14-3-3σ and Its Modulators

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14-3-3σ is an acidic homodimer protein with more than one hundred different protein partners associated with oncogenic signaling and cell cycle regulation.

Keywords: protein-protein interaction (PPI) ; 14-3-3σ ; dimer ; stabilizer ; inhibitor ; cancer

1. Introduction

The 14-3-3 proteins are a group of acidic polypeptides that are highly conserved in all eukaryotic cells[1][2][3]. The 14-3-3 family was initially described by Moore & Perez in 1967 as an abundant mammalian brain protein family which took its name based on its elution profile, specifically the fraction number of bovine brain homogenate from diethylaminoethyl (DEAE) cellulose column (14th fraction) and subsequent purified fraction 3.3 from gel electrophoresis[4][5][6][7][8]. The 14-3-3 family comprises seven human isoforms which are named after their respective elution positions on high performance liquid chromatography (HPLC) (β-beta, ε-epsilon, γ-gamma, η-eta, σ-sigma, τ-tau, and ζ-zeta) with at least 500 partners forming protein–protein interaction (PPI) in mammalian cells[9][10][11][12]. Moreover, 14-3-3 proteins have also been detected in non-vertebrate species such as plants and yeasts [13][14][15][16][17]. The overall structure of 14-3-3 proteins is highly conserved among the family members with a molecular mass of approximately 28–30 kDa and isoelectric point of 4–5[9][18]. Crystal structures of 14-3-3 proteins revealed that they are highly helical with a clamp-like shape dimer. All human 14-3-3 isoforms are expressed as both homo- and heterodimers. The dimer form of 14-3-3 proteins is capable of binding two ligand motifs at the same time, either from the same target or from two different partners[19].

The 14-3-3 proteins are also classified as phosphoserine/phosphothreonine (pSer/pThr)-recognition proteins, as they generally exert their activity through binding to the phosphoserine/phosphothreonine-containing motifs of a multitude of molecules with various functions such as kinases, phosphatases, transmembrane receptors, and transcription factors[2][20][21][22]. In general, there are two high-affinity phosphorylation-dependent binding motifs that are recognized by the amphipathic binding grooves of all 14-3-3 isoforms, i.e., Arg-Ser-Xaa-pSer-Xaa-Pro (R-S-X-pS-X-P, mode I, Figure 1a) and Arg-Xaa-Xaa-Xaa-pSer/Thr-Xaa-Pro (R-X-X-X-pS/T-X-P, mode II, Figure 1b), where X is any amino acid and pS/T represents phosphorylated serine or threonine[23][24][25][26][27]. A third binding motif recognized by the C-terminus of 14-3-3 proteins, i.e., pS/pT-X_{1-2}-COOH (mode III, Figure 1c) has also been reported [28][29]. Nevertheless, not all 14-3-3 interactions require a phosphorylated residue as 14-3-3 has also been reported to bind to several non-phosphorylated proteins and peptides, such as exoenzyme S, Cdc25B, and p190RhoGEF [30][31][32][33][34][35].

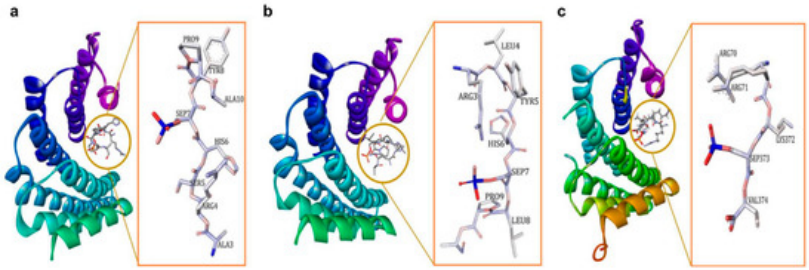

Figure 1. (**a**) 14-3-3ζ/phosphopeptide complex (mode 1, PDB: 1QJB), (**b**) 14-3-3ζ/phosphopeptide complex (mode II, PDB: 1QJA), (**c**) 14-3-3σ/TASK3 peptide (mode III, PDB: 6GHP).

Consistent with the ability of 14-3-3 proteins to bind to various binding motifs, 14-3-3 proteins are found to be involved in a wide range of physiological processes which include cell proliferation[36][37][38], cell cycle control [39][40][41][42][43], and cell apoptosis[44][45][46][47].

2. Role of 14-3-3σ in Cancer

The 14-3-3σ protein has attracted the attention of researchers as a vital target to fight against cancer growth and metastasis. Previous studies have demonstrated the role of 14-3-3σ in suppressing tumor metabolic reprogramming [48]. In addition, few reports have also highlighted the crucial role of 14-3-3σ against the cancer cell invasion and metastasis. For instance, a low level of 14-3-3σ has been shown to promote production of lactate which stimulates the migration of epithelial cancer cells to a distant organ through breaking down of extracellular matrix[48][49]. Studies have also showed that, among all seven well-known human 14-3-3 isoforms, 14-3-3σ is the only isoform that possesses tumor-suppressing activity[9][19][50][51][52]. It has been shown that 14-3-3σ protein directly controls the G2-M checkpoint of the cell cycle by protecting the tumor suppressor factor P53 against the MDM2-mediated ubiquitination and degradation[53][54][55]. In addition, 14-3-3σ was also reported to play a crucial role in the cell cycle arrest regulation by acting as a cyclin-dependent kinase (Cdk) inhibitor, i.e., through sequestering the cyclin-dependent kinase 1-cyclin B1 complex from entering nucleus and initiate mitosis, as well as binding to the cyclin-dependent kinases 2 and 4[56][57]. Moreover, 14-3-3σ was also found to negatively regulates the oncogenic activity of the Protein kinase B (also known as Akt) and thus protecting against Akt-mediated tumorigenesis[53]. Further, 14-3-3σ has also been reported as a target gene in mammary epithelial cells which regulates the antiproliferative activity of the transforming growth factor-beta 1 (TGF-b1) through the Smad3-dependent mechanism[58][59]. Furthermore, reports have demonstrated 14-3-3σ involvement in controlling cell proliferation and cancer metastasis via the termination of NF-κB signal in mammary cells by regulating the nuclear export of the p65 subunit of NF-κB transcription factor and subsequently inhibits its transcriptional activity[60][61]. Moreover, 14-3-3σ has also been reported to regulate the expression of human TASK-3 channel (which is believed to facilitate cancer cell's proliferation and survival), by blocking the endoplasmic reticulum retention sequences, and thereby promoting the surface expression of this channel[62][63][64]. 14-3-3σ also regulates the oncogenic activity of transcriptional coactivator TAZ which is an oncogenic protein that promotes cell proliferation and migration. The binding of TAZ to 14-3-3σ leads to cytoplasmic retention of TAZ which subsequently disabling its function[65][66].

Unlike other isoforms which show elevated expression in many types of cancer, 14-3-3σ protein level is downregulated in chronic myeloid leukaemia, nasopharyngeal carcinoma, as well as lung, breast, oesophageal, uterine, ovarian, and skin cancers[2][67][68][69][70][71]. The low expression level of 14-3-3σ protein in many cancer types has been linked to either promoter hypermethylation of Sfn gene (which encodes the 14-3-3σ protein) or direct 14-3-3σ degradation through ubiquitination which eventually aborts the normal physiological role of 14-3-3σ against tumor growth and metastasis[51][72][73][74][75]. Consistent with these observations, introduction of a DNA demethylating agent, 5-aza-20-deoxycytidine significantly upregulated the expression level of 14-3-3σ in salivary gland adenoid cystic carcinoma and nasopharyngeal carcinoma[76]. In addition, a separate study demonstrated that an upregulation of 14-3-3σ expression by *Marsdenia tenacissima* extract was able to mediate G2/M cell cycle arrest in breast cancer [78].

Although numerous studies have showed the vital role of 14-3-3σ in controlling the tumor formations and metastasis, some studies have also indicated that the 14-3-3σ could be a double-edged sword [68] as its upregulation has also been linked with resistance to chemotherapeutic agents[79][80][81]. In addition, studies have shown that 14-3-3σ also induces overexpression of matrix metalloproteinase 1 (MMP-1), a proteolytic enzyme that degrades native fibrillar collagens, and is often associated with poor prognosis in malignant tumor[62][82][83]. Furthermore, 14-3-3σ has also been reported to bind to the c-Abl protein, preventing its nuclear translocation and subsequently interfering with its pro-apoptotic effect[84][85].

3. Conclusions

In conclusion, the aberrant expression of 14-3-3σ has been observed in many cancers. Various protein partners and mechanisms involving 14-3-3σ in cancer growth and metastasis have been reported. This suggests that 14-3-3σ is an important target for anticancer drug discovery and development. Consistent with this observation, different chemical classes of 14-3-3σ PPI modulators have been developed as potential therapeutics against cancer. This includes 14-3-3σ PPI stabilizers such as fusicoccanes analogues and fragment-derived small molecule stabilizers, as well as phosphonate and non-phosphonate type 14-3-3σ PPI inhibitors. These modulators were successfully identified using a combination of techniques including in silico tools (ligand-based screening, docking, molecular dynamics simulations), biophysical techniques (NMR, X-ray crystallography, isothermal titration calorimetry), fluorescence polarization, as well as cell-based assays.

However, it is worth noting that both inhibitors and stabilizers of 14-3-3σ PPI available to date mainly target the amphipathic binding pocket. While inhibitors bind directly to the three key amino acids in the amphipathic binding pocket (Arg56, Arg129, and Tyr130), the stabilizers generally bind to the site adjacent to the amphipathic binding pocket, as the amphipathic binding pocket is often occupied by the protein partner of 14-3-3σ. Having said that, a direct interaction with

Lys122 at the amphipathic binding pocket of 14-3-3σ was observed in both inhibitors and stabilizers. This suggests that a 14-3-3σ PPI inhibitor is also likely to interfere with the binding of other 14-3-3σ partners which are involved in suppressing cancer cell growth, metabolism, and metastasis, such as the tumor suppressor gene P53, TASK-3, p65, and TAZ. Intriguingly, these amino acid residues are also conserved among all 14-3-3 isoforms. This suggests that modulators that target the amphipathic binding groove of 14-3-3σ may also bind to other isoforms, and may produce other undesirable effects since only 14-3-3σ is frequently downregulated in cancer while other isoforms are usually upregulated.

Although the molecular tweezer seems promising as a potentially selective 14-3-3σ inhibitor as it has been reported to bind to the C-terminal domain of 14-3-3σ, rather than the amphipathic binding pocket, and yet is effective in displacing the binding of the protein partner from 14-3-3σ, it is still unclear if this inhibitor is indeed selective to 14-3-3σ since recent finding seems to suggest that molecular tweezer may binds to any solvently exposed Lys residues. Moreover, the interacting amino acid residue Lys214 is also conserved across all isoforms. Nevertheless, it is clearly demonstrated that it is possible to target other sites on 14-3-3σ in modulating its PPI interaction and is potentially the way forward for the design of new highly selective modulators of 14-3-3σ in the future.

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