Journal of Nanomedicine & Biotherapeutic Discovery

Khan, J Nanomedine Biotherapeutic Discov 2014, 4:1
DOI: 10.4172/2155-983X.1000e126

Editorial Open Access

Molecular "debris": Trash or Treasure?

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The central dogma of molecular biology deals with the detailed residue-by-residue transfer of sequential information, which has been described as "DNA makes RNA makes protein" [1]. This does not preclude the reverse flow of information from RNA to DNA, but only excludes the reverse flow of information from protein to RNA or DNA. The transfer of DNA information to protein is the keystone of multiple biological functions. Not long ago we believed that a protein then either is further trimmed down into either or not functional (poly) peptides or is used as an intact unit that performs its biological functions. After exercising its job for a shorter or longer period, the protein is degraded as part of cellular turnover processes. Thereby generated debris is excreted or further broken down in order to re-use the remnants as building blocks for new synthesis. The same sequence of degradation processes we were inclined to understand about coding and non-coding RNA.

It is generally thought that a DNA sequence is not protein-coding unless it encodes a string of more than 100 amino acids. Even though 80% of the human genome is transcribed, only 1% encodes for proteins. On average 30% (in some cases as high as 90%) of new protein is suggested to be defective and/or improperly folded [2], and therefore transported back into the cytosol to be degraded by the ubiquitin/proteasome system [2,3]. While this may all be simple transcriptional and translational noise, it seems to be an unlikely waste of cellular energy resources to create such huge molecular debris trash.

Another example of seemingly waste of energy resources occurs during antigen presentation in which the cell uses its heavy duty ubiquitin/proteasome degradation machinery: it has been shown that the most efficient epitope forms are presented at a ratio of 1:100 (thus up to only one out of 100 degraded antigenic polypeptides leads to effective presentation), while this figure drops to 1:10,000 and below for less efficient forms [4]. It is clear that also here the cell pays a high price in terms of ATP for the degradation of all peptides that are not effectively presented and thus do not have an obvious function.

In the past few decades we have learnt that numerous functional small peptides exist in endocrine and neurocrine systems that are cleaved from larger polypeptides precursors to yield functional extracellular circulating molecules. In the same way antimicrobial peptides are produced by all kinds of organisms, from bacteria to mammals. In higher organisms these peptides are produced as an innate host defense mechanism to protect against pathogenic attack, whereas microorganisms presumably use these peptide weapons in the competition for limited resources [5]. A large variety of peptides are also generated in the gut lumen during normal digestion of dietary proteins. Large quantities of small peptides (i.e. dipeptides and tripeptides) are absorbed through the gut mucosa and represent the primary mechanism for absorption of dietary nitrogen. Larger peptide fragments are also absorbed with absorption decreasing with increasing chain length. Many of these dietary peptides have been shown to have biological activity. Such peptides may modulate neural, endocrine, and immune functions [5].

The question arises whether small peptides debris generated during the process of protein fragmentation/nicking and/or turnover can also be bioactive. We have started studies into this area in 2000 by using human pregnancy hormone, hCG, which is an evolutionary strongly conserved protein that is massively produced and extensively broken-down throughout pregnancy. There are various metabolic forms of hCG [6]. Small peptide fragments (oligopeptides) that may liberate as debris from the degradation of hCG had not been studied functionally before. This may be because of the belief that such small remnants, which are hardly detectable with presently available tools, are not biologically significant.

Contrary to this assumption we showed that oligopeptides (3 up to 7 amino acids) designed according to the known nick sites in loop-2 of β-hCG have profound effects on various physiological systems ranging from (auto)immunity to inflammatory, proliferative and regenerative responses [6-8]. Moreover, employing the same selection and design criteria on the primary structure of a few other human proteins, i.e. C-reactive protein, β-catenin, Bruton's tyrosine kinase and matrix metalloproteinase-2, we showed that several of the oligopeptides inhibit two important reporter genes (pCDG and DR:5GUS) involved in the proliferation in an *Arabidopsis* plant model [6,9]. Presumably these small oligopeptides ('micro-peptides') not just have regulatory functions which differ from those of the parent molecules, but constitute a conserved regulatory system in biology. We believe that this conserved regulatory system exists at all levels of the DNA → RNA → protein "information flow".

Similarly, in the last decade it has been found that various classes of small non-coding RNAs, a.o. micro RNAs (miRNAs) molecules (ca. 22 nucleotides), occur in plants, animals and some viruses, and that these miRNAs can account for transcriptional and post-translational regulation (mostly silencing) of gene expression [10]. Nowadays we believe that such small RNA species are well conserved in at least eukaryotic organisms and constitute a vital and evolutionarily ancient component of genetic regulation. It is estimated that miRNAs regulate the expression of 60% of the protein-coding genes by targeting mRNAs in the cytoplasm, leading to translational inhibition or RNA degradation [11,12].

New evidence indicates that more than 80% of our non-coding ('Junk') DNA, introns as well as 'non-coding' regions, actually code for most of the miRNAs. Recently, a completely new category of circular RNAs has been discovered [13], adding another layer of complexity to molecular biology. These circular RNAs are formed from the intron

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Received February 19, 2014; **Accepted** February 20, 2014; **Published** February 24, 2013

Citation: Khan NA (2014) Molecular "debris": Trash or Treasure? J Nanomedine Biotherapeutic Discov 4: e126. doi:10.4172/2155-983X.1000e126

regions inside a gene. In these circular intronic RNAs, the introns are excised from the initial gene transcript into smaller RNA molecules to form circles that enhance the gene's transcription [12,13]. Also extra chromosomal microDNAs have been identified, in mouse as well as human cell lines [14], so far with unknown function. As was the case with micro-peptides and micro-RNAs, future work on microDNAs may well surprise us too.

Studies with mammalian cells showed that cells can spit out intercellular packages (vesicles) that are taken up by other cells [15]. In 2007, it has been shown that mammalian cells can insert RNA, including microRNAs, into these packages. These findings suggest a novel way of how cells can influence each other's activity and/or function. Since then it turned out that other molecules and even pieces of DNA can be found packed into these vesicles ride as well [16]. It is tempting to suggest that regulating intracellular and extracellular micro-peptides that are generated during the metabolism of proteins can be transferred in the same way. Recently, researchers have found 'non-coding' RNAs with short open reading frames that directly encode for peptides (from 11 to 32 amino acids long), that can regulate fruit fly development [17]. It would be of great interest to investigate whether many more of these mysterious miRNAs molecules can code for micro-peptides, and whether these RNA's are related to micro-DNA.

We suggest that many so-called non-coding sequences are indeed transcribed and that the resulting peptides are further fragmented to micro-peptides by proteolytic enzymes to act as regulatory entities. If so, this would be, next to the normal proteolytic break down debris of the body's protein molecules, a second source of regulating oligopeptides. In this context genes encoding proteases and peptidases are equally important for the generation of regulatory micro-molecules. In our view 'non-coding' sequences not only contribute to the organisms' complexity, but also give rise to regulatory molecules (micro-peptides, micro-RNA, micro-DNA) that exhibit pleiotropy (multiple biological actions) and redundancy (shared biological actions) for the regulation and fine tuning of biological systems.We strongly believe that micro-peptides exhibit important functions and are, in the same way as microRNAs and possibly microDNAs, an important but long time overlooked class of bio-active molecules. Needless to say, that in our view micro-peptides in parallel with the development of nanotechnology for their delivery constitutes a potential new class of pharmaceuticals for addressing old and new scientific and medical challenges.

Acknowledgement

I thank Prof. Dr. R. Benner (emeritus) for comments and discussions.

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