Neoplasia • Vol. 9, No. 2, February 2007, pp. 90–100 90

www.neoplasia.com

Nonreceptor Tyrosine Kinases in Prostate Cancer

*Yu-Ming Chang**, Hsing-Jien Kung**,†,‡ and Christopher P. Evans**,‡

Departments of *Urology and †Biological Chemistry, University of California at Davis, Sacramento, CA 95817, USA; ‡Cancer Center, University of California at Davis, Sacramento, CA 95817, USA

Abstract

BACKGROUND: **Carcinoma of the prostate (CaP) is the most commonly diagnosed cancer in men in the United States. Signal transduction molecules such as tyrosine kinases play important roles in CaP. Src, a nonreceptor tyrosine kinase (NRTK) and the first proto-oncogene discovered is shown to participate in processes such as cell proliferation and migration in CaP. Underscoring NRTK's and, specifically, Src's importance in cancer is the recent approval by the US Food and Drug Administration of dasatinib, the first commercial Src inhibitor for clinical use in chronic myelogenous leukemia (CML). In this review we will focus on NRTKs and their roles in the biology of CaP.** ***MATERIALS AND METHODS:*** **Publicly available literature from PubMed regarding the topic of members of NRTKs in CaP was searched and reviewed.** ***RESULTS:*** **Src, FAK, JaK1/2, and ETK are involved in processes indispensable to the biology of CaP: cell growth, migration, invasion, angiogenesis, and apoptosis.** ***CONCLUSIONS:*** **Src emerges as a common signaling and regulatory molecule in multiple biological processes in CaP. Src's relative importance in particular stages of CaP, however, required further definition. Continued investigation of NRTKs will increase our understanding of their biological function and potential role as new therapeutic targets.**

Neoplasia (2007) **9,** 90–100

Keywords: Nonreceptor tyrosine kinase, prostate cancer, Src, FAK, ETK.

Introduction

Carcinoma of the prostate (CaP) is the most commonly diagnosed cancer in American men, consisting of more than 33% of all new cancer cases. Though many patients are diagnosed with CaP, it has a relatively low mortality rate when compared to other cancers. Nevertheless, it remains the third leading cause of cancer-related deaths in men in the United States, with about 27,350 estimated CaP-related deaths in 2006 in the United States [1]. Because CaP growth is facilitated by androgen exposure and because androgen withdrawal leads to apoptosis of CaP cells, the current treatment of choice for recurrent or metastatic CaP includes castration through chemical or surgical means. Nearly all patients, however, relapse with androgen-independent (AI) disease after androgen ablation therapy. Ultimately, the uncontrolled growth of AI metastatic tumors leads to patient mortality.

Tyrosine kinases (TKs) are signaling molecules well known for their roles in human diseases such as diabetes and cancer. Indeed, v-Src sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog (Src), a nonreceptor tyrosine kinase (NRTK), was the first proto-oncogene discovered. More than a quarter of a century has passed since the discovery of Src, and the studies on TKs are coming to fruition with the development and use of tyrosine kinase–based target-specific therapy such as Gleevec, Iressa, and Herceptin for therapy against chronic myelogenous leukemia (CML), lung cancer, and breast cancer, respectively. Dasatinib, a dual Src/v-Abl Abelson murine leukemia viral oncogene homolog (Abl) inhibitor with anti-migratory activity in prostate cancer cells in culture was recently approved by the US Food and Drug Administration for use in patients with CML [2]. Further underscoring the importance of NRTKs, AZD0530 is another dual Src/Abl inhibitor that is currently in multicenter phase II clinical trials for multiple types

Abbreviations: Abl, v-Abl Abelson murine leukemia viral oncogene homolog; AI, androgen-independent; Akt, v-akt murine thymoma viral oncogene homolog 1; AR, androgen receptor; *ARG*, Abelson-related gene; Bcr, breakpoint cluster region; BrK/PTK6, breast tumor kinase/protein tyrosine kinase 6; BPH, benign prostatic hypertrophy; *BRCA1*, breast cancer susceptibility gene 1; CaP, carcinoma of the prostate; CML, chronic myelogenous leukemia; CRKII, v-crk avian sarcoma virus CT10 oncogene homolog; CSK, C-terminal Src kinase; DOC-2/DAB2, differentially expressed in ovarian cancer-2/disabled-2; EGF, epidermal growth factor; ER, estrogen receptor; ERK1/2, extracellular signal–regulated kinase 1/2; ET1, endothelin; ETK/BMX, endothelial/epithelial tyrosine kinase/bone marrow X kinase; FAK, focal adhesion kinase; FeR, FpS/FeS–related tyrosine kinase; FeS/FpS, feline sarcoma oncogene/fujinami avian sarcoma viral oncogene homolog; FGR, Gardner-Rasheed feline sarcoma viral (v-FGR) oncogene homolog; Fyn, Fyn oncogene related to Src, FGR, Yes; HIF-1α, hypoxia-inducible factor 1α; IGF-1, insulin-like growth factor 1; IL, interleukin; JaK, Janus kinase; KAI1/CD82, Kangai 1/cluster designation 82; LcK, lymphocyte-specific protein tyrosine kinase; Lyn, v-Yes-1 Yamaguchi sarcoma viral-related oncogene homolog; LPA, lysophosphatidic acid; *Met*, met proto-oncogene (hepatocyte growth factor receptor); MMP, matrix metalloproteinase; NEP, neutral endopeptidase; NRTK, nonreceptor tyrosine kinase; p130CAS, p130 CRK-associated substrate; PAK1, p21-associated kinase 1; PDGF, platelet-derived growth factor; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; PSA, prostate-specific antigen; PTEN, phosphatase and tensin homolog; PYK2/CAKβ, proline-rich tyrosine kinase 2/cell adhesion kinase β; Raf, v-raf-1 murine leukemia viral oncogene homolog 1; Ras, v-Ha-ras Harvey rat sarcoma viral oncogene homolog; SH, Src homology; Src, v-Src sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog; STAT, signal and transducer of transcription; SYK, spleen tyrosine kinase; Tec, Tec protein kinase; TGF, tumor growth factor; TIMP, tissue inhibitor of metalloproteinase; TKIP, tyrosine kinase inhibitor peptide; TnK, tyrosine kinase nonreceptor; TyK2, tyrosine kinase 2; VEGF, vascular endothelial growth factor; Yes, v-Yes-1 Yamaguchi sarcoma viral oncogene homolog 1

Address all correspondence to: Christopher P. Evans, Department of Urology, University of California at Davis, Suite 3500, 4860 Y Street, Sacramento, CA 95817.

E-mail: cpevans@ucdavis.edu

Received 29 October 2006; Revised 2 January 2007; Accepted 2 January 2007.

DOI 10.1593/neo.06694

of malignancies, including prostate cancer. In this review we will focus on each of the NRTKs and what is known about their respective roles in the biological processes of cell proliferation, migration, invasion, apoptosis, and angiogenesis in CaP.

There are several NRTK families. These are classified based on their structural similarities (Figure 1): Abl, tyrosine kinase nonreceptor (TnK), C-terminal Src kinase (CSK), focal adhesion kinase (FAK), feline sarcoma oncogene/fujinami avian sarcoma viral oncogene homolog (FeS), Janus kinase (JaK), Src, Tec protein kinase (Tec), and spleen tyrosine kinase (SYK). Though these NRTK families are extensively and individually reviewed elsewhere, this

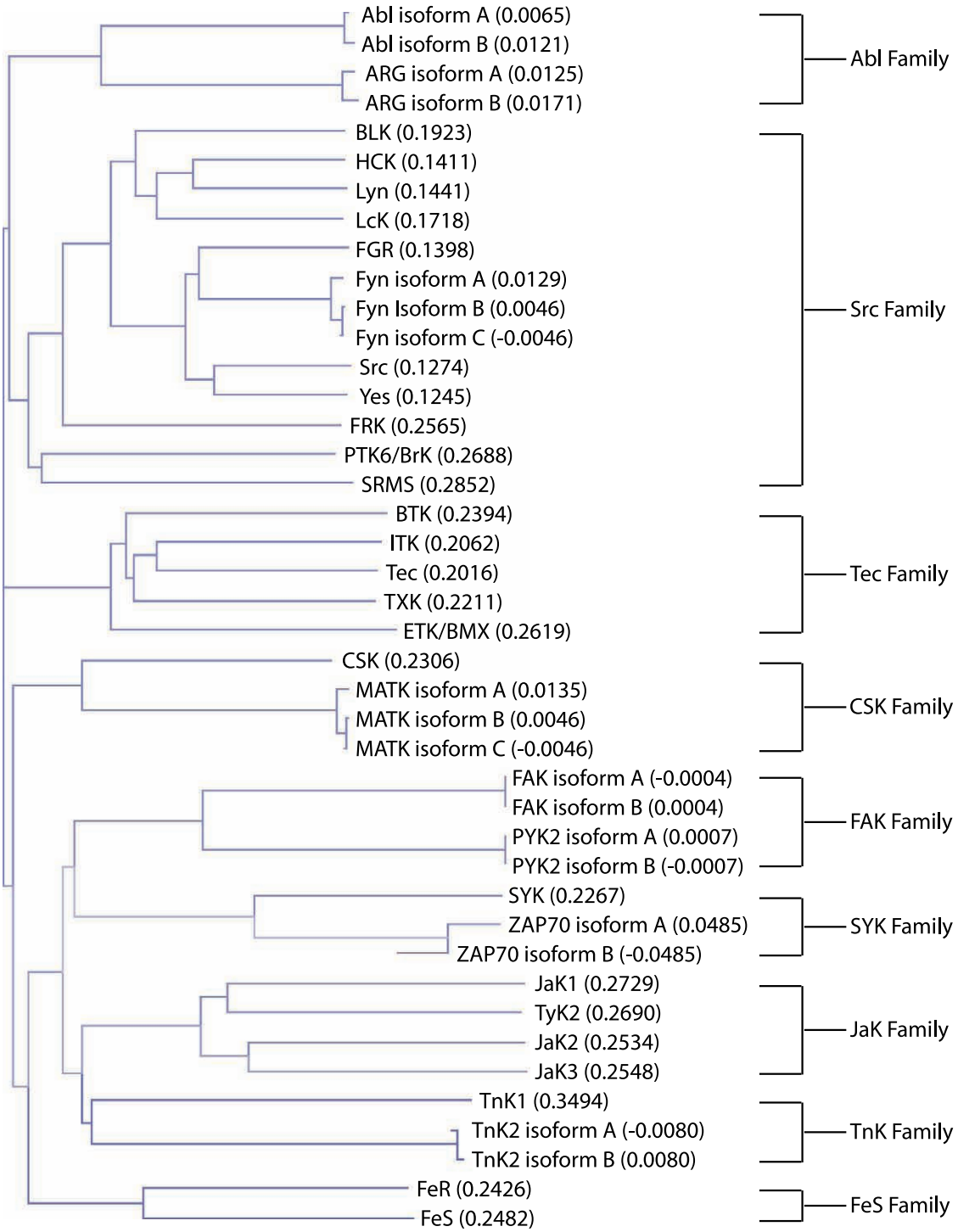

Figure 1. *NRTK families and their members in a guide tree. Protein sequences are obtained from Entrez Gene and aligned using Vector NTI Advance software (Invitrogen, Carlsbad, CA). Vector NTI Advance uses the neighbor-joining method of phylogenetic tree construction by Saitou and Nei [127]. The numbers in parentheses after each kinase reflect the calculated distance values between pairs of analyzed sequences.*