# FGFR-related phenotypic and functional profile of CAFs in prognostication of breast cancer (Review)

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**Abstract.** While preclinical studies consistently implicate FGFR-signalling in breast cancer (BC) progression, clinical evidence fails to support these findings. It may be that the clinical significance of FGFR ought to be analysed in the context of the stroma, activating or repressing its function. The present review aimed to provide such a context by summarizing the existing data on the prognostic and/or predictive value of selected cancer-associated fibroblasts (CAFs)-related factors, that either directly or indirectly may affect FGFR-signalling. PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Medline (https://www.nlm.nih.gov/medline/medline_home.html) databases were searched for the relevant literature related to the prognostic and/or predictive significance of: CAFs phenotypic markers (αSMA, S100A4/FSP-1, PDGFR, PDPN and FAP), CAFs-derived cognate FGFR ligands (FGF2, FGF5 and FGF17) or inducers of CAFs' paracrine activity (TGF-β1, HDGF, PDGF, CXCL8, CCL5, CCL2, IL-6, HH and EGF) both expressed in the tumour and circulating in the blood. A total of 68 articles were selected and thoroughly analysed. The findings consistently identified upregulation of αSMA, S100A4/FSP-1, PDGFR, PDPN, HDGF, PDGF, CXCL8, CCL5, CCL2, IL-6, HH and EGF as poor prognostic markers in BC, while evaluation of the prognostic value of the remaining markers varied between the studies. The data confirm an association of CAFs-specific features with BC prognosis, suggesting that both quantitative and qualitative profiling of the stroma might be required for an assessment of the true FGFR's clinical value.

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*Abbreviations:* BC, breast cancer; CAFs, cancer-associated fibroblasts; DFS, disease-free survival; ER, estrogen receptor; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; HER2, human epidermal growth factor receptor 2; OS, overall survival; PR, progesterone receptor; RFS, recurrence-free survival; TME, tumour microenvironment

*Key words:* FGFR, CAFs, biomarkers, secretome, BC

**Contents**



## 1. Introduction

Fibroblast growth factor (FGF) receptor (FGFR)-mediated interactions between tumour microenvironment (TME) and breast cancer (BC) cells in progression and response to therapy are well documented (1,2). While preclinical studies consistently implicate FGFR signalling in BC development, clinical evidence to support its pro-tumorigenic role is still missing (3,4). One of the possible reasons for the discordance between mechanistic and clinical findings as well as disappointing results of clinical trials with FGFR inhibitors in BC (5,6) may be an inability of *in vitro* models to truly represent an *in vivo* setting and biological complexity of the TME. As FGFR-pathway is regulated by TME-derived stimuli, the clinical value of FGFR in BC ought to be analysed in the context of the stromal component, activating or repressing its function, in particular, cancer-associated fibroblasts (CAFs), that either directly (cognate ligands; FGFs) or indirectly (various factors enhancing CAFs' paracrine activity), may affect FGFR signalling (7,8).

CAFs, the most abundant cellular component of the TME present a highly heterogenous population, whose remarkable phenotypic and functional diversity is due mostly to distinct cellular origins, such as resident fibroblasts, bone marrow-derived mesenchymal stem cells, pericytes, endothelial or cancer cell (9). Various factors produced by cancer cells, host immune or other stromal cells, for example

tumour growth factor β (TGF-β), platelet-derived growth factor (PDGF), sonic hedgehog (HH), interleukin 6 (IL-6), and a wide array of chemokines (9-18), induce differentiation and activation of CAFs. CAFs participate in various aspects of carcinogenesis, interacting directly and/or indirectly with tumour cells as well as various components of TME including myeloid cells. They have been most extensively investigated in the context tumour immunosuppressive microenvironment and its potential clinical significance (19,20). In BC, CAFs have been shown to promote cancer cell proliferation, remodelling of the extracellular matrix (ECM), angiogenesis and metastasis as well as modulate immune responses and drug resistance (19). This suggests that the overall impact of CAFs on tumour progression, and hence disease prognosis, is determined by the spatio-temporal pattern of their distribution and activation. A series of excellent recent reviews discuss various aspects of CAFs' biology, their impact on progression and responsiveness to therapy in several solid tumours, including BC.

Unequivocal documentation of CAFs is notoriously difficult, as none of the available phenotypic markers are entirely specific or exclusive. Inherent plasticity between CAFs subtypes further conceals their true phenotypic identity (20-23). Most commonly, CAFs are being detected on the basis of their morphology, positivity for mesenchymal biomarkers, for example alpha-smooth muscle actin (αSMA), fibroblast-activating protein (FAP), fibroblast-specific protein (FSP/S100A4) and platelet-derived growth factor receptor-β (PDGFRβ) as well as lack of expression of lineages markers for epithelial, endothelial or hematopoietic cells (20,21,23). However, because of their dynamic interactions with the tumour and other TME components, not a single marker, but a panel of phenotypically- and functionally-related features, so-called 'a stromal signature', is better positioned to define CAFs with regards to patients' prognosis (24). And indeed, several molecular stromal signatures have already been shown to have a prognostic and predictive value, complementary to that of phenotypic markers of the BC epithelial compartment (25,26).

There is growing evidence to suggest that through their secretome, encompassing a range of biologically active molecules such as growth factors, chemokines and cytokines, CAFs influence the course of BC development (1,27). In particular, being a source of FGF ligands, they act as paracrine upstream regulators of FGFR likely to affect BC evolution and development of therapy resistance (1,28-31).

Based on the reported data, a panel of stroma-derived factors was selected, called henceforth an 'FGFR-related CAFs' profile', that enables identification of a subpopulation of CAFs [phenotypic markers: αSMA, S100A4/fibroblast-specific protein 1 (FSP-1), PDGFR, podoplanin (PDPN), FAP (20,21)], with characteristics indicative of their potential regulatory effect on the FGF/FGFR axis [factors inducing CAFs paracrine activity: transforming growth factor (TGF)-β1, HDGF, PDGF, CXCL8, C-C motif chemokine ligand (CCL) 5, CCL2, IL-6, HH and EGF (32,33) and 3 CAFs-derived cognate FGF ligands: FGF2, FGF5 and FGF17 (34-38)] (Table I).

In the present study, existing data on the prognostic and, where available, predictive significance of the individual components of the so designed 'CAFs' profile' were summarized. To the best of our knowledge this is the first attempt to define the traits of CAFs specifically relevant to the activity of FGFR. Such a profile may represent a 'missing link' in the translation between mechanistic and clinical studies, thus supporting an evaluation of the true value of FGFR in BC prognostication (Fig. 1 and Table II).

The data have been organized into distinct paragraphs based on the tissue of origin of specific marker/s, whether expressed in the tissue (including the cytosol) or circulating in the blood (a substantial and easily accessible portion of the CAFs secretome). Details regarding the literature search, including a flowchart, are provided in Fig. 2.

## 2. Tissue proteins

*Phenotypic markers*

*αSMA.* αSMA, a general marker of mesenchymal cells, is the most reliable marker of CAFs with a myofibroblast morphology (39). Alpha SMA can exist in a globular (G-actin) or filamentous (F-actin) form. The incorporation of αSMA into stress fibres, associated with the transition between G and F actin states, enhances the contractile properties of CAFs as well as the tension of the surrounding ECM (30). Via a mechanical feedback loop, αSMA-containing stress fibres participate in multiple cellular functions, ranging from the maintenance of cell shape and polarity to endosome dynamics and secretory pathways (39,40). Phenotypic transition into myofibroblasts and acquisition of the contractile features is one of the central traits of the activated stroma. It can be induced through several mechanisms, including auto- and paracrine stimulation by growth factors or cytokines (41). Activated myofibroblasts, in turn, secrete a number of soluble modulators, which contribute to ECM remodelling and, in cancer, promote invasiveness (39).

In BC, overexpression of αSMA in the stroma is consistently shown to be associated with unfavourable prognosis-an increased risk of metastases, shorter overall survival (OS) and disease-free survival (DFS) (28,42-47). Upregulation of αSMA was found to correlate with tumour high grade and positive nodal status (44,47,48). In human epidermal growth factor receptor 2 (HER2)-enriched BC, co-expression of αSMA, FGF5 and FGFR2, associated with upregulated c-Src, correlated with poor response to treatment (28), implicating the CAF ($\alpha SMA^+$)-FGF5-FGFR2-c-Src axis in development of resistance to HER2-targeted therapies. This was further supported by a demonstration of a link between αSMA overexpression in the stromal compartment and resistance to trastuzumab in patients with BC (45).

*S100A4/FSP-1.* S100A4 protein or FSP-1, localized in the cytoplasm and/or nucleus, is involved in the regulation of a number of cellular processes including cell cycle progression and differentiation. S100A4 is a polypeptide with two calcium-binding motifs, known to regulate, in a calcium-dependent manner, various cytoplasmic proteins, including the cytoskeletal components. The structural conformation of S100A4 upon calcium binding facilitates its interaction with RAGE on fibroblasts, activating intracellular signalling cascades such as the MAPK/ERK pathway (49). Furthermore, being secreted to the TME by activated stromal cells such as fibroblasts and immune cells, S100A4 supports

Table I. Components of the 'FGFR-related CAFs' profile'.

| | |
|---|---|
| Phenotypic markers of CAFs | αSMA/ACTA2, S100A4/FSP-1, PDGFR, PDPN, FAP |
| Factors activating CAFs | TGF-β1, HDGF, PDGF, CXCL8, CCL2, CCL5, IL-6, HH, EGF |
| CAFs-secreted cognate ligands | bFGF (FGF2), FGF5, FGF17 |

CAF, cancer-associated fibroblast; αSMA/ACTA2, alfa smooth muscle actin; S100A4/FSP-1, fibroblast specific protein; PDGF, platelet-derived growth factor; PDGFR, PDGF receptor; PDPN, podoplanin; FAP, fibroblast activating protein; TGF-β, tumour growth factor β1; HDGF, heparin binding growth factor; CXCL, chemokine (C-X-C motif) ligand; CCL, C-C motif chemokine ligand; IL-6, interleukin 6; HH, sonic hedgehog; EFG, epidermal growth factor; FGF, fibroblast growth factor.

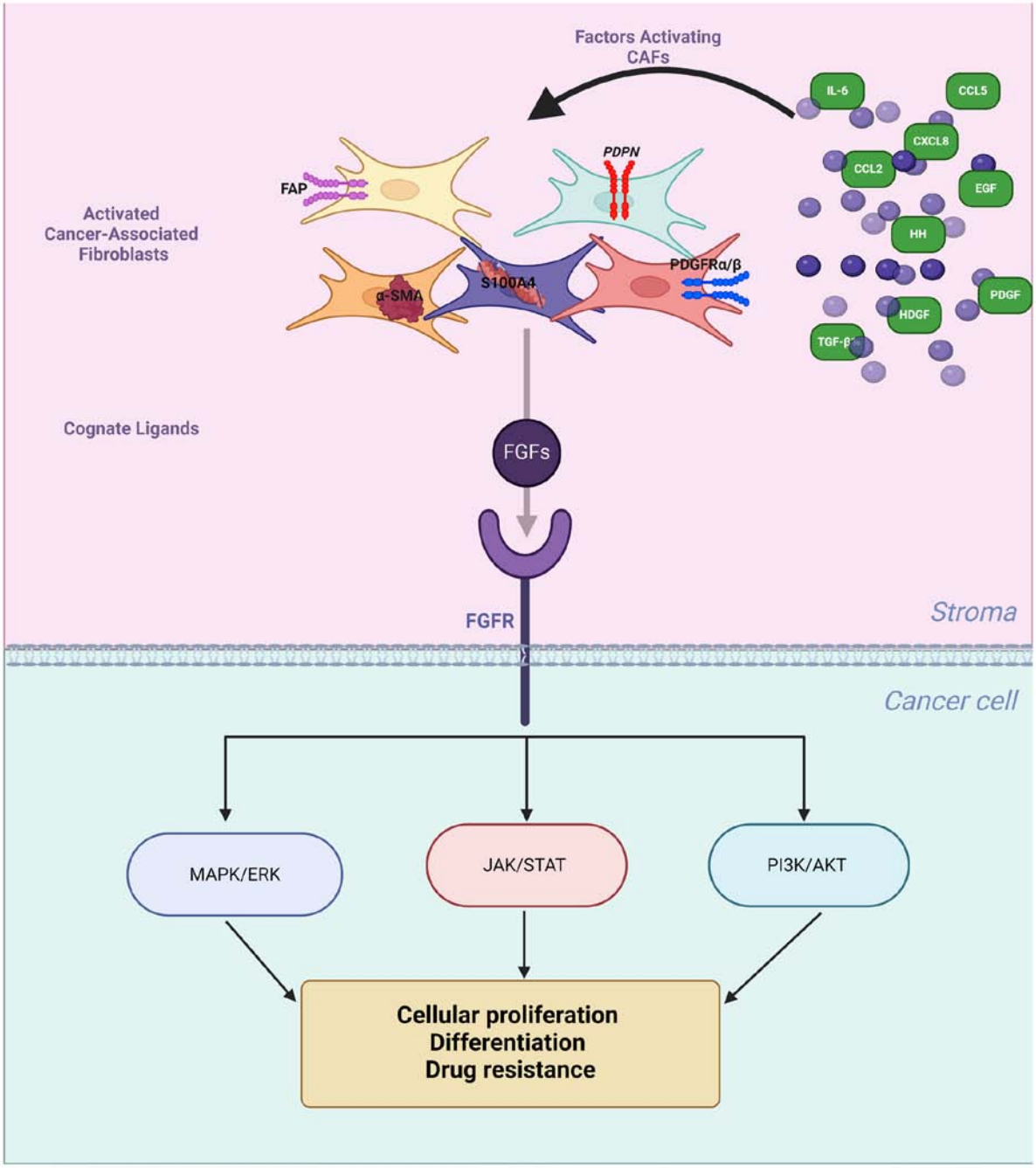


Figure 1. CAF subpopulations and factors inducing their paracrine activity. CAFs, originating from different cellular sources, represent a highly heterogenous population. Activated by various tumor microenvironment-secreted factors (included in Table I) are the main source of FGFRs' cognate ligands, FGFs. Activation of FGFR signalling, through various downstream pathways, including Ras dependent MAPK, PI3K/AKT or STATs, influences cellular proliferation, differentiation and drug resistance. CAF, cancer-associated fibroblast; FGFR, fibroblast growth factor receptor; PDGFR, platelet-derived growth factor receptor.

Table II. Reported associations between components of FGFR-related CAFs' profile, clinicopathological and prognostic variables.

| | | Marker | | | Correlation with clinicopathological values | | | | Correlation with | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | First author/s, year | CAFs' phenotypic markers | Expression of stromal marker | Grade | Tumour size (T) | Nodal metastasis (N) | Molecular subtype | Prognostic variables | Predictive variables | N | Methodology | Localization of the markers | (Refs.) |
| Tissue proteins | αSMA/ ACTA2 | Tashireva *et al*, 2017 | αSMA (CD68, RS1,FAP) | Upregulated | NA | NA | Positive | Luminal B HER2+ | NA | NA | 36 | RT-PCR | Stroma | (77) |
| | | Yamashita *et al*, 2012 | αSMA | Upregulated | Positive | NS | NS | NS | Shorter OS | NA | 60 | IHC | Stroma | (44) |
| | | Fernandez-Nogueira *et al*, 2020 | αSMA (FGF5, FGFR2, c-Src) | Upregulated | NA | NA | NA | HER2+ | Shorter OS | High risk of reccurence after trastuzumab | 64 | IHC | Stroma | (28) |
| | | Vathiotis *et al*, 2021 | αSMA | Upregulated | NA | NA | NA | HER2+ | Shorter DFS | Resistance to trastuzumab | 151 | GeoMx | Stroma | (45) |
| | | Kim *et al*,2019 | αSMA | Upregulated | NA | NA | NA | ER+ | Shorter RFS | NA | 209 | Online data (GSE2034) | Tumour + Stroma | (42) |
| | | Hu *et al*, 2018 | αSM (FSP-1, PDPN) | Upregulated | Positive | NS | Positive | ER- | Shorter DFS | NA | 3,680 | Meta-analysis | Stroma | (47) |
| | | Wang *et al*, 2016 | αSMA (THBS1, TNC, FN, SPARC) | Upregulated | NA | NA | NA | NA | Shorter OS, DFS | NA | 100 | IHC | Stroma | (43) |
| | | Busch *et al*, 2012 | αSMA (pERK) | Upregulated | NA | NA | NA | NA | shorter DFS | NS | 922 | IHC | Stroma | (46) |
| | | Yazhou *et al*, 2004 | αSMA (CD34) | Upregulated | Positive | NS | Positive | NA | NA | NA | 58 | IHC | Stroma | (48) |
| | S100A4/ FSP-1 | Park *et al*, 2016 | S100A4/ FSP-1 (FAP, PDGFRα, PDGFRβ, NG2, PDPN) | Down-regulated | NS | NS | Positive | ER- | Shorter DFS | NA | 628 | IHC | Stroma | (54) |

Table II. Continued.

| | First author/s, year | Marker: CAFs' phenotypic markers | Marker: Expression of stromal marker | Correlation with clinicopathological values: Grade | Correlation with clinicopathological values: Tumour size (T) | Correlation with clinicopathological values: Nodal metastasis (N) | Molecular subtype | Correlation with: Prognostic variables | Correlation with: Predictive variables | N | Methodology | Localization of the markers | (Refs.) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Hu *et al*, 2018 | S100A4/ FSP-1 (αSMA, PDPN) | Upregulated | NS | NS | NS | NS | Shorter OS | NA | 3,680 | Meta-analysis | Stroma | (47) |
| | de Silva Rudland *et al*, 2006 | S100A4/ FSP-1 (osteopo-nin) | Upregulated | NS | NS | NS | NS | Shorter OS | NA | 312 | IHC | Stroma | (55) |
| | Li *et al*, 2015 | S100A4/ FSP-1 | Upregulated | NA | NA | NA | NA | NA | Higher CR | 65 | IHC | Stroma | (57) |
| | Pedersen *et al*, 2002 | S100A4/ FSP-1 | Upregulated | Positive | NS | NS | ER- | NS | NA | 66 | IHC | Stroma | (56) |
| | McKiernan *et al*, 2011 | S100A4/ FSP-1 (S100A1, S100A2, S100A6, S100A8, S100A9, S100A10, S100A11, S100A14) | Upregulated | NS | NS | NS | Basal subtype | NS | NA | 295 | IHC | Stroma | (58) |
| PDGFRβ | Hu *et al*, 2021 | PDGFRβ | Upregulated | NA | NA | NA | NA | Shorter OS, DFS | NA | 1,455 | Meta-analysis | Stroma | (66) |
| | Paulsson *et al*, 2009 | PDGFRβ | Upregulated | Positive | Positive | NS | ER-, PR-, HER2+ | Shorter RFS | NA | 512 | IHC | Stroma | (64) |
| | Paulsson *et al*, 2017 | PDGFRβ | Down-regulated | NS | Nega-tive | NS | NS | NA | Longer RFS after tamoxifen treatment | 564 | IHC | Stroma | (65) |

Table II. Continued.

| | First author/s, year | Marker: CAFs' phenotypic markers | Marker: Expression of stromal marker | Correlation with clinicopathological values: Grade | Tumour size (T) | Nodal metastasis (N) | Molecular subtype | Correlation with: Prognostic variables | Predictive variables | N | Methodology | Localization of the markers | (Refs.) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PDPN | Park *et al*, 2016 | PDPN (S100A4/ FSP-1, FAP, PDGFRα, PDGFRβ, NG2) | Upregulated | NS | NS | Positive | ER- | Shorter DFS | NA | 628 | IHC | Stroma | (54) |
| | Hu *et al*, 2018 | PDPN (S100A4/ FSP-1, αSMA) | Upregulated | NS | NS | NS | NS | Shorter DFS | NA | 3,680 | Meta-analysis | Stroma | (47) |
| | Schoppmann *et al*, 2012 | PDPN | Upregulated | Positive | NS | NS | ER- | Shorter OS,DFS | NA | 367 | IHC | Stroma | (70) |
| | Niemiec *et al*, 2018 | PDPN | Upregulated | NS | Positive | Positive | NS | Shorter DFS | NA | 203 | IHC | Stroma | (69) |
| | Tanaka *et al*, 2020 | PDPN | Upregulated | NS | NS | NA | PR- | Shorter DFS, DSS | NA | 169 | IHC | Stroma | (71) |
| | Pula *et al*, 2011 | PDPN | Upregulated | Positive | Positive | Positive | ER- | Shorter OS | NA | 117 | IHC | Stroma | (72) |
| | Friedman *et al*, 2020 | PDPN (S100A4) | Upregulated | NA | NA | NA | NA | Shorter DFS | NA | 12 | IHC | Stroma | (52) |
| | Pula *et al*, 2013 | PDPN | Upregulated | Positive | Positive | NS | NS | NS | NA | 257 | IHC | Stroma | (73) |
| FAP | Tashireva *et al*, 2017 | FAP (αSMA, CD68, RS1) | Upregulated | NA | NA | NA | NA | Presence of distant metastases | NA | 36 | RT-PCR | Stroma | (77) |
| | Bonneau *et al*, 2020 | FAP (CD29, αSMA, PDGFRβ, FSP-1) | Upregulated | NA | NA | NA | NA | Decreased RFS | NA | 52 | IHC | Stroma | (79) |
| | Ariga *et al*, 2001 | FAP | Upregulated | NA | NA | NA | NA | Longer OS, DFS | NA | 112 | IHC | Stroma | (78) |

Table II. Continued.

| | First author/s, year | Marker: Factors activating CAFs | Marker: Expression of stromal marker | Correlation with clinicopathological values: Grade | Correlation with clinicopathological values: Tumour size (T) | Correlation with clinicopathological values: Nodal metastasis (N) | Molecular subtype | Correlation with: Prognostic variables | Correlation with: Predictive variables | N | Methodology | Localization of the markers | (Refs.) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TGF-β1 | Liu *et al*, 2022 (survivin) | TGF-β1 | Upregulated | NS | NS | NS | TNBC | Shorter OS, PFS | NA | 142 | ELISA | Stroma | (84) |
| | Koumoundourou *et al*, 2007 | TGF-β1 (pSmad 2/3) | Down-regulated | NS | NS | NA | PR- | Presence of distant metastases | NA | 61 | IHC | Stroma | (83) |
| HDGF | Chen *et al*, 2012 | HDGF | Upregulated | Positive | NA | Positive | NS | Shorter RFS | NA | 86 | IHC | Stroma | (87) |
| | Qiu *et al*,2021 | HDGF | Upregulated | NA | NA | NA | NA | Shorter DFS | NA | 1,111 | online data (TCGA) | Tumour+ Stroma | (88) |
| PDGF | Seymour *et al*, 1993 | PDGF-AA, PDGFR-BB | Upregulated | NS | NS | NS | NA | Shorter OS | Lower CR | 37 | IHC, ELISA | Stroma | (92) |
| | Jansson *et al*, 2018 | PDGF-CC (PDGFRα PDGFRβ) | Upregulated | Positive | Positive | Positive | TNBC | Shorter DFS | NA | 489 | IHC | Stroma | (91) |
| Cyto-kines | Yao *et al*, 2016 | CCL2 | Upregulated | NS | Nega-tive | NS | HER2- | Shorter DFS | NA | 427 | IHC | Stroma | (97) |
| | Heiskala *et al*, 2019 | CCL2 (CD14) | Upregulated | Positive | NS | Positive | NA | Shorter RFS | NA | 137 | IHC | Stroma | (98) |
| | Yaal-Hahoshen *et al*, 2006 | CCL5 | Upregulated | NA | NA | NA | NA | Shorter RFS | NA | 142 | IHC | Stroma | (100) |
| | Yamaguchi *et al*, 2021 | CCL5 (CCR3, CCRR1, CCR5) | Upregulated | positive | NS | NS | HER2-, ER-.PR- | Shorter RFS | NA | 111 | IHC | Stroma | (99) |
| HH | Arnold *et al*, 2017 | HH (Wnt) | Upregulated | NS | NS | NS | TNBC | Shorter RFS,OS | NA | 36 | IHC | Stroma | (102) |

Table II. Continued.

| | | Marker | | Correlation with clinicopathological values | | | | Correlation with | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | First author/s, year | Cognate ligands-FGFs | Expression of stromal marker | Grade | Tumour size (T) | Nodal metastasis (N) | Molecular subtype | Prognostic variables | Predictive variables | N | Methodology | Localization of the markers | (Refs.) |
| FGF | Surowiak *et al*, 2007 | FGF2 (bFGF) (Ki-67, VEGF) | Upregulated | NS | Negative | Negative | NS | Shorter OS, RFS | NA | 45 | IHC | Stroma | (107) |
| | Yiangou *et al*, 1997 | FGF2 | Upregulated | NS | NS | NS | NS | Longer OS, DFS | NA | 51 | RT-PCR and IHC | Stroma | (108) |
| | Faridi *et al*, 2002 | FGF2 | Upregulated | Positive | NS | NS | NS | NS | NA | 111 | IHC | Stroma | (110) |
| | Shee *et al*, 2018 | FGF2 | Upregulated | NA | NA | NA | Luminal | Shorter OS,RFS | Tamoxifen resistance | 2,054 | IHC | Stroma | (34) |
| | Granato *et al*, 2004 | FGF2 (VEGF) | Upregulated | NS | NS | NS | NS | NA | NA | 62 | IHC | Stroma | (109) |
| | Colomer *et al*, 1997 | FGF2 | Down-regulated | NS | Negative | NS | NS | Shorter OS, RFS | NA | 140 | ELISA | Cytosol | (105) |
| | Linderholm *et al*, 2003 | FGF2 (VEGF) | Upregulated | NS | Negative | Negative | NS | Longer OS, RFS | NS | 1,307 | ELISA | Cytosol | (106) |
| | Smith *et al*, 1999 | FGF2 | Upregulated | Negative | Negative | NS | ER+ | NS | NA | 149 | ELISA | Cytosol | (111) |
| | Fernandez-Nogueira *et al*, 2020 | FGF5 (αSMA, FGFR2, c-Src) | Upregulated Down-regulated | NA | NA | NA | NA | Shorter OS, RFS NA | NA Higher pCR | 64 | IHC | Stroma | (28) |
| | Meijer *et al*, 2008 | FGF17 (FGFR1-4) | Upregulated | Negative | NS | Negative | NA | NA | NS | 285 | RT-PCR | Stroma | (112) |
| Circulating proteins | Ao *et al*, 2015 | αSMA, FAP | Upregulated | NA | NA | NA | NA | Positive correlation with distant metastasis | NA | 47 | CTC | Serum | (41) |
| | Al-Ashkar *et al*, 2020 | αSMA | Upregulated | Positive | NS | NS | NS | Increased risk of metastasis | NA | 46 | ELISA | Serum | (119) |

Table II. Continued.

| First author/s, year | Marker | | Correlation with clinicopathological values | | | | Correlation with | | N | Methodology | Localization of the markers | (Refs.) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cognate ligands-FGFs | Expression of stromal marker | Grade | Tumour size (T) | Nodal metastasis (N) | Molecular subtype | Prognostic variables | Predictive variables | | | | |
| Seymour *et al*, 1993 | PDGF | Upregulated | NS | NS | NS | NA | Shorter OS | Lower CR | 37 | ELISA | Serum | (92) |
| El-Abd *et al*, 2008 | S100A4/ FSP-1 | Upregulated | NS | NS | Positive | NS | Shorter | NA | 100 | RT-PCR | Serum | (114) |
| Zhu *et al*, 2020 | PDPN | Upregulated | Positive | NA | NA | NA | Presence of distant metastases | NA | 159 | CTC | Serum | (116) |
| Cai *et al*, 2023 | TGF-β1 (MMP-9) | Upregulated | Positive | NS | Positive | TNBC | Shorter DFS | NA | 86 | ELISA | Serum | (118) |
| Panis *et al*, 2013 | TGF-β1 | Down-regulated | NA | NA | NA | TNBC | Presence of distant metastases | NS | 101 | ELISA | Serum | (121) |
| Ivanović *et al*, 2005 | TGF-β1 | Upregulated | NS | NS | NS | NS | Shorter OS, presence of distant metastases | NA | 53 | ELISA | Serum | (113) |
| Tripsianis *et al*, 2013 | TGF-β1 (IL-6, TNF-α) | Upregulated | NS | NS | Positive | HER2 | Shorter OS | NA | 130 | ELISA | Serum | (115) |
| Paccagnella *et al*, 2022 | TGF-β1, IL-4, IL-6, IL-8, IL-10, CCL-2, CCL-4 (analysed as cluster) | Down regulated | NA | NA | NA | NA | Shorter OS | Shorter OS after 4 courses of eribulin | 41 | Ella Simple Plex system | Serum | (124) |
| Wang *et al*, 2020 | CXCL8 | Down-regulated | NS | NS | NS | NS | NA | higher pCR rate | 303 | ELISA | Serum | (123) |
| Kjaer *et al*, 2020 | EGF | Down-regulated | NA | NA | NA | NA | NS | NA | 311 | ELISA | Serum | (126) |

Table II. Continued.

| First author/s, year | Marker | | Correlation with clinicopathological values | | | | Correlation with | | N | Methodology | Localization of the markers | (Refs.) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cognate ligands-FGFs | Expression of stromal marker | Grade | Tumour size (T) | Nodal metastasis (N) | Molecular subtype | Prognostic variables | Predictive variables | | | | |
| Tripsianis *et al*, 2013 | IL-6 (TNF-α) | Upregulated | NS | NS | Positive | HER2+ ER+ | Shorter OS | NA | 112 | ELISA | Serum | (117) |
| Tripsianis *et al*, 2013 | IL-6 (TGF-β1, TNF-α) | Upregulated | NS | NS | Positive | HER2 | Shorter OS | NA | 130 | ELISA | Serum | (115) |
| Yahia *et al*, 2023 | IL-6 | Down-regulated | NS | NA | Negative | NS | NA | NA | 70 | ELISA | Serum | (120) |
| Milanović *et al*, 2018 | IL-6 (IL-8) | Upregulated | NA | NA | NA | HER2+ | Longer OS | NA | 79 | ELISA | Serum | (122) |
| Granato *et al*, 2003 | FGF2 | Upregulated | NS | NS | NS | NS | NA | NA | 62 | ELISA | Serum | (109) |

In brackets are given markers additionally analysed in the study. ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; FGF, fibroblast growth factor; TGF-β, tumour growth factor β; HH, sonic hedgehog; IL-6, interleukin 6; α-SMA, smooth muscle actin α; FAP, fibroblast activating protein; FSP/S100A4, fibroblast specific protein; PDGF, platelet-derived growth factor; PDGFRβ, PDGF receptor β; PDPN, podoplanin; HDGF, heparin binding growth factor; CXCL, chemokine (C-X-C motif) ligand; CCL, C-C motif chemokine ligand; EFG, epidermal growth factor; OS, overall survival; DFS, disease-free survival; RFS,recurrence free survival; N, cohort size; IHC, immunohistochemistry; RT-PCR, reverse transcription PCR.

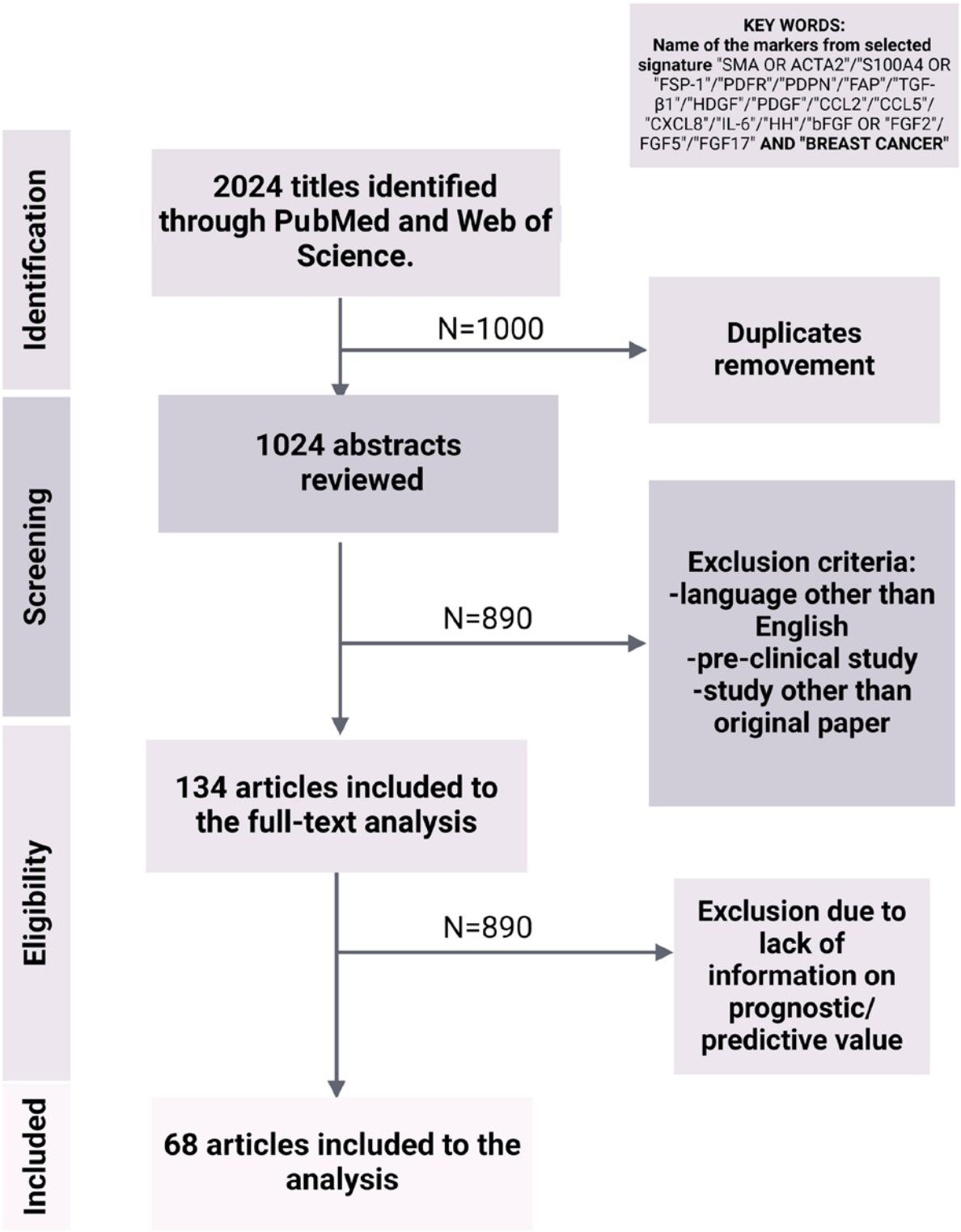


Figure 2. Flow chart of the literature search. PubMed and Medline databases were searched for the literature related to breast cancer and the prognostic and/or predictive significance of: CAFs phenotypic markers (αSMA/ACTA2, S100A4/FSP-1, PDGFR, PDPN and FAP), CAFs-derived cognate FGFR ligands (FGF2, FGF5 and FGF17) or inducers of CAFs paracrine activity (TGF-β1, HDGF, PDGF, CXCL8, CCL5, CCL2, IL-6, HH and EGF). Following exclusion criteria including pre-clinical (*in vitro* or animal) study and type of publication (review, case report), 68 out 1024 originally retrieved English language articles were finally selected and analysed. CAF, cancer-associated fibroblast; PDGFR, platelet-derived growth factor receptor; PDPN, podoplanin; FAP, fibroblast activating protein; HDGF, heparin binding growth factor; HH, sonic hedgehog; EFG, epidermal growth factor; CXCL, chemokine (C-X-C motif) ligand; CCL, C-C motif chemokine ligand; IL-6, interleukin 6.

growth factors release and angiogenesis, thus promoting tumour progression and metastasis (50). In macrophages, S100A4 binds to several intracellular proteins, which through the changes in cytoskeletal dynamics, promotes their recruitment to the tumour vicinity. In addition, S100A4 contributes to the pro-tumour macrophage polarization (51).

S100A4$^+$ CAFs derive from adipocytes, post-epithelial-mesenchymal transition (EMT) cancer cells or mesenchymal stem cells (52). S100A4$^+$ CAFs play a tumour-protecting role in immune surveillance. In S100A4-deficient mice, mammary tumours do not metastasize (52). Furthermore, through secretion of vascular endothelial growth factor and tenascin C, S100A4$^+$ CAFs participate in setting-up a pre-metastatic niche in the lung (53).

In patients with BC, S100A4 is an unfavourable prognostic factor and its upregulation correlates with tumour high grade and shorter OS (47,54-58). S100A4 expression varies between BC molecular subtypes and histologic features of the stroma (59). Upregulation of S100A4 in stromal cells was found to be associated with estrogen receptor (ER)-negativity and nodal metastases (54,56).

*PDGFRα/β*. PDGFR plays a critical role in tissue remodelling, scarring and fibrosis (60). It exists in two isoforms (PDGFRα and PDGFRβ) and is expressed in normal fibroblasts, pericytes, vascular smooth muscle cells, myocardiocytes and CAFs (21,61). Both PDGFRα and PDGFRβ are receptor tyrosine kinases with an extracellular ligand-binding domain, a single transmembrane helix, and an intracellular tyrosine kinase domain. Binding of PDGF ligands to PDGFRα/β expressed on CAFs, induces receptor dimerization, autophosphorylation and its subsequent activation. This promotes secretion of collagen and other ECM components, that by enhancing the formation of the fibrotic stroma, support tumour development (30). PDGFR-mediated signalling induces transformation of pericytes into CAFs with enhanced secretory and inflammatory features (61,62). In particular, through FGF2 and FGF7, PDGFR$^+$ CAFs promote neo-angiogenesis and cancer cell proliferation (63).

In BC, stromal PDGRFβ overexpression is associated with unfavourable clinicopathological characteristics such as high histological grade, larger tumour size (T), ER-negativity, upregulated HER2, as well as shorter DFS, recurrence-free survival (RFS) and OS (64-66). Expression of stromal PDGRβ was found prognostically significant particularly in tumours from premenopausal patients (67). Furthermore, randomized clinical studies of two BC cohorts identified stromal PDGFRβ as a marker of a therapeutic benefit of tamoxifen in early BC (65).

*PDPN*. PDPN, a mucin-type glycoprotein, promotes cancer cell migration and invasiveness and is expressed on fibroblasts, macrophages and tumour cells (20). PDPN is a transmembrane mucin-type glycoprotein with an extracellular domain rich in O-glycosylation sites. The single transmembrane helix anchors PDPN in the cell membrane and plays a role in transmitting signals from the extracellular environment to the intracellular activation of the RhoA/ROCK signalling pathway, which is involved in cytoskeletal dynamics, cell contractility and motility (68). Several studies demonstrated a positive association between increased levels of stromal PDPN, tumour grade, size (T), nodal status, ER- and progesterone receptor (PR)-negativity as well as shorter DFS and OS (47,52,69-73). Friedman *et al* (52) showed that, together with S100A4, PDPN may be instrumental in identification of CAF subpopulations, the ratio of which, having clinical implications across BC subtypes, is particularly correlated with BRCA mutations in triple-negative BC (TNBC). It was also demonstrated that the phenotypic composition of CAF population tends to fluctuate over time of cancer development. This supports the concept of CAFs' plasticity, as a key trait of a dynamic TME, co-evolving with the tumour, to nurture and provide a permissive microenvironment for its continuous growth (52).

*FAP*. FAP is a transmembrane serine protease with both dipeptidyl peptidase and endopeptidase activities. FAP's proteolytic activity allows it to degrade components of the ECM, such as gelatin, collagen and fibronectin. By ECM lysis, FAP generates bioactive fragments that can activate pro-tumorigenic signalling pathways in CAFs (74). FAP is a surface marker of activated fibroblasts in >90% of cancers (21). FAP-expressing CAFs are involved in various cancer-related processes, for example ECM-remodelling, but their key pro-tumorigenic role is ascribed to an impact on immune cell polarization and development of immunosuppressive TME (21). A number of FAP$^+$ CAF-derived soluble effector molecules, such as stromal-derived factor 1 and CCL2, have been implicated in creation of an environment facilitating tumour development (75). In particular, FAP$^+$ CAF-mediated activation of the uPAR-FAK-c-Src-JAK2-STAT3-CCL2 cascade enables recruitment of circulating myeloid-derived stem cells expressing CCR2, a cognate CCL2 receptor (21). Lo *et al* (76) demonstrated a correlation between FAP overexpression in CAFs and regulatory T cell-dependent immunosuppression. Accordingly, in BC, increased FAP$^+$ CAFs were associated with features of poor prognosis, such as distant metastases and decreased RFS (77-79). By contrast, Ariga *et al* (78) has found high density of FAP$^+$ CAFs prognostic of a longer OS and DFS (78), suggesting that FAP overexpression may also be related to extensive tissue remodelling and ECM turnover.

*Activating factors*

*TGF-β1*. The TGF-β, a large family of structurally related cytokines and growth factors, are involved in a vast number of cellular processes in development and homoeostasis of most human tissues. TGF-β1, in particular, a key regulator of the synthesis and expression of collagen, elastin and MMPs, acts through the canonical Smad-dependent and non-Smad pathways, that involve a number of receptors and interacting networks, and is strongly implicated in the pathogenesis of fibrosis (80,81). The major targets of TGF-β1 are fibroblasts, but other cell types, including macrophages, epithelial and vascular cells are also affected. In tumours, expressed at high level, TGF-β1 mediates EMT, promotes angiogenesis, and together with IL-1β, induces expression of FAP in fibroblasts (20). It is widely acknowledged, that an overall outcome of TGF-β1 activity depends on a type of a cell and its microenvironment. TGF-β1 was demonstrated to significantly affect both the fibroblast-myofibroblast transition and the rate of invasion (82). Koumoundourou *et al* (83) has also shown that downregulation of TGF-β1 in BC tissue was a marker of poor prognosis and recurrence. Using immunohistochemistry for TGF-β1, pSmad2/3 and Smad4, the authors demonstrated an inverse association between TGF-β1 and PR, as well as between Smad4 and ER, but not with any other clinicopathological features. Interestingly, although neither TGF-β1 nor pSmad2/3 were related to ER, loss of pSmad2/3 expression was prognostic of a shorter DFS in all patients, including those with ER-positive BC (83). Tissue expression of TGF-β1 and survivin was evaluated in BC samples by Liu *et al* (84),

who found that, although none of them, separately, had an independent prognostic value, increased TGF-β1/survivin co-expression was associated with shorter OS and PFS in patients with TNBC (84).

*HDGF*. Heparin binding growth factor or hepatoma-derived growth factor (HDGF) shares homology with the high mobility group 1 protein and was first purified from a human hepatoma-derived cell line (85). Widely expressed in normal tissues, HDGF promotes proliferation of various cells, including fibroblasts, as both a DNA-binding nuclear factor and a secreted protein via a receptor-mediated pathway (86). In BC, Chen *et al* (87) demonstrated that strong expression of nuclear HDGF was associated with high tumour grade, high stage, high proliferation index (Ki-67 index >20%), lymph node metastases and shorter RFS. This was confirmed by Qiu *et al* (88), who reported a negative correlation between high expression of HDGF and DFS.

*PDGF*. PDGF is a growth factor that is secreted by cancer cells and induces activation of fibroblasts (89). There are five PDGF isoforms (A-D) but only PDGF-A and -B can form functional heterodimers, that stimulate their cognate receptors (90). In most tumours, populations of PDGF-expressing cancer cells are markedly denser than those positive for PDGFR, which indicates that PDFG plays a role as a mediator of paracrine activity of cancer cells towards the neighbouring stroma (90). The primary effect of PDGF on fibroblasts is their recruitment and stimulation of proliferation with, unlike TGF-β, no influence on the phenotypic switch into myofibroblasts (90). In BC, high expression of PDGF (AA and BB) was found to be correlated with high grade, high Ki67, young age (<50 years), tumour size, triple negativity and shorter DFS (91). Moreover, confirmed to be associated with poor prognosis in stage IV BC, PDGF (AA, BB, CC) was also shown to be predictive of a low response rate to chemotherapy (92).

*Cytokines*. The role of CAFs in orchestration of inflammation in immune TME is well recognized (62). Both target and source of a number of immune-modulatory and chemo-attractive mediators such as Chemokine (C-X-C motif) ligand 8 (CXCL8), CCL5, CCL2 and IL-6, CAFs participate in the recruitment of suppressive myeloid and regulatory T cells, polarization of M2 macrophages, suppression of cytotoxic lymphocytes and dendritic cells, that contribute to the modulation of TME towards tumour-promoting immunosuppressive environment (62,93).

CXCL8, CCL2 and CCL5, essential components of the tumour-stroma-inflammatory network, are associated with aggressive BC phenotype and increased risk of recurrence. Produced mostly by macrophages, these pro-inflammatory chemokines attract and activate resident immune cells (93), induce EMT (94), promote tumour metastasis (95) as well as modify tumour response to therapy (96). Higher levels of these three chemokines were shown to be associated predominantly with basal BC (93). Several studies have demonstrated an association between high expression of CCL2, high grade, lymph node metastases and HER2-negativity as well as shorter DFS and RFS (97,98). CCL5 was analysed by Yamaguchi *et al* (99), who found that stromal CCL5 was negatively associated with tumour size, as well as ER and PR expression. CCL5 levels significantly correlated with the aggressive phenotype and this was noted particularly in the CCR3-positive tumours (99). Moreover, in another study, expression of CCL5 was prognostic of shortened RFS, suggesting that CCL5 promotes BC progression and contributes to the worse disease outcome (100).

*Hedgehog (HH)*. The HH-signalling pathway plays a fundamental role in embryonic development of various organs and its dysregulation has been associated with several malignancies. In mammary gland, overactivation of HH-signalling has been suggested to stimulate self-renewal of normal and tumorigenic stem cells, thus promoting BC formation (101). However, prognostic and predictive value of HH pathway in BC still remains largely understudied. In a single study comprising 36 patients with TNBC, activation of HH combined with Wnt pathway identified patients at risk for early recurrence (102).

*Cognate ligands-FGFs*. FGFs are a family of signalling proteins, which in humans comprises 23 members, with paracrine (FGF1-10, FGF 16-18, FGF 20 and FGF22) or endocrine (FGF19, FGF21 and FGF23) mode of action. FGFs bind with different affinity to one or several of the four transmembrane FGF receptors (FGFR1-4) (103), activation of which, through the Ras-dependent MAPK, PI3K/AKT or STATs-dependent pathways, influences cell proliferation, differentiation and survival (Fig. 1) (104). Cellular responses induced by FGF/FGFR vary between biological contexts, which are determined by a number of factors, including cell type-specific adaptor molecules, signal transduction enhancers, transcription factors and co-activators, as well as interacting other signalling networks (34). Whereas translational significance of FGFRs' alterations in human cancer is being analysed by numerous research groups, albeit with conflicting results, available data on the clinical value of their ligands (FGFs) in BC are scarce, often inconclusive, and restricted only to: FGF2, FGF5 and FGF17. For example, while downregulation of FGF2 was found a marker of poor prognosis (105), its upregulation was associated with both shorter and longer RFS and OS (34,106-108). In a study by Colomer *et al* (105), downregulation of FGF2 was associated with longer OS and RFS; whereas Granato *et al* (109) reported that an association with survival parameters was not significant. Moreover, although upregulation of FGF2 correlated with small tumour size and decreased incidence of nodal metastases, it was inconsistently (both low and high) linked to tumour grade (106,107,110,111). Predictive value of FGF2 was reported by Shee *et al* (34), who demonstrated that its upregulation in $ER^+$ BC was significantly predictive of anti-estrogen resistance and shorter RFS and OS. Upregulation of FGF5 was found to be associated with shorter OS and RFS (28). The only existing study of a prognostic value of FGF17 in BC demonstrated that its upregulation inversely correlated with tumour grade and nodal status (112).

## 3. Circulating proteins

*aSMA, FAP, PDGFR, S100A4/FSP-1, PDPN, TGF-β1, IL-6*. In most studies, increased serum (or plasma) level of *aSMA, FAP, PDGFR, S100A4/FSP-1, PDPN, TGF-β1, IL-6* markers have been found to be linked to unfavorable disease indicators such as high grade, metastases and shorter OS (41,92,113-120).

By contrast, for TGF-b1 and IL-6, several studies documented their association with a good disease outcome. For example, Panis *et al* (121), showed that an early presentation of TNBC (<45 years of age) was associated with high levels of circulating TGF-β1, while in metastatic BC, TGF-β1 plasma

concentration was lower than in non-metastatic disease. In a 40-month follow-up, women with low TGF-β1 levels (<20 pg/ml) were shown to have a tendency for a reduced OS and doxorubicin induced decrease in TGF-β1 concentration, promptly after drug infusion. Interestingly, levels of plasma TGF-β1 were not affected by surgical removal of the primary tumour and did not differ between patients with responsive and resistant disease (121). Milovanović *et al* (122) has found serum concentration of IL-6 as the independent prognostic factor of a good disease outcome.

The discrepancies between the studies are, at least partially, due to the well documented pleiotropy of both cytokines that, via either pro- or anti-inflammatory activity, may differently affect tumour progression.

*CXCL8*. Low level of serum CXCL8 was associated with higher pathological complete response of patients with TNBC in response to neoadjuvant chemotherapy (123).

*Cytokine clusters*. In an attempt to identify the cluster/s that would support the prognostic significance of longitudinal serum cytokine analysis, Paccagnella *et al* (124) have recently shown in patients with BC treated with eribulin that, after four courses of therapy, low levels of TGF-β, IL-4, IL-6, IL-8, IL-10, CCL-2 and CCL-4 (out of 18 cytokines evaluated) were associated with the best patient survival. This novel approach to design a kind of a prognostic 'serum signature', if validated, may prove very valuable in decision making related to the type and time course of applied therapy (124).

*EGF*. Known as the main ligand of the epidermal growth factor (EGF) receptor, a dominant oncogenic driver in numerous cancers, EGF plays also an important role in fibroblast differentiation and activation. Signalling from EGF downregulates Rho-GTP levels, which gives permissive signals for Rac1 activation and fibroblast polarization (125). This leads to fibroblast transformation into myofibroblasts which, together with growth-promoting action of TGF-β1, reciprocally promotes cancer cell invasion (125). However, at the clinical level, there is no evidence to demonstrate any translation value of stromal EGF in BC. Results of the only existing study evaluating EGF plasma level have demonstrated no significant associations with clinicopathological features or disease prognosis (126).

*FGF2*. The data on FGF2 showed that in a parallel evaluation in the serum and tissue, there was no correlation between its tumour expression and the corresponding serum level (105).

In summary, although determination of biomarkers obtainable by liquid biopsy appears to be very attractive for minimally invasive and inexpensive diagnosis and prognostication, the level of a secreted and/or shredded protein in the plasma, being not cell- or tissue-specific, does not faithfully reflect the expression in the analysed organ, and hence its role in the mechanisms of disease development. This implies that a more complex approach combining evaluation of a panel of both serum and histological biomarkers with imaging-based metrics may provide a more efficient tool for clinical practice.

## 4. Conclusion and perspectives

Available evidence clearly demonstrates that CAFs contain a valuable prognostic information in BC. While presented studies of single markers (for example αSMA, S100A4, PDGFR or PDPN) identify promising candidates, analyses combining several stromal, either CAFs-specific or CAF-derived features (for example S100A4/PDPN (52), αSMA/FGF5 (28), or PDGFR/FGF2/FGF7 (63) reveal the traits of clinically more significant implications. This indicates that comprehensive analyses of CAFs in relation to other components of the stroma might improve an assessment of CAFs involvement in the tumorigenic process and their value as prognostic and predictive biomarkers.

CAFs are not currently used in routine histopathological practice. The challenge is to design biologically meaningful signatures that would capture essential molecular profiles and could be exploited in prognostication. Given CAFs' heterogeneity, plasticity and an intricate cross-talk with other TEM components, it appears that this could be achieved by profiling the chosen (for example micro-dissected) area of the stroma towards carefully selected panel of makers relevant to specific aspects of BC biology. In particular, the proposed 'FGFR-related stromal profile of CAFs' might provide (after a necessary further clinical validation) the context for an assessment of the true FGFR's clinical value as well as the criteria for further classification of patients with BC for the FGFR-targeted therapy.

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## Authors' contributions

JS designed the framework, performed the literature search, prepared the figure and the tables, and wrote the manuscript. MB supervised the research and selection of the literature. RS provided substantive support and critical review. HMR provided the concept and edited the manuscript. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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