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HIGHLIGHTS

# *ENTPD5* splice variants: novel players in cancer?

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Ectonucleoside triphosphate diphosphohydrolases (NTPDases) are enzymes that are involved in the degradation of di- and triphosphate nucleotides, with important implications in several biological processes that underlie a number of physiological and pathological conditions, including cancer. This family consists of 8 members, among which NTPDase1 (CD39) is so far the best characterized [1], but there is growing interest in the literature around NTPDase5. This enzyme, encoded by the *ENTPD5* gene, hydrolyzes UDP to UMP and is mainly localized inside the cell, where it plays a critical role in the N-glycosylation and proper folding of proteins in the endoplasmic reticulum [2]. It can also be secreted into the extracellular space and can work as a soluble enzyme upon cleavage of a signal peptide [3].

NTPDase5 is often deregulated in cancer, likely as a consequence of *TP53* mutations, where it promotes and favours tumour progression and metastasis [4]. Furthermore, short NPTDase5 peptides were detected in normal and tumour cell lines, recalling the mt-PCPH oncoprotein, a truncated form of the enzyme originating from a single-nucleotide deletion described in Syrian hamster and lacking enzymatic activity [5].

The study by de Campo and colleagues [6], published in in this issue of Purinergic Signalling, describes the existence of splice variants of *ENTPD5* as a novel pattern of NTPDase5 deregulation and suggests this as the genetic mechanism that lead to shorter protein isoforms. By searching the TCGA PanCancer Atlas, the authors first found that truncated mutations of *ENTPD5* are infrequent (less than 0.2% of cases), while splice variants were frequently detected in large amounts of patients affected by 15 different types of tumour. Among splicing events in *ENTPD5*, the authors identify the usage of different acceptors for exon 6 (referred to exons 6.1, 6.2, 6.3), alternative terminators among exons 17 to 21 and skipping of exons 11, 13 and/or 14. The ultimate impact on the protein structure is the loss of important conserved domains, likely affecting the enzymatic activity of NTPDase5. The predicted functional outcome is that NTPDase5 variants originating from alternative transcripts lack the enzymatic activity and may contribute to tumour biology, although the implications can be remarkably different depending on the cancer type. By using a Cox proportional-hazard model, de Campo and colleagues here show that neither global *ENTPD5* expression levels nor alternative transcripts affect the overall survival of cancer patients in the same way. For example, high *ENTPD5* levels are a risk factor in lower-grade glioma and sarcoma, while being a protective factor for kidney clear cell carcinoma patients. Similarly, the usage of alternative terminators in exon 17 (AT17) or 19 (AT19) has opposite outcomes that vary according to tumour types: AT17 is a risk factor in lung and pancreatic adenocarcinoma and a protective factor in colon adenocarcinoma and in kidney clear cell carcinoma, opposite to AT19. This variability can be due, on the one hand, to the fact that NTPDase5 peptides are differentially expressed in normal and tumour tissues. On the other hand, intrinsic features of cancer cells, such as the deregulation of signalling pathways affecting, or not, proper protein folding, might also explain the different impact of NTPDase5 splice variants on the overall survival of cancer patients.

To fully address the role of NTPDase5 peptides, experimental evidence of protein expression and functional characterization should be assessed. Given the importance of this enzyme in regulating appropriate protein folding and intracellular ATP levels [2], it would be interesting to investigate whether the loss of enzymatic activity, predicted to occur in alternatively spliced variants, could influence the sensitivity of tumour cells to stress conditions, such as endoplasmic reticulum stress and nutrient deprivation [7].

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## Declarations

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

**Conflict of interest** The author declares that he/she has no conflict of interest.

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