Purinergic Signalling (2018) 14:321–329
https://doi.org/10.1007/s11302-018-9627-2

REVIEW ARTICLE

Expanding the clinical relevance of the 5′-nucleotidase cN-II/NT5C2

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Received: 20 July 2018 / Accepted: 20 September 2018 / Published online: 25 October 2018

Abstract
Purine metabolism is depending on a large amount of enzymes to ensure cellular homeostasis. Among these enzymes, we have been interested in the 5′-nucleotidase cN-II and its role in cancer biology and in response of cancer cells to treatments. This protein has been cited and studied in a large number of papers published during the last decade for its involvement in non-cancerous pathologies such as hereditary spastic paraplegia, schizophrenia, and blood pressure regulation. Here, we review these articles in order to give an overview of the recently discovered clinical relevance of cN-II.

Keywords GWAS · Diseases · Genetic variants · Mutations · NT5C2 · Purine metabolism

Introduction

Cytosolic 5′-nucleotidase II (cN-II) is a ubiquitously expressed and highly conserved enzyme that dephosphorylates purine nucleoside monophosphates (preferentially IMP and GMP) into their corresponding nucleosides and inorganic phosphate. Its enzymatic activity and biochemical features have been fairly well characterized on purified recombinant protein [1], and the crystal structure is known since 2007 [2]. Since our first observation on its prognostic value in nucleoside analogue-treated patients with acute myeloid leukemia showing that patients with high expression of cN-II in leukemic blasts have a worse outcome than those with a lower expression [3], the implication of cN-II in cancer cells and in the response to anticancer treatment has been extensively demonstrated [4]. Indeed, shRNA-based cell models with decreased cN-II expression are more sensitive to purine nucleoside analogues and nucleobases as compared to control cells [5]. Additional work with cell models and animals suggest important biological roles of this enzyme both in cancer cells and in physiological conditions. The role of the enzymatic activity of cN-II and the modifications in purine nucleotide pools in these observations is not always demonstrated. We showed that cN-II expression in human neuroblastoma cells and in lung cancer cells correlated to cell proliferation [6, 7], whereas it inhibition in human breast cancer cells was associated with a better defense towards reactive oxygen species and a better adaptability to glucose deprivation in culture media [8]. Further, the siRNA-mediated inhibition of cN-II expression in murine skeletal muscles induced an increase in the AMP/ATP ratio and a subsequent increase in the activation of AMPK [9], even though this was not confirmed in cN-II deficient mice [10].

In parallel to such biological studies, a number of genetic studies as well as genome wide association studies (GWAS) have identified the cN-II encoding gene *NT5C2* or some genetic variants therein as being associated to various pathological conditions. Here, we give an overview of these recently published data that show or suggest clinical importance of this enzyme in hereditary spastic paraplegia, psychiatric disorders, blood pressure, and body mass index.

Hereditary spastic paraplegia

Hereditary spastic paraplegia (HSP) is a group of neurodegenerative disorders with various genetic origins and clinical presentations [11, 12]. The locus harboring the *NT5C2* gene (10q24.3-q25.1) was identified as being associated with HSP in a consanguineous family (Table 1) [13]. This locus, named SPG45, contains 87 genes, and the authors suggested *MRPL43* to be the best candidate for the functionality of the observed disease, due to its role in mitochondria regulation

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Table 1 Deleterious mutations and genetic modifications observed in HSP SPG45 patients

Patients	Mutations	Reference
5 members of consanguineous family	10q24.3-q25.1	[13]
2 siblings of a consanguineous family 2 sisters of a consanguineous family	c.175+1 = splice variant c.988-1 = splice variant	[14]
2 sisters of a consanguineous family	c1225Gdel = premature stop at 436	
3 siblings of a consanguineous family	R29stop	
2 brothers of a consanguineous family	R149stop	
2 brothers Qatari consanguineous family	c.1159+1 = deletion of exon 14	[15]
3 siblings Iranian consanguineous family	p.258-271del	[16]
3 members of consanguineous family	L460P	[17]

and protein-folding. The association between HSP and *NT5C2* was further confirmed in another study on 55 families using whole-exome sequencing, where 5 families showed mutations in this gene [14]. Out of the 5 mutations observed, 3 induced a modification on the protein with two premature stop codons (R29X and R149X) and a frameshift (S409Vfs436X) and two were splice site mutations (c.175 and c.988). Of interest, two other proteins involved in nucleotide metabolism, the nucleotidase CD39/ENTPD1 and AMP-deaminase 2 (AMPD2), were also found to be mutated in HSP families. Both these enzymes, as well as cN-II, regulate the purine nucleotide pools through their enzymatic activity. This, together with the fact that purine nucleotides have protective roles in the brain [18], reinforces the possibility of the implication of cN-II activity in the development of HSP. *NT5C2* mutations in SPG45 and the autosomal recessive transmission mode were later validated with the observation of another splice site mutation (c.1159) resulting in a shortened cN-II protein in two brothers [15], a deletion of amino-acids 258–271 in three siblings [16] and a missense mutation (L460P) in three patients from another family [17]. *NT5C2* is since recognized as being the functional gene in the SPG45 locus.

Schizophrenia

A large number of GWAS studies on different ethnic populations has been performed in order to identify genetic causes for schizophrenia and other psychiatric diseases, and the *NT5C2*-containing locus was reported in several cases (Fig. 1). rs11191580 was first identified in a meta-analysis from 17 independent studies and confirmed within a validation set [19], and later in a South Chinese Han population [20] as well as for bipolar disorders in a Latino cohort [21]. rs11191580 was also confirmed in a meta-analysis, but the role of *AS3MT* through rs7085104 situated on the same locus was rather suggested as an important genetic variant in this study [22]. rs17094683 was found in another GWAS study [23] and rs1926034 in a Swedish cohort [24]. Later, rs11191454 in *AS3MT* situated close to *NT5C2* within 10q24 and in strong linkage disequilibrium with many surrounding SNP was associated with five psychiatric disorders [25]. The *NT5C2*-containing genomic region was further studied in a Chinese population, and the association with schizophrenia was again confirmed for rs11191419 and rs11191514 [26]. However, based on bioinformatics prediction of the involvement of genetic variants in gene regulation, the authors suggested that *NT5C2* was not functional in this correlation, but that rather other genes of the same cluster (*AS3MT*, *CNNM2*, and *CALHM1*) would be responsible for the clinical onset of schizophrenia. This was at least partially contested by a study on the *cis*-regulatory effect of SNP in this region [27]. Indeed, rs11191419 and rs202213518 influenced *NT5C2* gene expression as shown by differential allelic expression studies. This is in line with our previous study showing the presence of genetic regulation of *NT5C2* [28]. In addition to this, rs11191548 was shown to alter the binding site of miR-1/206/613 as the sequence with the minor allele (G) did not response to miR-1/206613 [29]. Even though these results do not show a clear functional role of cN-II in schizophrenia, at least one SNP (rs11191548) identified in GWAS studies regulates *NT5C2* gene expression.

Blood pressure

Genetic variants within the locus 10q24 were associated with high blood pressure in a large study including more than 84,000 individuals from European and Indian Asian origin [30]. A T at the position of rs11191548 in the intergenic region between *NT5C2* and *CNNM2* was associated with a higher systolic blood pressure as compared to patients with a C at the same position ($p = 3.10^{-7}$). This was later confirmed in studies on Europeans [31] and Asians [32], as well as on Asians in a study where rs11191580 also was associated with blood pressure [33]. The same region was also identified in another large-scale study, but with a better score for a genetic variant further away from *NT5C2* (rs1004467) [34]. Also,

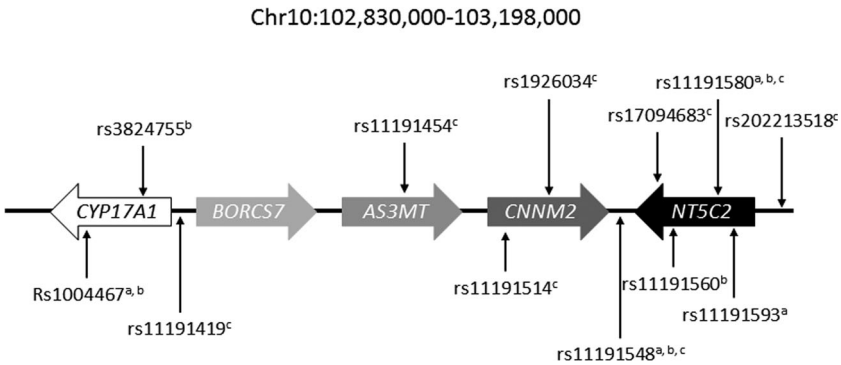

Fig. 1 Genetic variants within the studied genomic region with possible association between discussed pathologies and NT5C2. a blood pressure; b BMI/body fat; c schizophrenia

rs11191593 was associated with blood pressure [35]. Finally, a gene expression study showed that military pilots with hypertension had a lower cN-II expression than control pilots [36]. Interestingly, there was also a decreased expression of CD39/ENTPD1, confirming an additional link between these two proteins after the one in HSP. The direct involvement of cN-II in the regulation of blood pressure is not clearly demonstrated and needs further studies to be confirmed. Indeed, rs1004467 and rs11191548 have for example been reported to modulate *CYP17A1* and therefor potentially be functional through this gene even though the latter SNP is quite far from this gene.

Body mass index and body fat

Increased body mass and fat are risk factors for a number of diseases, such as high blood pressure. One SNP (rs11191548) already identified as a risk factor for increased blood pressure was also associated with subcutaneous fat area, in particular in women in a Japanese cohort [37]. However, the T-allele which is associated with increased blood pressure was here found to correlate with decreased fat. Another SNP (rs1004467), situated in the nearby *CYP17A1* gene and in linkage disequilibrium with rs11191548, was also associated with modified body fat. Another SNP (rs11191580) that is situated in a *NT5C2* intron and that is in complete linkage disequilibrium with rs11191548 was later found associated with body mass index in East Asian people [38], whereas rs11191560 also situated in an *NT5C2* intron and between rs11191548 and rs11191580 was associated with higher body mass index in a European meta-analysis [39]. Finally, rs3824755 was also associated to BMI in a series of more than 17,000 individuals [40] and further shown to increase within the population together with BMI [41]. However, this SNP is situated within the *CYP17A1* gene and not in *NT5C2* as reported in some of these papers, making the role for cN-II less evident. As for blood pressure, these studies are solely showing correlations, and no functional involvement of cN-II in the regulation of BMI and body fat exists today.

Relapsed leukemia and resistance to chemotherapy

In addition to the cited work on associations between genetic variants or germ-line mutations and pathologies, tumor-specific NT5C2-mutations have been reported to play a major role in leukemia relapse and their resistance to chemotherapy. This was first seen with hyperactivating mutations in relapsed pediatric patients with acute lymphoblastic leukemia (ALL) [42, 43]. Additional mutations were found in a subsequent study that also showed the relapse-specificity of the mutations [44]. Such mutations were then shown to be very rare in new leukemia and solid tumors, with only one case in adult acute myeloid leukemia (E240Q) and one in colorectal carcinoma (R363Q) from a total of 2496 tumors [45]. One ALL patient with testicular relapses showed also *NT5C2* mutations (R367Q and D407V) [46], whereas they were quite frequent in a series of 67 relapse leukemia patients [47] as well as in relapsed T-ALL patients (5/13 patients) [48] and acute promyelocytic leukemia patients [49]. The most frequent mutation (R367Q) was recently shown to be a key driver in the evolution of relapsed ALL [50], and additional mutations were found in more patients by the same group [51, 52]. Overall, these studies show that *NT5C2* mutations are frequent in relapsed leukemia (Table 2) and that this has a direct consequence on the response to treatments. However, this is known to be due to the enzymatic activity of cN-II, at least for the mutants for which the mutation has been shown to be associated with an enzymatic hyperactivity.

Conclusive remarks

The studies reviewed here are mostly based on the association between genetic variants or mutations and the risk to develop given diseases, but do rarely give any information about the potential molecular functionality of cN-II in the observed pathologies. Therefore, additional studies are warranted and dependent on various cell and animal models. cN-II deficient mice were recently published in a study on the role of cN-II in contracting muscles [10]. No particular phenotype or

Table 2 *NT5C2* mutations reported in various cancer patients at diagnosis or relapse. A total of 129 mutations are reported. *ALL* acute lymphoblastic leukemia, *AML* acute myeloid leukemia, *APL* acute promyelocytic leukemia, *CC* colorectal cancer

Reference	[43]	[42]	[44]	[48]	[45]	[46]	[47]	[50]	[52]	[51]	[49]	Total
Cancer	ALL	ALL	ALL	ALL	AML and CC	ALL	ALL	ALL	ALL	ALL	APL	
R34Q							1					1
R39Q			2				1	2		3		8
R195Q							1					1
R238G/Q/W/L	5	3	5				4	2		5	1	25
E240Q					1							1
R291W	1											1
K359Q	1								1			2
S360P			1									1
R363Q					1							1
R367Q	13	1	5	4		1	7	7	1	14	1	54
L375F	2						1					3
p396-400del							1					1
D384N										1		1
K404N/ins		1								1	1	3
D407A/V/H/Y/E	1			1		1	2	1		3		9
S408R		1	1									2
p408-415del										1		1
P414S/A				1			1	1		2		5
D415G										1		1
S445F		1							1			2
R446Q									1			1
V454M										1		1
R478S									1			1
T489M							1					1
Q523stop	1											1
P533L							1					1

behavior was described in this paper, but these mice could constitute a model of choice for studying the development of diseases discussed in this review.

cN-II is an extremely well-conserved protein with more than 90% homology as far as to fish [53]. Such sequence conservation not only limited to the active site is strongly suggestive of additional roles independent from the enzymatic activity and rather through protein-protein interactions. We already identified and confirmed physical interaction with the inflammation protein IPAF, even though we still have not deciphered the role of this interaction [53]. Additional interactions are highly possible and could explain many of the observed phenotypes, but request a large amount of additional research, especially due to the fact that such interactions could be specific over time during development as well as in particular cells expressing the two interacting proteins at the same time and in the same subcellular location. One possibility within this hypothesis is the presumed interaction between cN-II and the multimodal protein Kidins220 [53]. This physical interaction has not yet been confirmed in mammalian cells, but Kidins220 has been suggested to be implicated in Alzheimer's disease [54] and a recent study also showed a potential role of cN-II in this disease [55].

Another explanation is of course that all roles of cN-II are due to its enzymatic activity and regulation of the purine metabolism. This could be supported by the involvement of other genes in this metabolism as they could also have important effects on purine homeostasis. As already mentioned, AMPD2 and CD39/ENTPD1 were also involved in HSP [14]. AMPD2 converts AMP into IMP by deamination, whereas CD39 degrades extracellular ATP into AMP, and both enzymes thus regulate purine nucleotide pools together with cN-II. Other studies have shown that these are involved in cognitive disorders for CD39/ENTPD1 [56], in the maturation of neurons together with CD73 [57], and in the neurodegenerative brainstem disorder pontocerebellar hypoplasia for AMPD2 [58–61]. Finally, purine metabolism is shown to be a major regulator both in Parkinson's disease and in schizophrenia [62, 63]. As both several enzymes of purine metabolism are associated with neurological diseases and purine

metabolism and pools are regulating such pathologies, it is highly possible that the enzymatic activity of cN-II and its role in the maintenance of balanced purine pools is involved in the development of HSP-patients in particular.

In conclusion, the implication of the genomic region surrounding *NT5C2* on chromosome 10 is undoubtedly associated to and involved in discussed pathologies. Further studies are warranted to conclude on the functional role of cN-II in the corresponding pathogenesis.

Funding LPJ received funding for research on cN-II from Olav Raagholt og Gerd Meidel Raagholts stiftelse for forskning.

Compliance with ethical standards

Conflict of interest Lars Petter Jordheim declares that he has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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