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Review Article

Role of fibroblast growth factor 8 in different cancers

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ABSTRACT

Fibroblast growth factor 8 (FGF8), a secretory protein of the FGF family, is highly expressed during early developmental stages. The early-stage expression of FGF8 and its isoforms is crucial for the normal development of organisms, while their expressions in adulthood are limited to the steroid hormone-targeting tissues. Interestingly, differential expression of FGF8 has been associated with the progression of various cancer types including breast, prostate, and ovarian cancers. Specifically, in gynecological cancers, the expression of FGF8 is regulated by steroid hormones. FGF8 isoforms, that is, FGF8a, FGF8b, FGF8e, and FGF8f act through different fibroblast growth factor receptors in different cancers through three main signaling pathways – MAP/RAS kinase, AKT/PI3, and PCLγ. This short review article discusses the structure and functions of FGF-8, along with its role in different cancers.

Keywords: Fibroblast growth factor, Fibroblast growth factor 8, Fibroblast growth factor receptor, Cancer

INTRODUCTION

According to the latest data from GLOBOCAN 2020, a global cancer database, the global incidence of cancer was estimated at about 19.3 million new cases, resulting in approximately 10.0 million cancer-related deaths. The mortality rates were recorded at 120/100,000 for males and 84.2/100,000 for females, while the incidence rates were reported as 222.2/100,000 for males and 186/100,000 for females. Notably, India experienced a significant burden of cancer, with reported cases of 646,030 among males and 678,383 among females, leading to a total of 851,678 reported cancer deaths.[1] These findings emphasize the substantial impact of cancer globally and specifically highlight the concerning situation in India.

In the realm of male cancer cases, lung cancer (11.4%), prostate cancer (14.1%), colorectal cancer (CRC) (10.6%), and stomach cancer (5.6%) stand out as the most prevalent, while breast cancer (24.5%), CRC (9.4%), lung cancer (8.4%), and cervical cancer (6.5%) significantly impact the female population across the globe. In terms of prevalence, breast cancer (11.9%) has emerged as the most common, surpassing lung cancer (11.4%). This is followed by CRC (10%), prostate cancer (7.3%), stomach cancer (5.6%), and cervical cancer (3.1%).[1] It is important to note that the diagnosis and staging of different cancer types, along with their associated survival rates, exhibit considerable diversity.

Hormonal cancers arise from steroid tissues which are hormone-regulated such as breast and prostate cancer. Together with breast and prostate cancer, endometrial and ovarian cancers (OCs) have hormonal regulation functions. Some of the hormones, such as progestogens, androgens, and estrogens, are known to influence the development of tumors. These hormones

are governed by the paracrine and autocrine target molecules comprising various growth regulators and their receptors. Metastasis of tissues such as the prostate, breast, and ovarian is derived from mislaid growth of hormones or inhibition of their signaling pathways engendered by other growth factors. Numerous proteins and growth factors are known to be concerned with the development and advancement of hormonal as well as gynecological cancers. One of the potential candidates is fibroblast growth factor 8 (FGF8) which has been considered as an oncogene as well.[2]

FIBROBLAST GROWTH FACTORS (FGFS)

Fibroblast Growth Factors (FGFs) are sometimes also referred to as "pluripotent growth factors". It belongs to the family of cell signaling proteins, produced by macrophages and plays a key role in normal growth and development of animal cells. FGFs are small, secreted polypeptide growth factors with a highly homologous central core, constituting 140 amino acids.[3] They show a strong affinity for heparin. In vertebrates, the molecular weight of FGFs varies from 17 to 34 kDa. The human FGF family consists of 23 members, having structurally related signaling molecules. A stretch of 120 amino acids is conserved in all the members of the FGF family showing 16–65% sequence identity.[4] Some of the expression patterns of proteins belonging to the FGF family suggest their numerous biological roles, *in vivo* as well as *in vitro*, in mitogenesis, wound healing, angiogenesis, cellular migration, and differentiation. One of the important features of the FGF family comprises the talk between heparin or heparin sulfate proteoglycan and FGF,[5] which, in turn, prevent proteolysis and thermal denaturation of FGFs and may sternly reduce their release and diffusion to interstitial spaces.[6,7]

Many FGF proteins act as autocrine or paracrine factors for FGF receptor (FGFR). FGFRs belong to the tyrosine kinases (TKs) receptors family, encoded by four mammalian genes.[8] FGFs and FGF signaling pathways seem to play key roles in mechanisms such as normal development and metabolism, cell functioning like cell differentiation, metabolism, wound healing, repair and generation of tissues, and many more. Furthermore, these growth factors have been found to be concerned with tumor development and progression.[3]

In this review, we are emphasizing a particular family of FGF, that is, FGF8, its biological significance, receptors along with the signaling patterns and role of FGF8 in hormonal cancers such as breast, prostate, and OCs. The rationale of this review is to compile the existing facts and figures in the areas of cancer and the context of FGF8.

FIBROBLAST GROWTH FACTOR8 (FGF8)

FGF8 was initially discovered as an androgen-triggered growth factor known as an androgen-induced growth actor. Its validation came from analyzing the medium of a mouse mammary carcinoma cell line (SC-3) that relies on androgens for growth. Further, analysis of its structure revealed a significant resemblance to the FGF family, leading to its classification as a member of this family.[9] Members of the FGF8 subfamily including FGF18, FGF17, and FGF8 exhibit highly conserved protein sequences among species. FGF8 has 98% sequence homology among humans, mice, and cattle.[10] Human FGF8 protein, encoded by the *fgf8* gene, is positioned on chromosome 10q24[11] which is a single peptide, 26 kDa cell signaling protein consisting of 233 amino acids. The protein FGF8, which belongs to the growth factor family known as heparin-binding growth factors, is alternatively referred to as heparin-binding growth factor 8.[12]

The FGF8 gene consists of six exons from 1A to 1D, 2, and 3. Alternative splicing of four exons (1A–1D) brings diverse isoforms of FGF8 (FGF8a, FGF8b, FGF8e, and FGF8f),[12,13] which also govern its biological activity.[14] The spliced variants of FGF8 hold a similar signal peptide and reading frame and share homology at their C-terminal domains.[9,12-14] The N-terminal of FGF8 is hydrophobic in nature comprising 22 amino acids, which is a characteristic cleavable signal peptide.[15] FGF8 isoforms and family members preferably bind to the "c" splice form of FGFR1-3. Isoforms of FGF8 (a, b, e, and f) interact with FGFR1IIIc, FGFR2IIIc, FGFR3IIIc, and FGFR4 receptors. The experimental finding of the crystal structure of the FGF8b-FGFR4 complex confirms the molecular basis of FGFR specificity.[16] Among all the isoforms, FGF8b is having highest angiogenic potential.[17,18]

The practical impact of these distinct FGF8 isoforms is yet not completely known. However, regulation of these isoforms might play an important part in post-transcriptional activity and regulation of FGF8 expression.[13] Moreover, FGF8 expression is largely regulated by steroid hormones specifically by dihydrotestosterone.[9,11]

A correlation between the expression of androgen receptor and FGF8 in both prostate and breast cancer has been reported,[19,20] but on the other hand, higher expression of androgen receptors does not hold prognostic value.[21] Besides androgens, the expression of FGF8 is controlled by various means and is also tissue specific. The messenger ribonucleic acid (mRNA) level of FGF8 was induced by glucocorticoid and estradiol to a lesser extent in SC3 cell lines.[22] The androgen-dependent regulation of FGF8 is not limited to mouse cell lines. It has been shown that androgens induce the expression of FGF8 in human breast cancer cell lines MDA-MB-23 and prostate cancer cell line LNCaP.[2] In both cancers, the elevated expression of FGF8 also correlates with the higher expression of androgen receptors.[2] Hormones signaling through nuclear receptors seems to regulate the expression of FGF8. Vitamin D3 transcriptionally represses the expression of FGF8 which regresses the growth of the

SC-3 cell line.[23] Retinoids can induce a transformative effect on prostate cancer cell lines by shifting the mitogenic isoform b of FGF8 to a less active isoform.[24,25] Apart from hormones, nuclear factor-kappa was found to control the expression of FGF8 in prostate cancer cells.[26]

RECEPTORS OF FGF8 AND SIGNALING PATHWAYS

Figure 1 illustrates the key feature of FGFRs. FGF family receptors belong to the immunoglobulin (Ig) superfamily of TK receptors located on the cell surface. FGF8 transduces the signals through receptor 1–4 located on the surface of the cell.[27] Four FGFRs share high sequence similarities, especially among FGFR1, FGFR2, and FGFR3.[28] FGFRs are transmembrane receptors and consist of three domains: three extracellular Ig-like loop domains IgI, IgII, and IgIII, two intracellular TK domains TK1 and TK2, and a single transmembrane helix linking the extra- and intradomains.[28] The extracellular part of the transmembrane helix contains the conserved sequence of acidic amino acids, cell adhesion homology domain, and a heparin-binding region. Ig-loop II and Ig-loop III are ligand-specific and, therefore, are important for signal transduction. Alternative splicing in the Ig loop region gives rise to spliced variants of FGFR which confers different functions. Alternative splicing in the Ig-loop III of FGFR1–3 produces IIIb and IIIc isoforms. Expression of FGFR isoform IIIb in epithelial cells is predominant. While mesenchymal cells mostly express the FGFR IIIc isoform; also, Epithelial-Mesenchymal transition is related

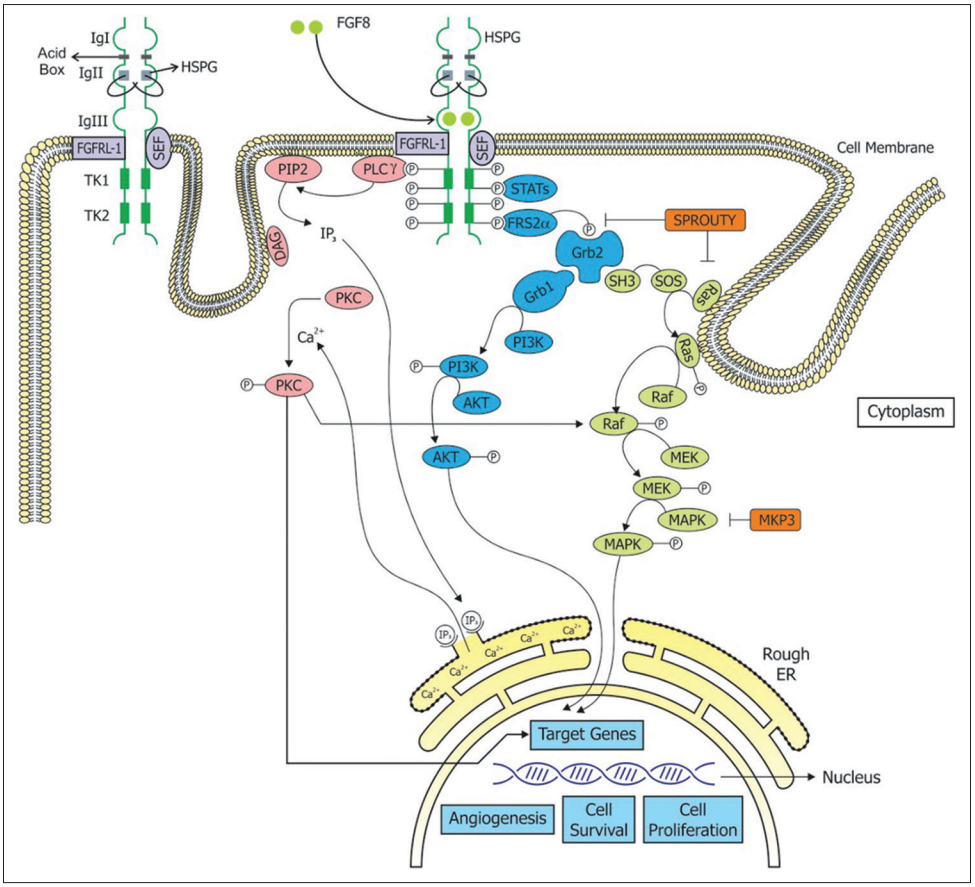

Figure 1: Structural features of FGFR and associated signaling pathways. Binding of FGF8 to IgIII domain leads to phosphorylation and activation of TK domains. FRS2α is phosphorylated by TK domain followed by the activation of adapter protein Grb2. Grb2 further activates AKT and MAPK pathways via Grb1 and SOS proteins, respectively. FRS2α independent pathway PLCγ/Ca^{2+} pathway is also activated by the phosphorylated TK domain leading to activation of Protein Kinase C. FGFRL1 controls FGFR activity negatively. SEF and MKP3 proteins inhibit the FGFR activity. Sprouty protein binds to Grb2 and Ras, thus inhibiting the signaling cascade. FGFR: Fibroblast growth factor receptor, FGF8: Fibroblast growth factor, Ig: Immunoglobulin, TK: Tyrosine kinase, SEF: Similar expression to FGF, MKP3: MKP phosphatase 3, FRS2α: FGFR substrate-2α, SOS: Son of seven less, PLCγ: Phospholipase Cγ, Grb2: Growth factor receptor bound protein 2.

to the transformation from IIIb to IIIc isoform, whereas the IgIIIa variant produces a protein that is unable to transduce the signal.[27] On the contrary, the absence of alternative splicing FGFR4 exon produces no isoform. The fundamental function of the Ig-loop III region is ligand recognition and this ligand-receptor spectrum is widened by creating the isoforms through alternative splicing. The binding of different isoforms of FGFRs to different FGFs gives flexible affinity without altering the specificity. Autoinhibition is one of the essential properties of FGFRs. The autoinhibition mechanism depends on a conserved sequence of 7–8 acidic residues, called the acid box containing a linker between Ig domain 1 and Ig domain 2. This acid box is involved in receptor autoinhibition and is the foremost checkpoint for unplanned FGF signaling.[29]

The signal peptide is the common feature among FGFs and subfamilies except for FGF1 and FGF2, and FGF9, FGF16, and FGF20. FGF family generally follows one of the three signal transduction pathways, that is, MAP/RAS kinase pathway, AKT/PI3 pathway, or PCLγ pathway among all three; MAP/RAS kinase pathway is predominant [Figure 1]. Phosphorylation is an intrinsic property of TK receptors. The binding of FGFR-FGF8 (ligand) leads to some conformational change resulting in transphosphorylation of intracellular TK domains and tails. This confirms the activation of the intracellular kinase domain. Two important adaptor proteins, phospholipase Cγ (PLCγ), and FGFR substrate-2α (FRS2α) are phosphorylated by FGFRs. Activation by phosphorylation of PLCγ and FRS2α results in their recruitment to FGFRs intracellular tail leading to the commencement of intracellular signaling events. Ultimately, the activation of PLCγ and FGFR substrate-2 (FRS2) initiates various signaling pathways. A few potential pathways are PLCγ/Ca^{2+} pathway, phosphoinositide-3-kinases (PI3K)/AKT pathway, and FRS2α-activated ras/mitogen protein kinase (MAPK) pathway.[30]

Ras/MAPK PATHWAY

The binding of FGF8 to FGFRs, trans-phosphorylates FGFRs on multiple sites on TK domain.[31] FRS2α binds to the phosphorylated site on FGFR and gets activated through self-phosphorylation. The activated FRS2α attracts a small adaptor protein termed growth factor receptor-bound protein 2 (Grb2). The SH3 domain of guanine nucleotide exchange factor, son of seven less (SOS), is recognized by Grb2 protein leading to the formation of a complex that permits SOS to activate Ras protein, a monomeric GTPase. The activated ras protein illicit a cascade of downstream effector kinase proteins such as Raf, MAPK kinase (MEK) and MAP kinase (MAPK). The activated kinase protein enters into the nucleus and phosphorylates various transcription factors. c-Myc and activation protein-1 are prime targets.[32,33]

PI3K/Akt PATHWAY

In an alternate pathway, Grb2-associated binding protein 1 (Grb1) binds to the FRS2α-Grb2 complex. The Grb2-Grb1 complex activates PI3K which eventually results in the activation of AKT protein.[34,35] AKT directly enters the nucleus to activate various effector genes.

PLCγ/Ca^{2+} PATHWAY

The phosphorylation of FGFRs also recruits proteins other than Grb2 initiating multiple signaling pathways at the same time. One of the signaling pathways is the PLCγ/Ca^{2+} pathway which is initiated by binding of PLCγ, directly to the phosphorylated tyrosine on the C terminal tail FGFRs. The prime substrate of PLCγ is phosphatidylino-sitol 4,5 biphosphate (PIP2) which is hydrolyzed by PLCγ into phosphatidylinositol-3,4,5-triphosphate (IP3) and diacylglycerol (DAG). Secondary messenger molecule IP3 moves toward the endoplasmic reticulum and binds to receptor-gated Ca^{2+} channel releasing sequestered Ca^{2+}, while DAG which is still membrane-bound binds with protein kinase C. Binding DAG and released calcium ions activates protein kinase C leading to the phosphorylation of downstream proteins.[36,37]

FGFRs also activate other pathways which are crucial in the initial development of an organism. Wingless-related integration site (Wnt) and signal transducer and activator of transcription (STAT) signaling pathways are specifically activated in tooth development.[38] Sonic hedgehog signaling pathway which is also activated by FGFRs plays a key role in palate development.[39] The interaction of these signaling pathways with other growth factor pathways regulates cell behavior.

FGF8 TISSUE EXPRESSION AND ITS BIOLOGICAL SIGNIFICANCE

Before delving into FGF8 expression in cancer, it is worth reviewing its expression patterns during development and in healthy tissues. During embryological development especially gastrulation, the development of the brain, limb, and face is largely controlled by FGF8 expression.[40] It has also been important to the healthy growth of the gonadotropin-releasing hormone and neuronal system. Expression of FGF8 and FGF17 is documented in the central nervous system, kidney, limb, heart, and in craniomaxillofacial development.[41]

During the early stage of development, the expression of FGF8 is prominent but as the organism moves to adulthood that the expression becomes limited to particular tissues. Tissues that are the target of steroid hormones express FGF8, reproductive, and genitourinary tract particularly. Other tissues such as the kidney, breast, prostate, and testis express FGF8 at a low level.[42-44] FGF8

can also be found in the human bowel.[45] The lactating mammary glands show higher expression suggesting its significant role in lactation. FGF8 expression has also been reported in the morphogenic outgrowth of the hepatic endoderm.[46] Expression of FGF8 in the bone marrow and peripheral blood leukocytes also indicates its role in hematopoiesis.[47]

The extensive-expression pattern indicates that FGF8 is necessary for the physiological changes in fetal development and adulthood.

The expression of FGF8 isoforms is tissue-specific and performs diverse functions. FGF8 isoforms are usually expressed in the epithelium tissues and their receptors are present in mesenchymal stromal tissues. FGF8 isoforms expressed in different tissues possess different functions. This is well understood by the expression pattern of FGF8a and FGF8b during the early development of the hindbrain and midbrain where they confer unrelated functions.[48] FGF8b has strong angiogenic potential as compared to other isoforms such as FGF8a and FGF8e.[17,18] The structural foundation of FGF8a and FGF8b binding to receptor FGF2IIIc was lately detailed by Olsen *et al*.[16] Their observations pointed out that the variances in the biological capability and function of the isoforms FGF8a and FGF8b could be described by the varied affinity of these FGF isoforms to their respective receptor.[16]

Based on its transforming potential of NIH3T3 cell lines, FGF8 is reported as one of the oncogenes which have shown its oncogenic potential in various types of cancers.[49] In adult organisms, the expression of FGF8 is more limited. However, in hormonal cancers, its activation becomes increasingly common. In malignant tissues such as breast and prostate cancers, various isoforms of FGF8[50,51] and receptors have been identified[52,53] have been indicated. In addition, FGF8 exerts an angiogenic effect in various cell lines. The autocrine and paracrine pathways of FGF8 tend to make changes in the angiogenic properties of cells. High expression of FGF8b in the S115 cell line stimulates tumor growth. Dilated and leaky blood vessels and vascular type of tumor morphology were detected in the S115 cell line.[17] A similar effect was observed in endothelial cells. Overexpression of FGF8 in endothelial cells has shown progression in tumorigenesis and the formation of tube-like structures.[17] Furthermore, the presence of FGFRs on endothelial cells seems to transduce the angiogenic signals of FGF8b expression. Angiogenesis in tumor cells can also be regulated by controlling various anti-angiogenic target genes in tumors. Coexpression of FGF8 and vascular endothelial growth factor in prostate cancer indicates that both growth factor works synergistically to carry out angiogenesis.[54]

FGF8 EXPRESSION IN CANCERS

Based on its altering expression profile, FGF8 has been anticipated as a biomarker in different malignancies such as endometrial cancer, OC, breast cancer, prostate cancer, uterine cancer, and many more. FGF8 mRNA and protein have been tracked down in OC cell lines and tumor samples.[55] Moreover, in both non-malignant and malignant breast tissues, FGF8 mRNA has been reported.[56,57] Originally, FGF8 mRNA was discovered in the ovary and testis of adult mouse (northern blotting)[43,58] and, later on, discovered in the human prostate and other tissues/organs.[59,60] Using techniques like immunohistochemistry (IHC), FGF8 protein has been identified in the corpus luteum (in human females).[45]

Hormonal cancers such as prostate, breast, and OC begin from steroid hormone-regulated tissues and share a unique mechanism of carcinogenesis. The expression of FGF8 is linked with the morphological changes in breast and prostate cancer. In addition to that, it has been indicated that expression of FGF8 in both these cancers promotes anchorage-dependent cell proliferation.[17,18,61]

Breast cancer

About 1 in 10 new cases of breast cancer are diagnosed each year. It ranks 1st in terms of cancer death among women.[62] During carcinogenesis, growth and regulation of hormones are mislaid or controlled by an improper stimulation of growth factor signaling cascades. FGF8 is one of those growth factors which help in the progression of breast carcinogenesis.[2] In lactating human breasts and in breast cancer, expression of FGF8 is elevated. In breast cancer cells, FGF8 mRNA expression is in comparison with normal and malignant tissues. IHC of tissues from breast cancer patients also confirms the aforementioned.[19,56] Furthermore, lactating breasts express high levels of FGF8 transcripts than non-lactating breasts, speculating on its possible role in lactation.[51] About 50% of breast cancer with FGF8 expression do not correlate with the clinic pathological feature.[19]

However, high expression of FGF8 upsurges the expression of androgen receptor yet it does not correlate with the prognostic value.[21] In breast cancer, the primary isoform identified is FGF8b.[51]

Although the upregulation of FGF8 has been found in at least half of human breast cancers, clinic pathological parameters do not correlate with its higher expression.[19] Various breast cancer cell lines such as MCF-7, BT-549, T47-D, SKBR-1, MDA-MB-231, and ZR-75-1 have shown upregulation of FGF8 expression.[51,59,63]

FGFR has also been found to be elevated in breast cancer samples and cell lines. FGFR1-4 has been expressed in both non-malignant and malignant breast tumors.[64-67] Furthermore, the elevated expression of particularly FGFR1, FGFR2, and FGFR4 is associated with breast cancer

malignancy.[62,68-71] About 10% of breast cancer show increased levels of FGFR4 in epithelial cells of malignant and non-malignant breast samples.[62,68-72] A slight variant of FGFR1 is expressed in malignant tumors; however, the level of expression is normal.[72,73]

Prostate cancer

Among men, prostate cancer is the most commonly diagnosed cancer and accounts for 5th most leading cause of death among cancer.[74,75] FGF8 has been expressed to play a significant role in prostate carcinogenesis. Various cell lines of prostate cancer, for example, DU145, LNCaP, ALVA-31, and PC3 have shown the expression of FGF8.[50,76] Over-expression of FGF8 protein has been shown in tissues of prostate malignancies.[56,57] Around 60–70% of the newly diagnosed prostate cancer cases have reported up-regulation of FGF8 mRNA.[53] Studies revealed some correlation of this up-regulation with factors such as pathological grade, disease-specific survival, and stage of the tumor.[50]

Overly expressed FGF8 mRNA in prostate cancer has been found to be linked with high-grade carcinoma and late staging of the disease.[50,53] Moreover, expression of FGF8 receptors, that is, FGFR2IIIc, FGFR3IIIc, and FGFR4 have been studied in prostate epithelium carcinoma[77,78] where the detection level of FGFR4 was low in cell lines of prostate cancers.[77-80] Splicing features of FGFR are distorted while prostate cancer progression. For example, during the advanced stage of cancers, up-regulation of the isoform FGFR2IIIc is observed whereas, in initial malignant stages, FGFR1IIIc is favorably expressed by cells of the epithelium.[81,82] In this circumstance, FGF8 can well implement both autocrine and paracrine functions. Different isoforms of FGF8 are recognized to comprise relatively specific binding characters.[81-83] For instance, no FGFR is known to be activated by FGF8a, whereas, FGFR3IIIc and FGFR4 are shown to interact with the other two isoforms, that is, FGF8b and FGF8e.[83] However, FGFR2IIIc is seen to interact with FGF8b only.

It is clear that prostate cancer progression is largely linked with the encouraging environment for FGF8, and in particular FGF8b. The overexpression of the FGF8b transcript in metastatic lesions also supported the above findings.[50,83] A study of the SC-3 prostate cancer cell line showed that the increased expression of FGF8 mRNA induces androgen secretion.[9] However, androgen receptor-negative cell lines such as DU 145 and PC-3 have shown increased FGF8 mRNA expression showing androgen-independent expression of FGF8 mRNA.[59,60] This androgen-independent growth is exerted by the binding of FGF8 to FGFR2IIIc and FGFR3IIIc receptors with high affinity expressed by the prostate gland.[77,84] In addition, in 88% of metastatic prostate cancer cases, the expression of Sef, a key inhibitor protein of FGF signaling, has been reported missing. Cells expressing Sef and FGF8 together do not turn metastatic.[85]

Ovarian cancer (OC)

OC is considered the most lethal among gynecological malignancies in females across the world mainly due to its asymptomatic behavior and silent growth of the tumor. OC occupies the eighth position in terms of both incidence and mortality rates among women.[1] Due to the higher number of ovulatory cycles, a female who undergoes early menarche (less than the age of 12) and late menopause (more than the age of 50) have been shown to be 1.4–1.5 times and 1.4–4.6 times higher risk of developing OC, respectively.[86]

A diverse range of histological types of OC exhibits the expression of FGF8 and its corresponding receptors. Moreover, heightened staining intensity of FGF8 has been linked to a decrease in tumor differentiation.[55] The expression of FGF-8 was detected in all ovarian tumor specimens, including those from benign, borderline, and malignant tumors. The findings indicated that among the four isoforms of FGF8, FGF8b exhibits the highest transforming potential in both *in vitro* and *in vivo* assays, promoting malignant growth and tumorigenesis.[13,59] The reduced expression of FGF8 in the normal ovarian surface epithelium and elevation in ovarian tumors suggests that activation of FGF8 is involved in the initial steps of malignancy of benign ovarian tumor.[55]

The expression patterns of FGFR in ovarian-cancer cell lines differ from that in ovarian tumors. Activation of receptors like FGFR1IIIC, and FGFR2IIIC by FGF8 in ovarian tumor samples and FGFR4 in cell lines, was associated with malignancy.[83]

Observations related to FGF8 receptors have shown that the transforming isoform FGF8b and its receptors FGFR1IIIc, FGFR2IIIc, and FGFR4 are upregulated in ovarian tumors of various histological types.[55]

Other cancers

In oral squamous cell carcinoma, the upregulation of FGF8 and its pro-metastatic function has been established by many studies. However, the chance of occurrence of metastasis is not the same as for breast or lung cancer.[87]

Western blot analysis and real-time PCR analysis of CRC patient tissues showed an increased level of FGF8. This was also inferred that the upregulation does not correlate with the enhanced metastasis of the patient's age or gender but with the lymph node metastasis. In protein and mRNA studies, expression of FGF8 was found to be upregulated in tissues in comparison with adjacent normal tissues. The results indicated that FGF8 expression was not allied with tumor

size, patient age, or gender, but with lymph node metastasis. Exogenous induction of FGF8 into the experimental CRC cell line resulted in the activation of YAP1 signaling which led to tumorigenesis and metastasis.[88]

Hepatocellular carcinoma is one of the frequent malignant tumors of the liver. Family members of FGF8 including FGF17 and FGF18 were overexpressed considerably in tum surrounding as compared to normal tissue. There was a 2-fold expression of FGF8 family members in more than 50% of tumor cases investigated. Furthermore, *in vitro* studies also showed higher levels of FGF8, FGF17, and FGF18 mRNA.[89]

CONCLUSION

Emerging clinical data and experimental findings provide compelling evidence supporting the involvement of FGF8 in the facilitation of the progression and development of various cancers. FGF8 has shown its capability to act as a potential growth factor that is involved in the proliferation of breast and prostate cancer cells. Clinical studies have validated the correlation between FGF8 expression and adverse outcomes in various cancers, while its precise role in tumor progression remains less elucidated. FGF8 is one of the growth factors which highly expressed in early fetal development where it is responsible for cell differentiation. In adulthood, the expression of FGF8 is reduced and becomes limited to hormonal-targeted tissues. FGF8 expression has been observed in certain cancers, and its signaling pathways may contribute to the growth and survival of cancer cells. Understanding the role of FGF8 in hormonal cancers, such as breast, prostate, and OCs, is of particular interest in research. Frequent reports of FGF8 expression in various cancers make it necessary to uncover the regulation of expression and functional aspects of FGF8 in cancer. Malignancies, like cervical, do not have clinical or expression data to establish the involvement of FGF8.

Future prospective

The mechanistic role of different FGF8 isoforms has not been revealed yet. There might be the possibility of different isoforms of FGF8 regulating the FGF8 activity post-transcriptionally. The mechanism by which FGF8 mediates tumorigenesis has not been explored entirely. The role of FGF8 in the progression of cervical cancer is not elucidated yet. FGF8 and its isoforms have immense potential as target molecules for multiple types of cancers. One will have to dig deeper to uncover its true potential.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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