SFK Inhibitors as New Strategy for RMS Treatment

Luigi Bagella1,2* and Irene Marchesi1

Department of Biomedical Sciences, and National Institute of Biostructures and Biosystems, University of Sassari, Sassari, Italy

1Sbarro Institute for Cancer Research and Molecular Medicine, Center for Biotechnology, College of Science and Technology, Temple University, Philadelphia, USA

*Corresponding author: Luigi Bagella, Adjunct Associate Professor Sbarro Health Research Organization Center of Biotechnology Department of Biology College of Science and Technology, Temple University, BioLife Science Building, Philadelphia, USA, Tel: 215-204-9524; Fax: 215-204-9522; E-mail: bagella@temple.edu

Received date: January 07, 2016; Accepted date: February 11, 2016; Published date: February 16, 2016

Copyright: © 2016 Bagella L, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

RMS (Rhabdomyosarcoma) is represented approximately half of the total pediatric soft tissue sarcoma (STS), slightly more frequent in males but equally distributed across racial groups [1]. RMS is characterized by the expression of genes involved in the early myogenesis which fail to complete differentiation and cell cycle arrest [2]. It can be divided into 2 major histological subtypes: embryonal (eRMS), mostly found in childhood, and alveolar (aRMS) common in both children and adults [1].

The outcome of RMS patients is improved in the last decades (5-year survival rates of ~70%), however, patients with tumor relapse after treatment or with metastasis at diagnosis are rarely cured [3,4]. Moreover, frequent toxicity and long-term side effects associated with the therapy, dramatically affect the quality of life [1]. Consequently, new specific therapeutic strategies, able to reduce toxicity and side effects, are required for the treatment of RMS. The induction of differentiation and/or cell death through the inhibition of specific enzyme involved in carcinogenesis and tumor progression can be a promising strategy for RMS patients. For instance, several studies focus on the role of epigenetic changes in RMS with the purpose to investigate if the modulation of the activity of some epigenetic enzyme involved in carcinogenesis and tumor progression can be a good strategy for RMS treatment.

Rhabdomyosarcoma (RMS) represents approximately half of the total pediatric soft tissue sarcoma (STS), slightly more frequent in males but equally distributed across racial groups [1]. RMS is characterized by the expression of genes involved in the early myogenesis which fail to complete differentiation and cell cycle arrest [2]. It can be divided into 2 major histological subtypes: embryonal (eRMS), mostly found in childhood, and alveolar (aRMS) common in both children and adults [1].

The outcome of RMS patients is improved in the last decades (5-year survival rates of ~70%), however, patients with tumor relapse after treatment or with metastasis at diagnosis are rarely cured [3,4]. Moreover, frequent toxicity and long-term side effects associated with the therapy, dramatically affect the quality of life [1]. Consequently, new specific therapeutic strategies, able to reduce toxicity and side effects, are required for the treatment of RMS. The induction of differentiation and/or cell death through the inhibition of specific enzyme involved in carcinogenesis and tumor progression can be a promising strategy for RMS patients. For instance, several studies focus on the role of epigenetic changes in RMS with the purpose to investigate if the modulation of the activity of some epigenetic enzyme involved in carcinogenesis and tumor progression can be a good strategy for RMS treatment.

Introduction

A new study investigates about the activity of a new SFK inhibitor in RMS. SI221 is a pyrazolo [3,4-d] pyrimidine derivative that showed an antiproliferative effects and differentiation in eRMS and aRMS. SFKs are frequently overexpressed in RMS and their inhibition can be a good strategy for RMS treatment.

Rhabdomyosarcoma (RMS) represents approximately half of the total pediatric soft tissue sarcoma (STS), slightly more frequent in males but equally distributed across racial groups [1]. RMS is characterized by the expression of genes involved in the early myogenesis which fail to complete differentiation and cell cycle arrest [2]. It can be divided into 2 major histological subtypes: embryonal (eRMS), mostly found in childhood, and alveolar (aRMS) common in both children and adults [1].

The outcome of RMS patients is improved in the last decades (5-year survival rates of ~70%), however, patients with tumor relapse after treatment or with metastasis at diagnosis are rarely cured [3,4]. Moreover, frequent toxicity and long-term side effects associated with the therapy, dramatically affect the quality of life [1]. Consequently, new specific therapeutic strategies, able to reduce toxicity and side effects, are required for the treatment of RMS. The induction of differentiation and/or cell death through the inhibition of specific enzyme involved in carcinogenesis and tumor progression can be a promising strategy for RMS patients. For instance, several studies focus on the role of epigenetic changes in RMS with the purpose to investigate if the modulation of the activity of some epigenetic enzyme involved in carcinogenesis and tumor progression can be a good strategy for RMS treatment.

The outcome of RMS patients is improved in the last decades (5-year survival rates of ~70%), however, patients with tumor relapse after treatment or with metastasis at diagnosis are rarely cured [3,4]. Moreover, frequent toxicity and long-term side effects associated with the therapy, dramatically affect the quality of life [1]. Consequently, new specific therapeutic strategies, able to reduce toxicity and side effects, are required for the treatment of RMS. The induction of differentiation and/or cell death through the inhibition of specific enzyme involved in carcinogenesis and tumor progression can be a promising strategy for RMS patients. For instance, several studies focus on the role of epigenetic changes in RMS with the purpose to investigate if the modulation of the activity of some epigenetic enzyme involved in carcinogenesis and tumor progression can be a good strategy for RMS treatment.

SFK is a family of non-receptor tyrosine kinases that includes c-SRC, FYN, YES, BLK, YRK, FGR, HCK, LCK and Lyn. These enzymes are involved in several biological processes as cell proliferation, adhesion, invasion and motility; their expression or activity is frequently altered in cancer [14]. SKFs modulate adhesion, invasion and cell motility mainly through the disruption of adherents and focal junctions.

Adherent junctions are responsible for cell–cell adhesion and they are composed by E-cadherin homodimers of adjacent cells connected to the actin cytoskeleton through the complex α-catenin–β-catenin and p120 catenin. c-SRC activated by protein tyrosine phosphatase 1B-dependent de-phosphorylation, associates to this complex promoting the disassembly of adherents junction. Focal adhesions are responsible for the binding of cells to the extracellular matrix through heterodimers α- and β-integrin. A cytoplasmic complex connects integrins to the cytoskeleton. SFKs activate focal-adhesion kinase (FAK) that in turn phosphorylate several component of the junctions promoting cytoskeleton changes and focal adhesion disruption (reviewed in [14]). Furthermore, c-SRC induces tyrosine phosphorylation of RRAS, suppressing integrin activity, cell-matrix adhesion and disrupting focal adhesion [15].

Moreover, SFKs induce phosphorylation, ubiquituation and endocytosis of E-cadherin, promoting the release of cells from the matrix and from each other [16].

Several papers explore the role of SFK and associated pathways in sarcomas.

A first screening showed that SRC is activated in human sarcomas and sarcoma cell lines [17]. Moreover, global tyrosine phosphorylation analysis in sarcoma cell lines and human tumor samples showed an increase of the expression and phosphorylation of tyrosine kinases including several members of SFKs as, for instance, c-SRC, Lyn, and FAK [18]. Furthermore, the treatment of several sarcoma cell lines with Dasatinib, a SFK inhibitor, blocks SRC downstream pathways inhibiting FAK and p130cas signaling. Dasatinib inhibited cell motility and invasion, indicating SFKs as good targets for sarcoma treatment [17] (Table 1).

<table>
<thead>
<tr>
<th>Table 1: SFK inhibitors tested in RMS.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical phase (ClinicalTrials.gov)</strong></td>
</tr>
<tr>
<td>Dasatinib</td>
</tr>
<tr>
<td>PP2</td>
</tr>
<tr>
<td>Saracatinib</td>
</tr>
<tr>
<td>SI221</td>
</tr>
</tbody>
</table>

For what concern specifically RMS, it has been shown that SFKs have a role in both eRMS and aRMS. For instance, SFC increases oncogenic activity of Caveolin-1 through its phosphorylation...
(pCav-1), indeed high levels of pCav-1 augment cell proliferation, migration, invasiveness and chemoresistance of RMS cells. On the contrary, treatment with PP2, a SFK inhibitor, decreases cell proliferation [19].

Interestingly, aRMS SFKs are also involved in acquired resistance to the PDGFRA inhibitors. Indeed treating the resistant cell cultures with a combination of PDGFRA and inhibitors has a synergic effect on cancer cell viability. Moreover, treatment with Sorafenib, targeting both PDGFRA and Raf (downstream in the SFKs signaling), inhibits cell growth and tumor progression in vitro and in vivo [20].

Similar mechanism happens also when RMS cells are treated with insulin-like growth factor 1 receptor (IGF-1R) inhibitors. After treatment with BMS-754807, eRMS and aRMS cells develop resistance to IGF-1R blockade, a small molecular inhibitor of IGF-1R/insulin receptor or with an antibody against IGF-1R (R1507). This process is mediated by an increased activation of SFKs. Indeed the combination of IGF-1R inhibition with the SFK inhibitor Dasatinib rescues antitumoral activity of drugs [21].

In 2013, Yeung and coworkers performed a loss-of-function screening in eRMS and aRMS identifying the CRKL-YES as a crucial pathways for tumor growth [12]. CRKL is a member of the Crk adapter proteins, a protein family involved in intracellular signaling pathways able to transduce signals downstream of several receptor tyrosine kinases. In this study, the authors demonstrated that CRKL signaling is associated with the activity of YES kinase. Indeed loss of CRKL decreased specifically level of phosphorylated YES in both eRMS and aRMS. In addition, the treatment with SFK inhibitors, Dasatinib and Saracatinib, decreased phosphorylation of CRKL and SFK confirming the hypothesis of a functional relationship between SFK and CRKL in RMS. The treatment with both SFK inhibitor suppressed RMS cell growth in vitro and in vivo [12].

The important role of YES in RMS induced scientist to find molecules more specific for this tyrosine kinase. For instance, Patel and coworkers performed an assay to combine high throughput screening with a biochemical assay for Yes kinase in order to identify new and specific inhibitors [22].

SI221 is a new specific inhibitor of SFK and its ability to inhibit specifically YES and to induce both apoptosis and differentiation makes it a promising molecule for the treatment of RMS.

References