ELSEVIER

Seminars in Cancer Biology 18 (2008) 123–130

seminars in
CANCER BIOLOGY

www.elsevier.com/locate/semcancer

Review

Role of non-coding RNA and heterochromatin in aneuploidy and cancer

Željka Pezer, Đurđica Ugarković *

Department of Molecular Biology, Ruđer Bošković Institute, Bijenička 54, P.O. Box 180, HR-10002 Zagreb, Croatia

Abstract

Abnormal chromosome content known as aneuploidy is the most common characteristic of human solid tumours. The molecular roots of aneuploidy lie in defective centromere/kinetochore assembly and function leading to improper chromosome segregation. These defects can be caused by mutations and/or by altered expression of diverse kinetochore proteins. In addition to proteins, non-coding RNA deriving from centromeric repeats plays an active role, mostly through the RNAi pathway, in the formation of pericentromeric and centromeric heterochromatin, both of them important for proper centromere function. We propose that stoichiometric expression of major kinetochore components such as non-coding centromeric RNA and proteins is crucial for centromere/kinetochore assembly and function. Slight changes in expression of non-coding RNA or mutations in the RNA metabolic pathways induce chromosome instability, mis-segregation and aneuploidy, facilitating finally tumourigenesis.

Keywords: Aneuploidy; Cancer; Non-coding RNA; Centromere; Heterochromatin

Contents

1. Introduction

The genetic and chromosomal profiles of similar tumours are characterized by high diversity and complexity. The aberrations which occur include mutations in coding and regulatory regions, changes in overall ploidy, small changes in gene copy number, high amplification and structural rearrangements [1]. Almost a century ago German biologist Theodor Boveri noticed the strange imbalance in cancer cells between the numbers of maternal versus paternal chromosomes which lead him to the suggestion that this might cause disease [2]. Aneuploidy and chromosome instability are often induced by improper function of centromere and kinetochore or by defects in heterochromatin formation. Recent years have revealed numerous molecular details related to heterochromatin structure and function as well as to the structure of centromere/kinetochore components. New biological pathways leading to heterochromatin formation have been discovered and models for centromere/kinetochore establishment have been proposed [3]. In both processes non-coding RNA plays an important role: it mediates specific chromatin modifications characteristic for heterochromatin and necessary for its establishment, and possibly acts also as

* Corresponding author. Tel.: +385 1 4561197; fax: +385 1 4561177.
E-mail address: ugarkov@irb.hr (Đ. Ugarković).

1044-579X/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.semcancer.2008.01.003

a structural component of the centromere/kinetochore complex [4,5]. It has been shown recently that aneuploidy caused by defects in kinetochore/centromere components can drive tumourigenesis [6]. This actualizes Boveri's hypothesis about chromosome instability and mis-segregation as a major cause of cancer.

This review summarizes recent results on the role of non-coding RNA in the establishment of pericentromeric heterochromatin and centromere/kinetochore as components indispensable for proper chromosome segregation. In addition, the connection between aberrant mitotic divisions caused by defects in heterochromatin formation or in centromere/kinetochore components, and aneuploidy/carcinogenesis has been discussed in light of recent discoveries in this field.

2. Non-coding RNAs

The majority of the genomes of eukaryotes is transcribed into non-coding RNA, which in general refers to RNA that does not encode a protein. This large and heterogeneous group of sequences includes small interfering RNAs (siRNAs) and microRNAs (miRNAs), both groups having a similar size of 20–25 nt and produced from larger precursors, either double-stranded RNA (dsRNA) or hairpins [7]. In addition, small nucleolar RNAs (snoRNAs) involved in the modification of ribosomal RNA (rRNA) and small nuclear RNA (snRNA) participating in splicing are classified as non-coding RNA. Numerous long transcripts, some of them polyadenylated and conserved among related species, some fast evolving and species specific, also belong to the non-coding RNA class [8,9]. Although the function of many non-coding RNAs is still not known there is clear evidence for their importance in physiology, embryology and development. Recent results point to their active role in controlling multiple regulatory layers including chromosome architecture, chromatin modulation and epigenetic modification, transcription, RNA maturation and translation. Some non-coding RNAs are developmentally and temporally regulated or restricted to particular tissues and organs which indicates their role in fine-tuning gene expression. Since many non-coding RNAs are involved in complex regulatory networks characteristic of higher eukaryotes, it can be proposed that mutations in their sequences could have a major influence on developmental differences and abnormalities, cancer and other complex diseases such as neurological disorders [10]. In addition, changes in the expression level of particular non-coding RNAs could affect chromosomal architecture influencing in this way cell growth, development and division.

The molecular mechanisms by which non-coding RNAs function are in some cases well understood. They commonly act as adaptors that position a target molecule, which is also a nucleic acid, for enzyme activity. Activity of non-coding RNA is driven by base pairing and includes several proteins which all together form a functional non-coding ribonucleoprotein unit [11].

3. Heterochromatin

Heterochromatin has been cytologically distinguished from euchromatin based on differential compaction in interphase nuclei [12]. Euchromatin is more diffuse and generally more transcribed containing numerous genes that give rise to most of cellular mRNAs. In contrast, the heterochromatin fraction of the genome is generally gene poor and corresponds to highly condensed chromosomal regions. At the sequence level, heterochromatin is composed of highly repetitive DNA, mostly satellite DNAs and transposons, with little or no protein-coding potential [13]. The main chromosomal targets of heterochromatin establishment are centromeres and telomeres. These regions remain condensed throughout the cell cycle, and are referred to as constitutive heterochromatin. In addition, heterochromatin is found at developmentally regulated loci where the chromatin state is changed in response to cellular signals and gene activity. Such regions are known as facultative heterochromatin [4].

Heterochromatin has important roles in chromosomal segregation, genome stability and gene regulation. The heterochromatin state is stably inherited during cell divisions and its nucleation and spreading to surrounding DNA sequences occurs under sequence-independent epigenetic control. When heterochromatin spreads across a domain it generally induces repression of nearby sequences and genes, a process known as silencing. Heterochromatin proteins that surround centromeres are necessary for sister chromatid cohesion and chromosome segregation [14,15]. Long repetitive DNA arrays, characteristic of the centromere and telomere, are also stabilized by a heterochromatic state which represses recombination in these regions. Localization of numerous transposable elements within tightly packed heterochromatin prevents their activation and movement throughout genome and thus protects genome against insertional mutagenesis. Besides playing a role in genome integrity, heterochromatin controls gene expression during development and cellular differentiation. Heterochromatin participates in the stable inactivation of developmental regulators such as the homeotic genes in mammals and insects. In addition, equalization of X-linked gene expression in mammals involves silencing one of the two X chromosomes in females by heterochromatization of the whole chromosome [4,16].

4. Non-coding RNAs in heterochromatin formation

It has been recently shown that RNA interference (RNAi)-based silencing mechanism mediates heterochromatin assembly in the fission yeast *Schizosaccharomyces pombe* [3]. Subsequent studies showed that the RNAi machinery also affects heterochromatin in plants, flies and mammals [17–19]. Many of the factors involved in heterochromatin assembly in *S. pombe* are conserved in mammals [4]. The mechanism involves an orchestrated array of chromatin modifications: deacetylation of histone H3 amino termini followed by methylation of histone H3 at lysine 9 creating a binding site for heterochromatin protein 1 (HP1). The limited number of chromatin modifying enzymes in animals indicates that they are targeted to their sites of action, which