Ribosome Heterogeneity in Normal Cellular Function

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The traditional perception of ribosomes as uniform molecular machines has been revolutionized by recent discoveries, revealing a complex landscape of ribosomal heterogeneity. Opposing the conventional belief in interchangeable ribosomal entities, emerging studies underscore the existence of specialized ribosomes, each possessing unique compositions and functions. Factors such as cellular and tissue specificity, developmental and physiological states, and external stimuli, including circadian rhythms, significantly influence ribosome compositions.

ribosome heterogeneity translation regulation

1. Introduction

Ribosomes play a pivotal role in the flow of genetic information by translating mRNAs into proteins across all living organisms [1]. This conserved function is mirrored in their structural composition, which consists of a ribonucleoprotein complex encompassing ribosomal proteins (RPs) and ribosomal RNAs (rRNAs) [2]. In humans, the ribosome is formed of over 80 distinct RPs and four different rRNAs, forming a small (40S) subunit and a large (60S) subunit [3].

A series of studies over the past few decades suggested a potential correlation between alterations in RPs and/or rRNAs and cancer progression. The term “oncoribosome” has been introduced to highlight the perceived heterogeneity of ribosomes in the context of cancer. Moreover, ribosomes are not merely viewed as protein synthesis machinery but as potential contributors to tumorigenesis [4]. Changes in RPs and rRNAs are not just events that passively occur in cancer cells but instead are active participants in the carcinogenic process [5][6][7]. Indeed, as observed in various cancers, such defects in ribosome biogenesis and function can trigger a spectrum of cellular outcomes, from apoptosis to uncontrolled proliferation [7][8][9].

The molecular mechanisms behind these phenomena are complex. While alterations in RPs and rRNAs can disrupt regular cellular processes, leading to ribosomal stress [5][9][10], they might also provide a proliferative advantage to cancerous cells, allowing them to thrive under adverse conditions. There is an expanding body of evidence on the amplification, mutation, and deletion of RPs, which primarily affects ribosome biogenesis and protein biosynthesis [6][9][11].

An additional layer of complexity is due to RP and rRNA modifications that are essential for the proper functioning of ribosomes. Over 14 types of chemical modifications are known to occur on rRNA, such as methylation, pseudouridylation, and base modifications, affecting over 200 sites [12][13]. These modifications play crucial roles in ribosome assembly, stability, and activity [14]. Specifically, pseudouridylation is significant, accounting for approximately 1.4% of all base modifications with a total of 106 predicted sites in human rRNAs [15][16].

Furthermore, the role of rRNA alteration in cancer is an emerging focus of research. Although mutations in RPs are established carcinogenic agents, the role of rRNA mutations remains relatively uncharted. The conventional perspective of the ribosome as a static unit has evolved such that it is now viewed as a dynamic apparatus responsive to specific cellular conditions, adjusting its protein composition for selective mRNA translation [1][16]. Correspondingly, it is postulated that cancer cells might harbor specialized ribosomes, termed ”oncoribosomes”, to facilitate protein synthesis [17][18][19]. This notion of cancer-specific ribosomal heterogeneity raises the important question of its potential therapeutic exploitation.

2. Ribosome Heterogeneity in Normal Cellular Function

The traditional understanding of ribosomes as uniform entities in cellular translation is undergoing a paradigm shift. Emerging research suggests the existence of specialized ribosomes with unique compositions and functions [20][21].

So far, several different potential mechanisms are believed to contribute to ribosome heterogeneity [22]. For example, quantification of 15 core RPs in polysomes from mouse embryonic stem cells revealed that 6 of the 15 RPs measured were substoichiometric, with 4 of those present on only 60–70% of polysomal ribosomes, indicating the existence of actively translating ribosomes lacking at least one core ribosomal protein [23].

Cellular and tissue specificities further accentuate this heterogeneity. For instance, muscle cells might possess a distinct ribosomal protein repertoire compared with other cells, thereby modulating ribosomal functions [17]. Also, in neurons, the dynamic behavior of ribosomal proteins showed that they can be rapidly and selectively incorporated into existing ribosomes. This dynamic exchange is context-dependent and varies based on the subcellular location and physiological conditions. In detail, it has been observed that a group of RPs was associated with rapidly translating ribosomes in the cytoplasm, and the incorporation probability of some RPs was regulated by their location (neurites vs. cell bodies) and changes in the cellular environment, such as in response to oxidative stress [24].

The developmental and physiological states of the cell further contribute to this complexity. As cells undergo differentiation, growth, or environmental adaptations, ribosomal compositions may evolve dynamically [25]. RNA-seq analyses across mouse and human tissues and cell lines have indicated a broader variety in RP expression patterns than previously anticipated [26][27]. A case in point is the ribosomal protein RPL38, which is implicated in the specialized translation of *Hox* genes, vital for mammalian development. It does this by aiding the formation of the 80S complex on these specific mRNA molecules, thereby affecting transcript-specific translation. Studies using 80S cryo-electron microscopy have pinpointed the location of RPL38 on the ribosomal surface, close to an area of

rRNAs known as expansion segment 27. This particular ribosomal area is highly dynamic and undergoes various shape changes that seem to be regulated by RPL38. This evidence implies that RPL38 may influence the translation specificity of certain mRNA subsets by controlling unique structural alterations in the ribosome [26].

Furthermore, evidence from zebrafish embryos indicates variations in rRNA types during embryogenesis, namely, 5.8S, 18S, and 28S rRNA, and in silico analyses indicate that the 5′UTR of the maternal transcript might preferentially bind to certain regions of the expansion segment that are present in the maternal 18S rRNA subtype but not in the somatic type [28]. Also, in mice and human cells that express reduced levels of the rRNA pseudouridine synthase diskerin, the translation of p27 and p53 is impaired [29].

External stimuli, including physiological cues such as circadian rhythms, can also shape ribosome composition. For instance, Sinturel et al. suggested a coordination between ribosome biogenesis and daily rhythms, suggesting a circadian influence on ribosomal functions in metabolically active tissues [30]. Additionally, rRNA sequence variants and their posttranscriptional modifications introduce another dimension to ribosomal heterogeneity, which is believed to be systematically influenced by spatial, temporal, and conditional determinants [19][20][31], allowing for the existence of a wide array of specialized ribosomes, each with potentially unique functions. Improved rDNA locus mapping has suggested extensive human and mouse RNA sequence variation both across and within individuals. Also, certain rRNA alleles display tissue-specific expression in mice [32]. The functional consequences of the rRNA variations have not yet been established; one hypothesis is that they may contribute to the preferential recruitment of specific mRNAs [28], suggesting that rRNAs may have a direct role in the regulation of translation. Ribosomal heterogeneity does not only occur at the cellular and tissue levels. A single cell may simultaneously contain various subpopulations of ribosomes that differ in protein and rRNA composition and modification. This can alter the structure and function of the ribosome, leading to functional variety within the cell. Understanding these factors opens new avenues for exploring how ribosome specialization can modulate cellular functions, including the control of mRNA translation and gene expression. The implications of specialized ribosomes extend far beyond cellular differentiation and tissue development, reaching into the critical area of cancer research. Emerging evidence suggests that specialized ribosomes may play a pivotal role in the selective translation of oncogenes or tumor suppressor genes, thereby influencing tumorigenesis and cancer progression [33][34]. This information could be invaluable for the development of personalized cancer therapies aimed at modulating ribosomal function.

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