy *et al.*, Amplification, expression, and steroid regulation of the preprogalanin gene in human breast cancer. *Cancer Res* **58**, 1353-1357 (1998).
16. L. A. Brown *et al.*, Amplification of 11q13 in ovarian carcinoma. *Genes Chromosomes Cancer* **47**, 481-489 (2008).
17. P. Ramos-Garcia *et al.*, Relevance of chromosomal band 11q13 in oral carcinogenesis: An update of current knowledge. *Oral Oncol* **72**, 7-16 (2017).
18. C. R. Leemans, B. J. Braakhuis, R. H. Brakenhoff, The molecular biology of head and neck cancer. *Nat Rev Cancer* **11**, 9-22 (2011).
19. A. Ooi *et al.*, Amplicons in breast cancers analyzed by multiplex ligation-dependent probe amplification and fluorescence in situ hybridization. *Hum Pathol* **85**, 33-43 (2019).
20. M. C. Barros-Filho *et al.*, Oncogenic drivers in 11q13 associated with prognosis and response to therapy in advanced oropharyngeal carcinomas. *Oral Oncol* **83**, 81-90 (2018).
21. F. Wang *et al.*, Association of frequent amplification of chromosome 11q13 in esophageal squamous cell cancer with clinical benefit to immune check point blockad. *J Clin Oncol* **37 (Suppl. 15)**, 4036 (2019).
22. S. Dou *et al.*, EGFR Mutation and 11q13 Amplification Are Potential Predictive Biomarkers for Immunotherapy in Head and Neck Squamous Cell Carcinoma. *Front Immunol* **13**, 813732 (2022).

23. H. Zhang *et al.*, The association of chromosome 11q13 amplification with the hyperprogressive disease in unresectable hepatocellular carcinoma patients underwent the immunotherapy. *Journal of Clinical Oncology* **40**, e16156-e16156 (2022).
24. X. T. L. F. G. C. W. G. F. Q. J. W. J. G. L. C. P. Z. W. S. K. W. W. Wang, Higher level of tumor mutational burden and 11q13 amplification in Chinese hepatocellular carcinoma patients. *Cancer Research* **78** 4349 (2018).
25. K. S. D. Kothapalli, H. G. Park, J. T. Brenna, Polyunsaturated fatty acid biosynthesis pathway and genetics. implications for interindividual variability in prothrombotic, inflammatory conditions such as COVID-19(,, bigstar, bigstar bigstar). *Prostaglandins Leukot Essent Fatty Acids* **162**, 102183 (2020).
26. W. Wahli, L. Michalik, PPARs at the crossroads of lipid signaling and inflammation. *Trends Endocrinol Metab* **23**, 351-363 (2012).
27. S. D. Clarke, The multi-dimensional regulation of gene expression by fatty acids: polyunsaturated fats as nutrient sensors. *Curr Opin Lipidol* **15**, 13-18 (2004).
28. E. A. Dennis, P. C. Norris, Eicosanoid storm in infection and inflammation. *Nat Rev Immunol* **15**, 511-523 (2015).
29. W. J. Park, K. S. Kothapalli, P. Lawrence, J. T. Brenna, FADS2 function loss at the cancer hotspot 11q13 locus diverts lipid signaling precursor synthesis to unusual eicosanoid fatty acids. *PLoS One* **6**, e28186 (2011).
30. N. Morina, G. Bocari, A. Iljazi, K. Hyseini, G. Halac, Maximum Time of the Effect of Antileukotriene - Zileuton in Treatment of Patients with Bronchial Asthma. *Acta Inform Med* **24**, 16-19 (2016).
31. H. G. Park, W. J. Park, K. S. Kothapalli, J. T. Brenna, The fatty acid desaturase 2 (FADS2) gene product catalyzes Delta4 desaturation to yield n-3 docosahexaenoic acid and n-6 docosapentaenoic acid in human cells. *FASEB J* **29**, 3911-3919 (2015).
32. H. G. Park *et al.*, Palmitic acid (16:0) competes with omega-6 linoleic and omega-3 a-linolenic acids for FADS2 mediated Delta6-desaturation. *Biochim Biophys Acta* **1861**, 91-97 (2016).
33. H. G. Park *et al.*, The role of fatty acid desaturase (FADS) genes in oleic acid metabolism: FADS1 Delta7 desaturates 11-20:1 to 7,11-20:2. *Prostaglandins Leukot Essent Fatty Acids* **128**, 21-25 (2018).
34. J. Y. Zhang, K. S. Kothapalli, J. T. Brenna, Desaturase and elongase-limiting endogenous long-chain polyunsaturated fatty acid biosynthesis. *Curr Opin Clin Nutr Metab Care* **19**, 103-110 (2016).
35. Z. Wang *et al.*, Fatty acid desaturase 2 (FADS2) but not FADS1 desaturates branched chain and odd chain saturated fatty acids. *Biochim Biophys Acta Mol Cell Biol Lipids* **1865**, 158572 (2020).
36. A. Marquardt, H. Stohr, K. White, B. H. Weber, cDNA cloning, genomic structure, and chromosomal localization of three members of the human fatty acid desaturase family. *Genomics* **66**, 175-183 (2000).
37. C. Garcia *et al.*, Conversion of dietary trans-vaccenic acid to trans11,cis13-conjugated linoleic acid in the rat lactating mammary gland by Fatty Acid Desaturase 3-catalyzed methyl-end Delta13-desaturation. *Biochem Biophys Res Commun* **505**, 385-391 (2018).
38. G. Karsai *et al.*, FADS3 is a Delta14Z sphingoid base desaturase that contributes to gender differences in the human plasma sphingolipidome. *J Biol Chem* **295**, 1889-1897 (2020).
39. J. T. Brenna, K. S. D. Kothapalli, New understandings of the pathway of long-chain polyunsaturated fatty acid biosynthesis. *Curr Opin Clin Nutr Metab Care* **25**, 60-66 (2022).
40. N. Zaidi *et al.*, Lipogenesis and lipolysis: the pathways exploited by the cancer cells to acquire fatty acids. *Prog Lipid Res* **52**, 585-589 (2013).
41. D. Wang, R. N. Dubois, Eicosanoids and cancer. *Nat Rev Cancer* **10**, 181-193 (2010).
42. E. R. Greene, S. Huang, C. N. Serhan, D. Panigrahy, Regulation of inflammation in cancer by eicosanoids. *Prostaglandins Other Lipid Mediat* **96**, 27-36 (2011).

43. P. C. Calder, Omega-3 fatty acids and inflammatory processes: from molecules to man. *Biochem Soc Trans* 10.1042/BST20160474 (2017).
44. M. T. Nakamura, T. Y. Nara, Structure, function, and dietary regulation of delta6, delta5, and delta9 desaturases. *Annu Rev Nutr* **24**, 345-376 (2004).
45. S. I. Grammatikos, P. V. Subbaiah, T. A. Victor, W. M. Miller, Diversity in the ability of cultured cells to elongate and desaturate essential (n-6 and n-3) fatty acids. *Ann N Y Acad Sci* **745**, 92-105 (1994).
46. A. Jaudszus *et al.*, Loss of FADS2 function severely impairs the use of HeLa cells as an in vitro model for host response studies involving fatty acid effects. *PLoS One* **9**, e115610 (2014).
47. H. T. Reardon *et al.*, Insertion-deletions in a FADS2 intron 1 conserved regulatory locus control expression of fatty acid desaturases 1 and 2 and modulate response to simvastatin. *Prostaglandins Leukot Essent Fatty Acids* **87**, 25-33 (2012).
48. K. S. Kothapalli *et al.*, Positive Selection on a Regulatory Insertion-Deletion Polymorphism in FADS2 Influences Apparent Endogenous Synthesis of Arachidonic Acid. *Mol Biol Evol* **33**, 1726-1739 (2016).
49. P. Li *et al.*, A regulatory insertion-deletion polymorphism in the FADS gene cluster influences PUFA and lipid profiles among Chinese adults: a population-based study. *Am J Clin Nutr* **107**, 867-875 (2018).
50. G. Heravi *et al.*, Fatty acid desaturase 1 (FADS1) is a cancer marker for patient survival and a potential novel target for precision cancer treatment. *Front Oncol* **12**, 942798 (2022).
51. J. Koreth, C. J. Bakkenist, J. O. McGee, Chromosomes, 11Q and cancer: a review. *J Pathol* **187**, 28-38 (1999).
52. A. R. Schroder *et al.*, HIV-1 integration in the human genome favors active genes and local hotspots. *Cell* **110**, 521-529 (2002).
53. X. Huang, S. M. Gollin, S. Raja, T. E. Godfrey, High-resolution mapping of the 11q13 amplicon and identification of a gene, TAOS1, that is amplified and overexpressed in oral cancer cells. *Proc Natl Acad Sci U S A* **99**, 11369-11374 (2002).
54. K. Debacker *et al.*, The molecular basis of the folate-sensitive fragile site FRA11A at 11q13. *Cytogenet Genome Res* **119**, 9-14 (2007).
55. K. Zainabadi *et al.*, One in four individuals of African-American ancestry harbors a 5.5kb deletion at chromosome 11q13.1. *Genomics* **103**, 276-287 (2014).
56. A. H. Puspurs, E. Baker, D. F. Callen, A. Fratini, G. R. Sutherland, Translocation breakpoint in t(11;14) in B-cell leukemia is not at the rare fragile site at 11q13.3. *Cancer Genet Cytogenet* **31**, 25-30 (1988).
57. K. Zainabadi *et al.*, A 700-kb physical and transcription map of the cervical cancer tumor suppressor gene locus on chromosome 11q13. *Genomics* **85**, 704-714 (2005).
58. M. E. Hurles, E. T. Dermitzakis, C. Tyler-Smith, The functional impact of structural variation in humans. *Trends Genet* **24**, 238-245 (2008).
59. J. R. Kutasovic *et al.*, Breast cancer metastasis to gynaecological organs: a clinico-pathological and molecular profiling study. *J Pathol Clin Res* **5**, 25-39 (2019).
60. P. Gerami *et al.*, Copy number gains in 11q13 and 8q24 [corrected] are highly linked to prognosis in cutaneous malignant melanoma. *J Mol Diagn* **13**, 352-358 (2011).
61. D. Muller *et al.*, Amplification of 11q13 DNA markers in head and neck squamous cell carcinomas: correlation with clinical outcome. *Eur J Cancer* **33**, 2203-2210 (1997).
62. M. E. Williams *et al.*, Chromosome 11Q13 amplification in head and neck squamous cell carcinoma. *Arch Otolaryngol Head Neck Surg* **119**, 1238-1243 (1993).
63. C. Jin *et al.*, Molecular cytogenetic characterization of the 11q13 amplicon in head and neck squamous cell carcinoma. *Cytogenet Genome Res* **115**, 99-106 (2006).
64. J. Bartkova, J. Lukas, M. Strauss, J. Bartek, The PRAD-1/cyclin D1 oncogene product accumulates aberrantly in a subset of colorectal carcinomas. *Int J Cancer* **58**, 568-573 (1994).

65. L. V. Debelenko *et al.*, Allelic deletions on chromosome 11q13 in multiple endocrine neoplasia type 1-associated and sporadic gastrinomas and pancreatic endocrine tumors. *Cancer Res* **57**, 2238-2243 (1997).
66. S. L. Zheng *et al.*, Two independent prostate cancer risk-associated Loci at 11q13. *Cancer Epidemiol Biomarkers Prev* **18**, 1815-1820 (2009).
67. D. Ronchetti *et al.*, Molecular analysis of 11q13 breakpoints in multiple myeloma. *Blood* **93**, 1330-1337 (1999).
68. N. J. Farber *et al.*, Renal cell carcinoma: the search for a reliable biomarker. *Transl Cancer Res* **6**, 620-632 (2017).
69. V. Mlakar *et al.*, 11q deletion in neuroblastoma: a review of biological and clinical implications. *Mol Cancer* **16**, 114 (2017).
70. A. Juan Ribelles *et al.*, Clinical Features of Neuroblastoma With 11q Deletion: An Increase in Relapse Probabilities In Localized And 4S Stages. *Sci Rep* **9**, 13806 (2019).
71. E. Sanmartin *et al.*, Deletion of 11q in Neuroblastomas Drives Sensitivity to PARP Inhibition. *Clin Cancer Res* **23**, 6875-6887 (2017).
72. C. Rodriguez *et al.*, Amplification of the BRCA2 pathway gene EMSY in sporadic breast cancer is related to negative outcome. *Clin Cancer Res* **10**, 5785-5791 (2004).
73. J. Karlseder *et al.*, Patterns of DNA amplification at band q13 of chromosome 11 in human breast cancer. *Genes Chromosomes Cancer* **9**, 42-48 (1994).
74. C. Global Burden of Disease Cancer *et al.*, Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. *JAMA Oncol* **3**, 524-548 (2017).
75. R. L. Siegel, K. D. Miller, A. Jemal, Cancer Statistics, 2017. *CA Cancer J Clin* **67**, 7-30 (2017).
76. F. Bray *et al.*, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* **68**, 394-424 (2018).
77. R. Lidereau *et al.*, Amplification of the int-2 gene in primary human breast tumors. *Oncogene Res* **2**, 285-291 (1988).
78. N. O'Brien *et al.*, Mammaglobin a: a promising marker for breast cancer. *Clin Chem* **48**, 1362-1364 (2002).
79. J. M. Rosa-Rosa *et al.*, A 7 Mb region within 11q13 may contain a high penetrance gene for breast cancer. *Breast Cancer Res Treat* **118**, 151-159 (2009).
80. M. Bocanegra *et al.*, Focal amplification and oncogene dependency of GAB2 in breast cancer. *Oncogene* **29**, 774-779 (2010).
81. E. Karlsson *et al.*, High-resolution genomic analysis of the 11q13 amplicon in breast cancers identifies synergy with 8p12 amplification, involving the mTOR targets S6K2 and 4EBP1. *Genes Chromosomes Cancer* **50**, 775-787 (2011).
82. C. J. Ormandy, E. A. Musgrove, R. Hui, R. J. Daly, R. L. Sutherland, Cyclin D1, EMS1 and 11q13 amplification in breast cancer. *Breast Cancer Res Treat* **78**, 323-335 (2003).
83. C. Turnbull *et al.*, Genome-wide association study identifies five new breast cancer susceptibility loci. *Nat Genet* **42**, 504-507 (2010).
84. D. Lambrechts *et al.*, 11q13 is a susceptibility locus for hormone receptor positive breast cancer. *Hum Mutat* **33**, 1123-1132 (2012).
85. A. B. Schrock *et al.*, Pan-cancer genomic landscape of the cyclin D1/FGF3,4,19 (11q13) amplicon including associations with HPV status, and ESR1 and AR alterations. *Annals of Oncology* **30**, v29 (2019).
86. S. P. Kar *et al.*, Genome-Wide Meta-Analyses of Breast, Ovarian, and Prostate Cancer Association Studies Identify Multiple New Susceptibility Loci Shared by at Least Two Cancer Types. *Cancer Discov* **6**, 1052-1067 (2016).
87. K. Lu *et al.*, Clinicopathological and genomic features of breast mucinous carcinoma. *Breast* **53**, 130-137 (2020).

88. K. S. Purrington *et al.*, Genome-wide association study identifies 25 known breast cancer susceptibility loci as risk factors for triple-negative breast cancer. *Carcinogenesis* **35**, 1012-1019 (2014).
89. Z. Zhuang, M. J. Merino, R. Chuaqui, L. A. Liotta, M. R. Emmert-Buck, Identical allelic loss on chromosome 11q13 in microdissected in situ and invasive human breast cancer. *Cancer Res* **55**, 467-471 (1995).
90. L. C. Richardson, S. J. Henley, J. W. Miller, G. Massetti, C. C. Thomas, Patterns and Trends in Age-Specific Black-White Differences in Breast Cancer Incidence and Mortality - United States, 1999-2014. *MMWR Morb Mortal Wkly Rep* **65**, 1093-1098 (2016).
91. D. R. Williams, S. A. Mohammed, A. E. Shields, Understanding and effectively addressing breast cancer in African American women: Unpacking the social context. *Cancer* **122**, 2138-2149 (2016).
92. E. A. Ruiz-Narvaez *et al.*, Admixture Mapping of African-American Women in the AMBER Consortium Identifies New Loci for Breast Cancer and Estrogen-Receptor Subtypes. *Front Genet* **7**, 170 (2016).
93. J. Zhang, H. Zhang, X. Xu, M. Wang, Z. Yu, Comparative genomic hybridization analysis of invasive ductal breast carcinomas in the Chinese population. *Oncol Lett* **10**, 2100-2106 (2015).
94. A. B. Ortiz *et al.*, Prognostic significance of cyclin D1 protein expression and gene amplification in invasive breast carcinoma. *PLoS One* **12**, e0188068 (2017).
95. V. Fantl *et al.*, Gene amplification on chromosome band 11q13 and oestrogen receptor status in breast cancer. *Eur J Cancer* **26**, 423-429 (1990).
96. F. S. Kenny *et al.*, Overexpression of cyclin D1 messenger RNA predicts for poor prognosis in estrogen receptor-positive breast cancer. *Clin Cancer Res* **5**, 2069-2076 (1999).
97. P. G. Roy *et al.*, High CCND1 amplification identifies a group of poor prognosis women with estrogen receptor positive breast cancer. *Int J Cancer* **127**, 355-360 (2010).
98. C. Park *et al.*, Integrative molecular profiling identifies a novel cluster of estrogen receptor-positive breast cancer in very young women. *Cancer Sci* **110**, 1760-1770 (2019).
99. H. G. Park *et al.*, A Rare Eicosanoid Precursor Analogue, Sciadonic Acid (5Z,11Z,14Z-20:3), Detected In Vivo in Hormone Positive Breast Cancer Tissue. *PLEFA*, DOI: https://doi.org/10.1016/j.plefa.2018.1005.1002 (2018).
100. J. Lane, R. E. Mansel, W. G. Jiang, Expression of human delta-6-desaturase is associated with aggressiveness of human breast cancer. *Int J Mol Med* **12**, 253-257 (2003).
101. A. Berger, J. B. German, Extensive incorporation of dietary delta-5,11,14 eicosatrienoate into the phosphatidylinositol pool. *Biochim Biophys Acta* **1085**, 371-376 (1991).
102. A. Berger *et al.*, Epidermal anti-Inflammatory properties of 5,11,14 20:3: effects on mouse ear edema, PGE2 levels in cultured keratinocytes, and PPAR activation. *Lipids Health Dis* **1**, 5 (2002).
103. T. Tanaka, J. Morishige, T. Takimoto, Y. Takai, K. Satouchi, Metabolic characterization of sciadonic acid (5c,11c,14c-eicosatrienoic acid) as an effective substitute for arachidonate of phosphatidylinositol. *Eur J Biochem* **268**, 4928-4939 (2001).
104. F. Destaillats, R. L. Wolff, P. Angers, A new delta 7-polyunsaturated fatty acid in Taxus spp. Seed lipids, dihomotaxoleic (7,11-20:2) acid. *Lipids* **36**, 319-321 (2001).
105. J. S. Klingensmith, Distribution of methylene and nonmethylene-interrupted dienoic fatty acids in polar lipids and triacylglycerols of selected tissues of the hardshell clam (Mercenaria mercenaria). *Lipids* **17**, 976-981 (1982).
106. G. Barnathan, Non-methylene-interrupted fatty acids from marine invertebrates: Occurrence, characterization and biological properties. *Biochimie* **91**, 671-678 (2009).
107. D. Panigrahy, A. Kaipainen, E. R. Greene, S. Huang, Cytochrome P450-derived eicosanoids: the neglected pathway in cancer. *Cancer Metastasis Rev* **29**, 723-735 (2010).
108. J. R. Vane, Y. S. Bakhle, R. M. Botting, Cyclooxygenases 1 and 2. *Annu Rev Pharmacol Toxicol* **38**, 97-120 (1998).
109. Y. F. Wei, R. W. Evans, A. R. Morrison, H. Sprechert, B. A. Jakschik, Double bond requirement for the 5-lipoxygenase pathway. *Prostaglandins* **29**, 537-545 (1985).

110. N. Vasan, E. Toska, M. Scaltriti, Overview of the relevance of PI3K pathway in HR-positive breast cancer. *Ann Oncol* **30**, x3-x11 (2019).
111. T. D. Bunney, M. Katan, Phosphoinositide signalling in cancer: beyond PI3K and PTEN. *Nat Rev Cancer* **10**, 342-352 (2010).
112. T. W. Miller, J. M. Balko, C. L. Arteaga, Phosphatidylinositol 3-kinase and antiestrogen resistance in breast cancer. *J Clin Oncol* **29**, 4452-4461 (2011).
113. M. D. Rosenthal, M. C. Garcia, H. Sprecher, Substrate specificity of the agonist-stimulated release of polyunsaturated fatty acids from vascular endothelial cells. *Arch Biochem Biophys* **274**, 590-600 (1989).
114. H. Endogenous *et al.*, Sex hormones and risk of breast cancer in premenopausal women: a collaborative reanalysis of individual participant data from seven prospective studies. *Lancet Oncol* **14**, 1009-1019 (2013).
115. C. A. Marra, M. J. de Alaniz, R. R. Brenner, Effect of various steroids on the biosynthesis of arachidonic acid in isolated hepatocytes and HTC cells. *Lipids* **23**, 1053-1058 (1988).
116. H. G. Park, J. H. Kim, A. N. Dancer, K. S. Kothapalli, J. T. Brenna, The aromatase inhibitor letrozole restores FADS2 function in ER+ MCF7 human breast cancer cells. *Prostaglandins Leukot Essent Fatty Acids* **171**, 102312 (2021).
117. F. S. Kenny *et al.*, Gamma linolenic acid with tamoxifen as primary therapy in breast cancer. *Int J Cancer* **85**, 643-648 (2000).
118. J. A. Menendez, R. Colomer, R. Lupu, Omega-6 polyunsaturated fatty acid gamma-linolenic acid (18:3n-6) is a selective estrogen-response modulator in human breast cancer cells: gamma-linolenic acid antagonizes estrogen receptor-dependent transcriptional activity, transcriptionally represses estrogen receptor expression and synergistically enhances tamoxifen and ICI 182,780 (Faslodex) efficacy in human breast cancer cells. *Int J Cancer* **109**, 949-954 (2004).
119. J. A. Menendez *et al.*, Effects of gamma-linolenic acid and oleic acid on paclitaxel cytotoxicity in human breast cancer cells. *Eur J Cancer* **37**, 402-413 (2001).
120. M. Chas *et al.*, Low eicosapentaenoic acid and gamma-linolenic acid levels in breast adipose tissue are associated with inflammatory breast cancer. *Breast* **45**, 113-117 (2019).
121. D. F. Horrobin, M. S. Manku, Premenstrual syndrome and premenstrual breast pain (cyclical mastalgia): disorders of essential fatty acid (EFA) metabolism. *Prostaglandins Leukot Essent Fatty Acids* **37**, 255-261 (1989).
122. F. Caiazza, B. J. Harvey, W. Thomas, Cytosolic phospholipase A2 activation correlates with HER2 overexpression and mediates estrogen-dependent breast cancer cell growth. *Mol Endocrinol* **24**, 953-968 (2010).
123. N. W. Chang, C. T. Wu, D. R. Chen, C. Y. Yeh, C. Lin, High levels of arachidonic acid and peroxisome proliferator-activated receptor-alpha in breast cancer tissues are associated with promoting cancer cell proliferation. *J Nutr Biochem* **24**, 274-281 (2013).
124. S. C. Larsson *et al.*, Genetically predicted plasma phospholipid arachidonic acid concentrations and 10 site-specific cancers in UK biobank and genetic consortia participants: A mendelian randomization study. *Clin Nutr* **40**, 3332-3337 (2021).
125. H. Harizi, J. B. Corcuff, N. Gualde, Arachidonic-acid-derived eicosanoids: roles in biology and immunopathology. *Trends Mol Med* **14**, 461-469 (2008).
126. L. R. Howe, Inflammation and breast cancer. Cyclooxygenase/prostaglandin signaling and breast cancer. *Breast Cancer Res* **9**, 210 (2007).
127. P. M. Maloberti *et al.*, Functional interaction between acyl-CoA synthetase 4, lipooxygenases and cyclooxygenase-2 in the aggressive phenotype of breast cancer cells. *PLoS One* **5**, e15540 (2010).
128. P. Yang, Y. Jiang, S. M. Fischer, Prostaglandin E3 metabolism and cancer. *Cancer Lett* **348**, 1-11 (2014).
129. C. C. Leslie, Properties and regulation of cytosolic phospholipase A2. *J Biol Chem* **272**, 16709-16712 (1997).

130. K. Larsson *et al.*, COX/mPGES-1/PGE2 pathway depicts an inflammatory-dependent high-risk neuroblastoma subset. *Proc Natl Acad Sci U S A* **112**, 8070-8075 (2015).
131. S. L. Amaral, K. G. Maier, D. N. Schippers, R. J. Roman, A. S. Greene, CYP4A metabolites of arachidonic acid and VEGF are mediators of skeletal muscle angiogenesis. *Am J Physiol Heart Circ Physiol* **284**, H1528-1535 (2003).
132. F. Caiazza *et al.*, Cytosolic phospholipase A2-alpha expression in breast cancer is associated with EGFR expression and correlates with an adverse prognosis in luminal tumours. *Br J Cancer* **104**, 338-344 (2011).
133. C. Stewart, C. Ralyea, S. Lockwood, Ovarian Cancer: An Integrated Review. *Semin Oncol Nurs* **35**, 151-156 (2019).
134. I. M. Shih, Y. Wang, T. L. Wang, The Origin of Ovarian Cancer Species and Precancerous Landscape. *Am J Pathol* **191**, 26-39 (2021).
135. T. Y. Prudnikova, J. Chernoff, The Group I Pak inhibitor Frax-1036 sensitizes 11q13-amplified ovarian cancer cells to the cytotoxic effects of Rottlerin. *Small GTPases* **8**, 193-198 (2017).
136. I. Nakazawa, J. F. Mead, R. H. Yonemoto, In vitro activity of the fatty acyl desaturases of human cancerous and noncancerous tissues. *Lipids* **11**, 79-82 (1976).
137. K. Vriens *et al.*, Evidence for an alternative fatty acid desaturation pathway increasing cancer plasticity. *Nature* **566**, 403-406 (2019).
138. M. Triki *et al.*, mTOR Signaling and SREBP Activity Increase FADS2 Expression and Can Activate Sapienate Biosynthesis. *Cell Rep* **31**, 107806 (2020).
139. M. Carbone, G. Melino, Stearoyl CoA Desaturase Regulates Ferroptosis in Ovarian Cancer Offering New Therapeutic Perspectives. *Cancer Res* **79**, 5149-5150 (2019).
140. L. Tesfay *et al.*, Stearoyl-CoA Desaturase 1 Protects Ovarian Cancer Cells from Ferroptotic Cell Death. *Cancer Res* **79**, 5355-5366 (2019).
141. M. Gao *et al.*, Ferroptosis is an autophagic cell death process. *Cell Res* **26**, 1021-1032 (2016).
142. N. Gene, https://www.ncbi.nlm.nih.gov/gene/2495. (2021).
143. R. S. Stern, Prevalence of a history of skin cancer in 2007: results of an incidence-based model. *Arch Dermatol* **146**, 279-282 (2010).
144. P. Jain *et al.*, Runx1 Role in Epithelial and Cancer Cell Proliferation Implicates Lipid Metabolism and Scd1 and Soat1 Activity. *Stem Cells* **36**, 1603-1616 (2018).
145. M. Miyazaki, J. M. Ntambi, Role of stearoyl-coenzyme A desaturase in lipid metabolism. *Prostaglandins Leukot Essent Fatty Acids* **68**, 113-121 (2003).
146. S. Prouty, A. Pappas, Sapienic Acid: Species-Specific Fatty Acid Metabolism of the Human Sebaceous Gland. . *In: Pappas, A. (eds) Lipids and Skin Health. Springer, Cham.* https://doi.org/10.1007/978-3-319-09943-9_10 (2015).
147. S. Wongtangtintharn, H. Oku, H. Iwasaki, T. Toda, Effect of branched-chain fatty acids on fatty acid biosynthesis of human breast cancer cells. *J Nutr Sci Vitaminol (Tokyo)* **50**, 137-143 (2004).
148. J. A. Curtin *et al.*, Distinct sets of genetic alterations in melanoma. *N Engl J Med* **353**, 2135-2147 (2005).
149. P. Gerami *et al.*, Sensitivity of fluorescence in situ hybridization for melanoma diagnosis using RREB1, MYB, Cep6, and 11q13 probes in melanoma subtypes. *Arch Dermatol* **146**, 273-278 (2010).
150. N. Dippenaar, J. Booyens, D. Fabbri, I. E. Katzeff, The reversibility of cancer: evidence that malignancy in melanoma cells is gamma-linolenic acid deficiency-dependent. *S Afr Med J* **62**, 505-509 (1982).
151. Y. Geng, J. Jiang, C. Wu, Function and clinical significance of circRNAs in solid tumors. *J Hematol Oncol* **11**, 98 (2018).
152. V. Mathieu *et al.*, Aggressiveness of human melanoma xenograft models is promoted by aneuploidy-driven gene expression deregulation. *Oncotarget* **3**, 399-413 (2012).
153. H. J. Lee *et al.*, FADS2-mediated fatty acid desaturation and cholesterol esterification are signatures of metabolic reprogramming during melanoma progression.

https://www.biorxiv.org/content/10.1101/2020.07.12.198903v1.full 10.1101/2020.07.12.198903 (2020).
154. P. M. Wilkerson, J. S. Reis-Filho, The 11q13-q14 amplicon: clinicopathological correlations and potential drivers. *Genes Chromosomes Cancer* **52**, 333-355 (2013).
155. L. Q. M. Chow, Head and Neck Cancer. *N Engl J Med* **382**, 60-72 (2020).
156. S. A. Forbes *et al.*, COSMIC: mining complete cancer genomes in the Catalogue of Somatic Mutations in Cancer. *Nucleic Acids Res* **39**, D945-950 (2011).
157. N. K. Biswas, S. Das, A. Maitra, R. Sarin, P. P. Majumder, Somatic mutations in arachidonic acid metabolism pathway genes enhance oral cancer post-treatment disease-free survival. *Nat Commun* **5**, 5835 (2014).
158. C. C. Ragin *et al.*, 11q13 amplification status and human papillomavirus in relation to p16 expression defines two distinct etiologies of head and neck tumours. *Br J Cancer* **95**, 1432-1438 (2006).
159. P. M. van Kempen *et al.*, Clinical relevance of copy number profiling in oral and oropharyngeal squamous cell carcinoma. *Cancer Med* **4**, 1525-1535 (2015).
160. Y. Cheng *et al.*, Mapping of nasopharyngeal carcinoma tumor-suppressive activity to a 1.8-megabase region of chromosome band 11q13. *Genes Chromosomes Cancer* **34**, 97-103 (2002).
161. M. Perez Sayans *et al.*, Comprehensive Genomic Review of TCGA Head and Neck Squamous Cell Carcinomas (HNSCC). *J Clin Med* **8** (2019).
162. F. Carinci *et al.*, Molecular classification of nodal metastasis in primary larynx squamous cell carcinoma. *Transl Res* **150**, 233-245 (2007).
163. Q. Wei *et al.*, Genome-wide association study identifies three susceptibility loci for laryngeal squamous cell carcinoma in the Chinese population. *Nat Genet* **46**, 1110-1114 (2014).
164. V. K. Vincent-Chong, I. Salahshourifar, R. Razali, A. Anwar, R. B. Zain, Immortalization of epithelial cells in oral carcinogenesis as revealed by genome-wide array comparative genomic hybridization: A meta-analysis. *Head Neck* **38 Suppl 1**, E783-797 (2016).
165. H. G. Weed *et al.*, Lean body mass gain in patients with head and neck squamous cell cancer treated perioperatively with a protein- and energy-dense nutritional supplement containing eicosapentaenoic acid. *Head Neck* **33**, 1027-1033 (2011).
166. M. Newell, V. Mazurak, L. M. Postovit, C. J. Field, N-3 Long-Chain Polyunsaturated Fatty Acids, Eicosapentaenoic and Docosahexaenoic Acid, and the Role of Supplementation during Cancer Treatment: A Scoping Review of Current Clinical Evidence. *Cancers (Basel)* **13** (2021).
167. Y. Lu *et al.*, FADS1 is a Prognostic Biomarker in Bladder Cancer: A Study Based on TCGA Data. *Comb Chem High Throughput Screen* 10.2174/1386207323666200925104911 (2020).
168. K. Ng, A. Stenzl, A. Sharma, N. Vasdev, Urinary biomarkers in bladder cancer: A review of the current landscape and future directions. *Urol Oncol* **39**, 41-51 (2021).
169. B. M. Zaharieva *et al.*, High-throughput tissue microarray analysis of 11q13 gene amplification (CCND1, FGF3, FGF4, EMS1) in urinary bladder cancer. *J Pathol* **201**, 603-608 (2003).
170. M. A. Knowles, C. D. Hurst, Molecular biology of bladder cancer: new insights into pathogenesis and clinical diversity. *Nat Rev Cancer* **15**, 25-41 (2015).
171. F. Jiao *et al.*, Identification of FADS1 Through Common Gene Expression Profiles for Predicting Survival in Patients with Bladder Cancer. *Cancer Manag Res* **12**, 8325-8339 (2020).
172. J. Liu *et al.*, Construction and External Validation of a Ferroptosis-Related Gene Signature of Predictive Value for the Overall Survival in Bladder Cancer. *Front Mol Biosci* **8**, 675651 (2021).
173. M. K. Ben Fradj *et al.*, Decreased Oleic Acid and Marine n - 3 Polyunsaturated Fatty Acids in Tunisian Patients with Urothelial Bladder Cancer. *Nutr Cancer* **70**, 1043-1050 (2018).
174. L. Costantini *et al.*, Docosahexaenoic Acid Reverted the All-trans Retinoic Acid-Induced Cellular Proliferation of T24 Bladder Cancer Cell Line. *J Clin Med* **9** (2020).
175. B. Parada *et al.*, Omega-3 fatty acids inhibit tumor growth in a rat model of bladder cancer. *Biomed Res Int* **2013**, 368178 (2013).

176. M. E. Salem *et al.*, Comparative Molecular Analyses of Esophageal Squamous Cell Carcinoma, Esophageal Adenocarcinoma, and Gastric Adenocarcinoma. *Oncologist* **23**, 1319-1327 (2018).
177. W. Jiang *et al.*, Amplification and expression of the human cyclin D gene in esophageal cancer. *Cancer Res* **52**, 2980-2983 (1992).
178. J. W. Janssen *et al.*, MYEOV, a gene at 11q13, is coamplified with CCND1, but epigenetically inactivated in a subset of esophageal squamous cell carcinomas. *J Hum Genet* **47**, 460-464 (2002).
179. S. Yamashita, Y. Tsujino, K. Moriguchi, M. Tatematsu, T. Ushijima, Chemical genomic screening for methylation-silenced genes in gastric cancer cell lines using 5-aza-2'-deoxycytidine treatment and oligonucleotide microarray. *Cancer Sci* **97**, 64-71 (2006).
180. J. Y. Lee *et al.*, Polyunsaturated fatty acid biosynthesis pathway determines ferroptosis sensitivity in gastric cancer. *Proc Natl Acad Sci U S A* **117**, 32433-32442 (2020).
181. Y. Du *et al.*, Decreased Expression of FADS1 Predicts a Poor Prognosis in Patients with Esophageal Squamous Cell Carcinoma. *Asian Pac J Cancer Prev* **16**, 5089-5094 (2015).
182. R. Li, P. Li, W. Xing, H. Qiu, Heterogeneous genomic aberrations in esophageal squamous cell carcinoma: a review. *Am J Transl Res* **12**, 1553-1568 (2020).
183. A. M. Ryan *et al.*, Enteral nutrition enriched with eicosapentaenoic acid (EPA) preserves lean body mass following esophageal cancer surgery: results of a double-blinded randomized controlled trial. *Ann Surg* **249**, 355-363 (2009).
184. Y. Shirai *et al.*, Fish oil-enriched nutrition combined with systemic chemotherapy for gastrointestinal cancer patients with cancer cachexia. *Sci Rep* **7**, 4826 (2017).
185. K. Holzmann *et al.*, Genomic DNA-chip hybridization reveals a higher incidence of genomic amplifications in pancreatic cancer than conventional comparative genomic hybridization and leads to the identification of novel candidate genes. *Cancer Res* **64**, 4428-4433 (2004).
186. R. Gorjao *et al.*, New insights on the regulation of cancer cachexia by N-3 polyunsaturated fatty acids. *Pharmacol Ther* **196**, 117-134 (2019).
187. S. Lee *et al.*, Dietary n-3 and n-6 polyunsaturated fatty acids, the FADS gene, and the risk of gastric cancer in a Korean population. *Sci Rep* **8**, 3823 (2018).
188. M. Sehgal *et al.*, Colorectal Cancer Incidence after Colonoscopy at Ages 45-49 or 50-54 Years. *Gastroenterology* 10.1053/j.gastro.2021.02.015 (2021).
189. B. Zhang *et al.*, Large-scale genetic study in East Asians identifies six new loci associated with colorectal cancer risk. *Nat Genet* **46**, 533-542 (2014).
190. J. Tian *et al.*, Risk SNP-Mediated Enhancer-Promoter Interaction Drives Colorectal Cancer through Both FADS2 and AP002754.2. *Cancer Res* **80**, 1804-1818 (2020).
191. Y. S. Xiao *et al.*, CircFADS2: A potential prognostic biomarker of colorectal cancer. *Exp Biol Med (Maywood)* **245**, 1233-1241 (2020).
192. F. de Fraipont, S. Gazzeri, W. C. Cho, B. Eymin, Circular RNAs and RNA Splice Variants as Biomarkers for Prognosis and Therapeutic Response in the Liquid Biopsies of Lung Cancer Patients. *Front Genet* **10**, 390 (2019).
193. H. T. Reardon *et al.*, The polypyrimidine tract binding protein regulates desaturase alternative splicing and PUFA composition. *J Lipid Res* **52**, 2279-2286 (2011).
194. S. B. Rifkin *et al.*, Differences in erythrocyte phospholipid membrane long-chain polyunsaturated fatty acids and the prevalence of fatty acid desaturase genotype among African Americans and European Americans. *Prostaglandins Leukot Essent Fatty Acids* **164**, 102216 (2021).
195. U. Swami, T. R. McFarland, R. Nussenzveig, N. Agarwal, Advanced Prostate Cancer: Treatment Advances and Future Directions. *Trends Cancer* **6**, 702-715 (2020).
196. G. Thomas *et al.*, Multiple loci identified in a genome-wide association study of prostate cancer. *Nat Genet* **40**, 310-315 (2008).
197. R. A. Eeles *et al.*, Multiple newly identified loci associated with prostate cancer susceptibility. *Nat Genet* **40**, 316-321 (2008).
198. S. Akamatsu *et al.*, Common variants at 11q12, 10q26 and 3p11.2 are associated with prostate cancer susceptibility in Japanese. *Nat Genet* **44**, 426-429, S421 (2012).

199. B. Johanneson *et al.*, Suggestive genetic linkage to chromosome 11p11.2-q12.2 in hereditary prostate cancer families with primary kidney cancer. *Prostate* **67**, 732-742 (2007).
200. R. S. E. Young *et al.*, Apocryphal FADS2 activity promotes fatty acid diversification in cancer. *Cell Rep* **34**, 108738 (2021).
201. J. Xu, T. Tyan, E. Cedrone, N. Savaraj, N. Wang, Detection of 11q13 amplification as the origin of a homogeneously staining region in small cell lung cancer by chromosome microdissection. *Genes Chromosomes Cancer* **17**, 172-178 (1996).
202. L. Wang *et al.*, Cross-Cancer Pleiotropic Analysis Reveals Novel Susceptibility Loci for Lung Cancer. *Front Oncol* **9**, 1492 (2019).
203. F. Zhao *et al.*, circFADS2 regulates lung cancer cells proliferation and invasion via acting as a sponge of miR-498. *Biosci Rep* **38** (2018).
204. B. S. van der Meij *et al.*, Oral nutritional supplements containing (n-3) polyunsaturated fatty acids affect the nutritional status of patients with stage III non-small cell lung cancer during multimodality treatment. *J Nutr* **140**, 1774-1780 (2010).
205. S. Takahashi, K. Chayama, Integration of hepatitis B virus DNA and hepatocellular carcinoma. *J Gastroenterol Hepatol* **20**, 1141-1142 (2005).
206. A. Tamori *et al.*, Hepatitis B virus DNA integration in hepatocellular carcinoma after interferon-induced disappearance of hepatitis C virus. *Am J Gastroenterol* **100**, 1748-1753 (2005).
207. N. Kusano *et al.*, Genetic aberrations detected by comparative genomic hybridization in hepatocellular carcinomas: their relationship to clinicopathological features. *Hepatology* **29**, 1858-1862 (1999).
208. L. Mathers, M. J. Bailey, Enzyme deletions and essential fatty acid metabolism in cultured cells. *J Biol Chem* **250**, 1152-1153 (1975).
209. D. F. Horrobin, The reversibility of cancer: the relevance of cyclic AMP, calcium, essential fatty acids and prostaglandin E1. *Med Hypotheses* **6**, 469-486 (1980).
210. N. Okazaki, E. Araki, Eicosatrienoic acid omega9 in serum lipids of patients with hepatocellular carcinoma. *Clin Chim Acta* **53**, 11-21 (1974).
211. T. Tanaka *et al.*, Non-methylene-interrupted polyunsaturated fatty acids: effective substitute for arachidonate of phosphatidylinositol. *Biochem Biophys Res Commun* **264**, 683-688 (1999).
212. B. Skawran *et al.*, Gene expression profiling in hepatocellular carcinoma: upregulation of genes in amplified chromosome regions. *Mod Pathol* **21**, 505-516 (2008).
213. J. H. Medicine, https://www.hopkinsmedicine.org/health/conditions-and-diseases/gliomas. (2021).
214. J. M. Kros *et al.*, Spatial variability of genomic aberrations in a large glioblastoma resection specimen. *Acta Neuropathol* **102**, 103-109 (2001).
215. R. Buschges *et al.*, Amplification and expression of cyclin D genes (CCND1, CCND2 and CCND3) in human malignant gliomas. *Brain Pathol* **9**, 435-442; discussion 432-433 (1999).
216. J. Korbecki *et al.*, Expression of SCD and FADS2 Is Lower in the Necrotic Core and Growing Tumor Area than in the Peritumoral Area of Glioblastoma Multiforme. *Biomolecules* **10** (2020).
217. D. D. Martin, M. E. Robbins, A. A. Spector, B. C. Wen, D. H. Hussey, The fatty acid composition of human gliomas differs from that found in nonmalignant brain tissue. *Lipids* **31**, 1283-1288 (1996).
218. M. E. Elsherbiny, M. Emara, R. Godbout, Interaction of brain fatty acid-binding protein with the polyunsaturated fatty acid environment as a potential determinant of poor prognosis in malignant glioma. *Prog Lipid Res* **52**, 562-570 (2013).
219. W. Lian, R. Wang, B. Xing, Y. Yao, Fish intake and the risk of brain tumor: a meta-analysis with systematic review. *Nutr J* **16**, 1 (2017).