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Review

Intersection of selenoproteins and kinase signalling ☆

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ABSTRACT

The small, obscure group of selenoprotein oxidoreductases and the huge clan of kinases, the workhorses of cellular signalling, are rarely discussed together. Focusing on selenoproteins of unknown structures, we predict a thioredoxin-like fold for the Selenoprotein N (SelN) family and use the structure to rationalise effects of the muscular myopathy-linked mutations in the gene coding SelN. Discussing the recent prediction of a protein kinase-like domain in the Selenoprotein O (SelO), we reiterate evidence for an oxidoreductase function alongside the predicted kinase domain. Thus, we propose that SelO, the strongly conserved kinase-cum-tentative-oxidoreductase may reflect oxidoreductase regulation of kinase networks. Also, we use bibliometric and systems biology approach to explore the kinase–selenoprotein relationships that begin to emerge from the literature. This article is part of a Special Issue entitled: Inhibitors of Protein Kinases (2012).

1. Introduction

Selenoproteins are a unique group of proteins, featuring an atypical amino acid residue, the selenocysteine, in the polypeptide chain. They are found in eukaryotes, bacteria and archaea alike. On the proteome scale, selenoproteins are a small group of proteins, typically making up less than 0.1% of the proteome. There are 25 human selenoprotein genes, and most of the selenoproteins with known functions are oxidoreductases whereas a selenocysteine is found in the active site. Still, some human selenogenes are functionally uncharacterised [1,2]. It seems plausible that also in the uncharacterised selenoproteins, a selenocysteine residue, conserved in evolution, has a catalytic or regulatory function. Although preservation of the cellular infrastructure for selenium acquisition, selenocysteine synthesis and incorporation is not without a cost [3] the advantages of catalytic selenocysteine (Sec) as compared to cysteine (Cys) partly offset these problems. Selenocysteine in enzymatic active sites has been reported to exhibit higher nucleophilicity, higher oxidoreductase efficiency, and lower pKa, as compared to cysteine [3,4].

In contrast to selenoproteins, protein kinases are numerous, often making up 2–3% of a proteome. Protein kinases are essential effectors of cellular signalling [5,6], and the human kinome includes more than 500 proteins [7]. Although the kinome has been the subject of very intensive research, there is still a lot to be learned [8] and new protein kinase families are still being discovered [9,10]. The reason to discuss selenoproteins and kinases together in this work stemmed from a structural survey of human selenoproteins that we undertook. Most mammalian selenoproteins either have known structures, or contain domains of known structure, and the most common fold is the thioredoxin-like one (Thx) [11,12] (see Fig. 1A), in full agreement with the oxidoreductase function reported for most of the characterised selenoproteins [13]. Focusing on the few selenoproteins of unknown structure, as expanded below, we predicted the Thx fold for selenoprotein N, SelN. Finally, an unexpected protein kinase-like structure prediction result has been recently obtained by us for another uncharacterised selenoprotein, SelO. This has been, to our knowledge, the first direct link between selenoprotein functions and kinase signalling networks. More generally, presence of a protein kinase-like domain and probably a kinase function together with a selenocysteine-containing region in a single protein chain allows a hypothesis of a two-layered regulatory mechanism in a single molecule.

Although several human selenoproteins are not functionally characterised, a general functional picture emerges. Selenoproteins can be classified as “housekeeping” or stress-related [14]. On the biological process level, selenoproteins have been found to be involved in various processes, including cancer prevention and promotion, thyroid hormone metabolism, central nervous system function, male fertility, and muscle development [13,15]. On the molecular function level, most selenoproteins have been reported to perform various oxidoreductase functions, e.g. peroxide and thioredoxin reduction, and thiol–disulphide exchange.

In this paper, we first present a brief structural survey of selenoproteins. Then, we discuss the rather expected, yet instructive, thioredoxin-like structural prediction for the SelN family. Thirdly, we discuss the recent unexpected kinase structural prediction for

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Gene symbols	Domain architecture (Pfam)	Clan assignments for domains (Pfam), comments
GPx1, GPx2, GPx3, GPx4, GPx6		GSHPx: Thioredoxin clan (CL0172)
DI1, DI2, DI3		T4_Deiodinase: Thioredoxin clan (CL0172)
SPS2		
Sel15, SelM		Sep15_SelM: similar to Thioredoxin clan, see text
SelH		Rdx: similar to Thioredoxin clan (CL0172), see text
SelI		
SelK		
SelN		Contains an EF-hand domain and a Thioredoxin-like domain (this work)
SelO		UPF0061: similar to Pkinase clan, see text
SelP		SelP_N: Thioredoxin clan (CL0172)
SelR		SelR: Mss4-like clan (CL0080)
SelS		
SelT, SelW1		Rdx: similar to Thioredoxin clan, see text
SelV		Rdx: similar to Thioredoxin clan, see text
TR1, TR2		Pyr_redox_2: NADP_Rossmann clan (CL0063)
TR3		Glutaredoxin: Thioredoxin clan (CL0172)

Fig. 1. Domain arrangements (Pfam) in human selenoproteins. * Rdx: similarity to thioredoxin clan reported in [48]. ** Sep15_SelM: similarity to thioredoxin clan reported in [49]. *** UPF0061: similarity to protein kinase clan reported in [40].

the SelO family and focus on the uniqueness of SelO both among selenoproteins and among kinases. Next, we briefly look into the bibliometric and systems biology aspects of the selenoprotein/kinase connection.

2. Methods

For structure predictions, the sequence profile-based FFAS method [16] and the HMM-based HHpred algorithm [17] were used. For known protein domain assignments, HMMER3 [18] on the Pfam database as of 09.2012 was used [19]. The secondary structure predictions were performed by several algorithms implemented in the Genesilico metaserver [51].

For the prediction of selenocysteine codons in the bacterial homologues of selenoprotein N, the SECISearch algorithm was used [20]. The SelN structure model for the thioredoxin-like domain (residues 400–490) was constructed automatically using the programme MODELLER9 v 8 [21] applying standard comparative modelling and using the thioredoxin disulphide isomerase, (PDB ID: 2ju5) as template. FFAS sequence alignment was used for modelling (see Suppl. Fig. SF5). The domain diagrams (Fig. 3) were drawn by the programme DomainDraw [22].

For systems biology analysis, the DAVID system was used [52,53] which explores functional classifications and annotations overrepresented in a protein set in a statistically significant way. As input, a set of 516 known human kinases [7] and 25 known human selenoproteins was used. The functional annotations considered included Gene Ontology terms, and KEGG pathways. Standard DAVID parameters were used, and Benjamini correction was applied to account for multiple testing. The PubMed queries were executed in January 2013.

3. Results and discussion

3.1. Three-dimensional structures of human selenoproteins

In all human selenoproteins except one (SelN) known protein structural domains are easily detected (see Fig. 1A). Further, for most of these

selenoproteins or their close homologues (15 out of 25) three-dimensional structures are known, covering most or parts of the respective polypeptide chains. Strikingly, decisive majority of human selenoproteins (16 out of 25) possess a thioredoxin-like domain, covering most of (in 14 cases) or parts of the protein sequence. Only three human selenoproteins are not assigned easily to known structural domains, SelK, SelN and SelO. SelK and SelO possess Pfam domains termed 'Domain of Unknown Function' (DUF2763) or 'Uncharacterised Protein Family' (UPF0061), respectively. SelN possesses no structural domains that can be detected automatically by the PfamHMM tool [19]. SelK has been shown to be involved in endoplasmic reticulum-associated degradation (ERAD) of glycosylated misfolded proteins [50]. Out of these three proteins, we could not assign any structural similarity for the SelK protein (annotated as Pfam DUF2763 domain). The other two selenoproteins, however, provided interesting results.

3.2. Selenoprotein N possesses a C-terminal thioredoxin-like domain

Selenoprotein N has been said to act "at the crossroads of redox signalling, cell stress, and calcium homeostasis". The cysteine/selenocysteine motif in SelN, SCUG, whereas U stands for selenocysteine, has been noted to be "reminiscent of" the thioredoxin reductase GCUG active site motif [23], different from the CxxC/CxxU motif that is present in most thioredoxin-like families. It has been also noted that thioredoxin reductases normally contain two other functional domains, the FAD and the NADPH-binding domains, apparently missing from SelN [23].

Application of specialised structure prediction methods allowed to partly resolve the SelN structure problem. Indeed, for the region 400–590 of the human SelN protein which covers the selenocysteine site, several protein structure prediction methods detected remote yet significant similarity to thioredoxin fold proteins. Specifically, FFAS, HHpred and Superfamily HMM detected significant similarity to structure of the UAS domain of human UBX domain-containing protein 7 (PDB ID: 2dlx) [24–26]. The FFAS Z-score was −11, and the HHpred P-value was 6E-8 and HHpred E-value was 0.0064, while sequence identity in the HHpred alignment was 17%. In protein domain family terms, the prediction tools detected similarity to thioredoxin-like superfamily in the SCOP database (http://scop.mrc-lmb.cam.ac.uk/scop/data/scop.b.d.gi.html), and to the DUF255 family within the Thx-like clan in the Pfam database (http://pfam.sanger.ac.uk/family/duf255). Alignment of SelN to known thioredoxin-like proteins and conservation of many typical thioredoxin fold features are shown in Suppl. Fig. SF1. The statistical scores of magnitude reported here for the Thx-like domain prediction in SelN have been repeatedly found to represent bona fide biologically relevant similarity [40,46].

In the N-terminal part of the SelN protein (approx. the region 70–100), a single EF-hand Ca^{2+}-binding domain has been noted previously [27]. The prediction of this domain is highly significant (HHpred P-value 7E-18). The EF-hand in SelN is somewhat atypical, lacking an ultra-conserved glycine residue at position 6 in the ion-binding loop. However, the conservation of all calcium ion ligands suggests that the EF-hand domain is functional (see Suppl. Fig. SF1).

The remaining regions of the SelN protein did not produce any significant structure predictions in an automated approach. However, one of sub-significant hits of the HHpred method was the structure of bacterial flavodoxin reductase (PDB ID: 1fdr) [28], HHpred P-value 0.0008, in a region corresponding to the oxidoreductase FAD-binding domain (classified as Pfam domain FAD_binding_6, PF00970 [29]). Although this FAD-binding domain (see Fig. 3 and the alignment in Suppl. Fig. SF1) should be treated as a very weak, tentative prediction, unconfirmed by other methods, it offers a possibility that indeed a FAD binding domain envisaged previously [23] may be present in SelN and enable a complex oxidoreductase function.

SelN proteins have a scattered phylogenetic spread in Metazoa, including vertebrates, and the sea anemone *Nematostella vectensis*, the hemichordate *Saccoglossus kowalevskii*, the echinoderm *Strongylocentrotus purpuratus*, the lancelet *Branchiostoma floridae*, the tunicate *Ciona intestinalis*, and the tick *Ixodes scapularis*. Yet, many Metazoa, including insects, nematodes and plocozoans, lack SelN homologues. Interestingly, outside eukaryotes, the only two obvious SelN homologues are present in *Poribacteria*, a taxon of ancient bacterial symbionts within extracellular matrix of marine sponges [30,31]. The two poribacterial SelN homologues (RefSeq identifiers ZP_06386948.1 and ZP_06386878.1 from *Candidatus Poribacteria* sp. WGA-A3, sharing approx. 53% sequence identity), as annotated in the genome sequencing study, are short and possess only partial similarity to the human SelN protein. However, a tblastn analysis shows that two genomic regions coding the two proteins exhibit strong and significant similarity to the region 195–540 of human SelN. A prediction of selenocysteine insertion sequence (SECIS) elements using the bSECISearch server [20] yielded SECIS elements in the two genomic regions, and as a consequence, selenocysteine codons in both proteins, corresponding to the predicted active site Sec residue of human SelN. After this correction, one of SelN homologues turns out to be a fusion protein whereas SelN Thx-like domain is fused to an AhpC-TSA redoxin-like domain (Pfam: PF00578), supporting SelN role in oxidative stress response. Selenoprotein N binds ryanodine receptors and is necessary for their calcium release channel activity [32]. Interestingly, *Poribacteria* possess unique nucleus-like structures within cells. Thus, just as vertebrate SelN have role in mediating intracellular calcium ion fluxes, the unique presence of SelN homologues in *Poribacteria* may be related to the unique cell compartmentalisation seen in these peculiar bacteria [33]. The SECIS element found and the proposed full-length sequences of SelN homologues from *Poribacteria* are shown in Suppl. Fig. SF2.

Selenoprotein N is the only human selenoprotein associated with a genetic disease [34]. Several known polymorphisms of the *SEPN1* gene that codes the SelN protein cause *SEPN1*-related myopathy (SEPN1-RM), a congenital life-threatening muscle disorder with an early onset [35–39]. However, a correlation between particular mutations and disease phenotype has not been elucidated [39]. Our structure prediction allows rationalisation of the known *SEPN1* mutations. There are three major nonsense polymorphisms linked to SEPN1-RM, Sec462Gly, Arg466Gln and Trp453Ser [32,36,37]. The significance of first mutation, leading to the loss of the predicted active site selenocysteine, is obvious. The change of positively charged arginine Arg466 to neutral glutamine, in a location very close to the active site (see Fig. 2A) may change the micro-environment of the catalytic site, e.g. resulting in a changed pKa of the catalytic selenocysteine. The hydrophobic tryptophan Trp453, occupying a hydrophobic pocket, when changed to the hydrophilic serine may lead to protein conformation changes not far from the active site, again disrupting thus the function.

3.3. Selenoprotein O possesses a protein kinase-like domain and probably an oxidoreductase region

The third human selenoprotein that could not be automatically assigned to known structural domains, SelO, has been recently proven to be similar to protein kinases, making up thus a remote family of the protein kinase-like clan [40]. Actually, almost a decade ago, Koonin and colleagues nominated SelO to the list of top ten most-wanted "unknown unknowns", i.e. proteins of unknown structure and function that had been remaining challenges for structure predictors and structural biologists [41]. The statistically significant prediction of protein kinase structure and function for SelO has been obtained for the central region of the protein (see Fig. 3). Far from the kinase domain, the single selenocysteine residue of SelO is located two residues away from the C-terminus, in a CxxUxx motif. In general, CxxC, UxxU and

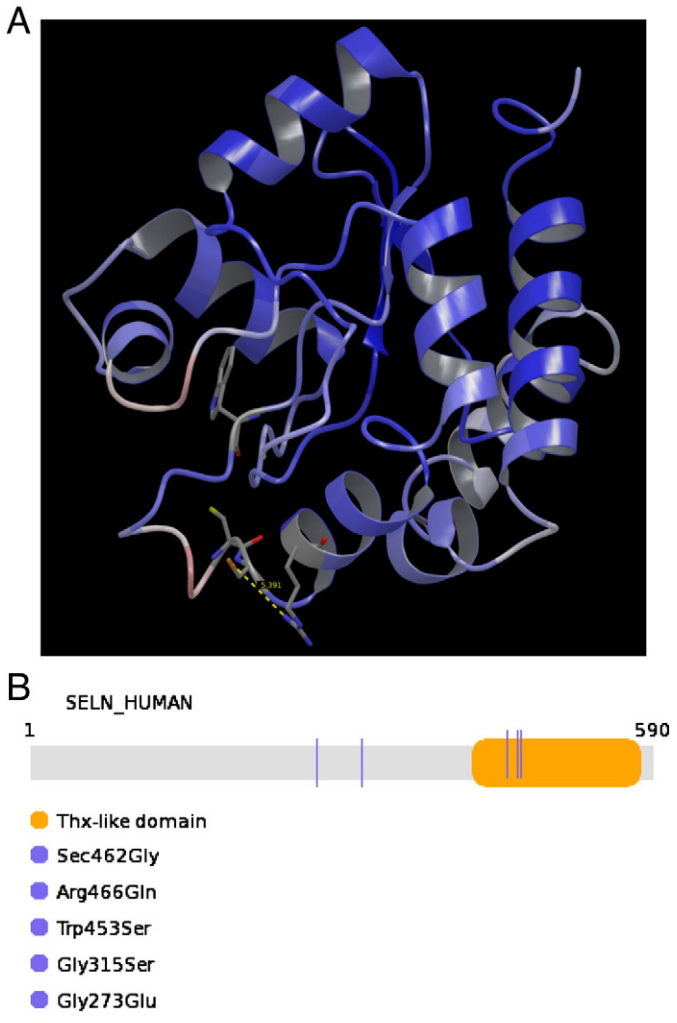

Fig. 2. A. Location of SEPN1-related myopathy mutations in the Thx-like structure model of human SelN C-terminal region. Model built using Modeller, includes residues 423–582 of SelN and uses thioredoxin disulphide isomerase, (PDB ID: 2ju5) as template. Cys461 and Sec462 sidechains shown as sticks, as well as Trp453 and Arg466 residues that are locations of disease mutations. B. Location of SEPN1-related myopathy mutations (as listed in the OMIM database) in the sequence of human SelN protein.

CxxU motifs are the very centres of the active sites, characteristic of thiol–disulphide oxidoreductases of the thioredoxin-like fold [12,42,43]. Although CxxC motifs occur also in other proteins, e.g. in zinc fingers [44], the presence of a selenocysteine-containing CxxU motif very strongly suggests an oxidoreductase role. Also, some high-throughput experimental and in silico evidence for yeast and bacterial homologues of SelO support a hypothesis that SelO proteins function in oxidative stress response [40] (e.g. gene expression experiments involving stress such as peroxide treatment or aerobic conditions as compared to anaerobic ones and genomic neighbourhood analysis). However, in typical thioredoxin-like proteins, the CxxC/CxxU motif is located in the central part of the molecule. Thus, if SelO proteins possess an oxidoreductase domain, it is either of a structure different from thioredoxin-like, or it may be some kind of a circularly permuted thioredoxin-like fold. However, according to secondary structure predictions (see Supplementary Fig. SF3), the C-terminal domain of SelO contains eight alpha helices and only two very short beta strands, and therefore is unlikely to adopt a thioredoxin fold. As discussed elsewhere, SelO is predicted to have kinase activity [40].

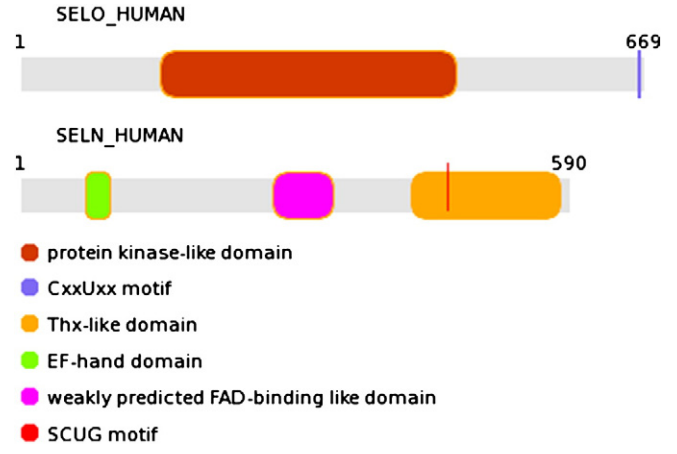

Fig. 3. Domain and motifs identified in human SelN and SelO proteins.

Novel protein kinase families are still being discovered, e.g. the Golgi casein kinase family [9,45] or the predicted FAM69 kinase family [10]. Likewise, novel thioredoxin-like families are being identified, e.g. the evolutionarily widespread P-DUDES family [46]. However, the SelO family is unique in combining a predicted kinase domain with a speculatively proposed oxidoreductase domain in a single molecule. Its uniqueness is also manifested by the very broad phylogenetic spread of SelO homologues. Indeed, SelO family is present in majority of main bacterial and eukaryotic taxa [40]. More strikingly, SelO appears to be unique both among kinases and among selenoproteins in its very strict conservation between distant organisms, e.g. humans and bacteria (see Fig. 4). When closest bacterial homologues are sought either for human kinases or for human selenoproteins, in both analyses human SelO clearly stands out from the rest as being the most conserved protein. This suggests a very ancient, very conserved and probably very important function. Ultimately, the validation of the SelO kinase function and its cellular roles can be only achieved by various experimental assays, including for example standard assays for ATP binding and hydrolysis or analysis of cell phenotypes upon disruption of the predicted SelO kinase active site.

3.4. Bibliometry and systems biology approach links selenoproteins and kinases

The direct connection ("A is a B") between selenoproteins and kinases has been described only in a single article [40]. Yet, in a very simple, primitive almost bibliometric analysis, one can explore co-occurrence of the two concepts in PubMed. A query for kinase or kinome yielded 599,960 publications, a query for selenoprotein or selenoproteome yielded 1859 while a query for both brought 122 articles. Taking into account the size of PubMed, Fisher's exact test provides a P-value equal to 1.5E-18 which means that there is a non-random association between the two categorical variables (article being about kinases and being about selenoproteins). Thus, a significant over-representation of papers discussing selenoproteins and kinases together suggests a functional link between the two may be embedded in the literature.

Expectedly, many protein kinases contain cysteine residues. The mean cysteine content in kinase domains of the human kinome is 2 per 100 residues, which is somewhat less than the mean for the human proteome in general (approximately 2.5) [47]. Notably, some novel kinase families, e.g. FAM20 and FAM69 [9,10] have higher Cys content. Also, among the established kinomes, some kinases reach 5 cysteines per 100 residues (see Suppl. Fig. SF4). Thus, kinases may be expected to be sensitive to oxidative stress, but also oxidation/reduction may be expected to be a regulatory factor.

Obviously, kinases and selenoproteins are involved in many cellular processes and functions. In order to explore these, we performed a systems biology analysis of known biological functions and processes that involve kinases and selenoproteins together using the DAVID system (see Methods). Among the functions that were most significant for

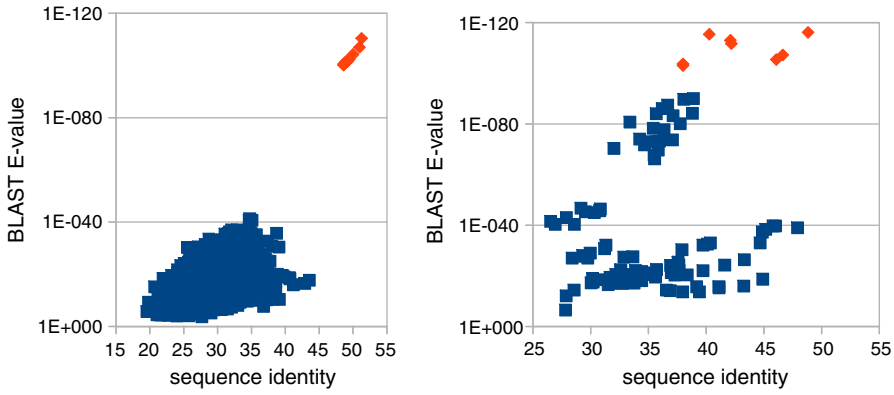

Fig. 4. SelO is uniquely conserved between humans and bacteria. Left: results of Blast search in SwissProt database limited to Bacteria, using known human kinase domains [7], blue, and SelO, red, as queries. Right: as in left, using SelO, red, and other human selenoproteins, blue as queries. In both searches up to 10 bacterial hits are shown, with E-value below 0.001. Thus, 493 out of 516 known human kinases pass this criterion as well as 12 out of 25 human selenoproteins.

the common set of human kinases and human selenoproteins, there were "response to oxidative stress" (18 proteins, including 8 selenoproteins, P-value 2.8E-3), "cellular response to stress" (66 proteins, including 4 selenoproteins, P-value 7.4E-13) and "regulation of programmed cell death" (73 proteins, including 2 selenoproteins, P-value 1.0E-8). These connections obtained using a large-scale approach are just examples of a more complex network of relationships that remain to be explored. This expectation is supported by several examples of recently elucidated relationships whereas kinases and selenoproteins together regulate processes such as cell cycle progression (MAPK4 and selenoprotein W) [54], mitochondrial biogenesis (PKA, PKB and selenoprotein H) [55] and cell growth (p53 and methionine sulfoxide reductase A) [56].

4. Conclusions

Among selenoproteins in humans, majority are thioredoxins, and others are also usually oxidoreductase-related proteins. Including our SelN prediction, 17 out of 25 human selenoproteins possess a thioredoxin-like domain. Very crudely speaking, if a selenoprotein has unknown structure, then one might bet it is thioredoxin-like. Likewise, if a selenoprotein has unknown function, one may suppose it will turn out to be an oxidoreductase. Thus, judging from the very wide taxonomic presence of the ultra-conserved kinase-cumtentative-oxidoreductase, SelO, one may speculate that oxidoreductase-dependent regulation of kinase networks may turn out to be an important factor in cellular signalling. This sounds more plausible considering the growing appreciation of the extracellular activities of some kinases [9,45].

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