Kurdistan Regional Government-Iraq

Council of Ministry

Ministry of Higher Education and Scientific Research

University of Salahaddin-Erbil

College of Education

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License of the DNA

replication, cancer and differentiation

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Study Year

2019-2020

ABSTRACT

Gens are the units of an alive organism's heredity. It usually establishes on a length of DNA which codes for a protein type or chains of RNA which has a functions of the organisms. All living organisms depend on genes, as both proteins and functional RNA chain are known. Current studies have proof of a practical interaction among duplication of DNA and the apparently different areas of cancer, growth, and pluri-potence . Protein structures that engage in the license of DNA reproduction source are now considered to have developmental functions, although their regulation may proceed to cancer. Furthermore, transcription factors concerned in sustaining or restoring the multi-potent stage have relations with the pre-replicative mechanism. Many researches found the fact which an extra expression of those aspects has relation with tumor.

Key Words: DNA Duplication, Cancer, Pluripotency And Licensing of DNA Replication

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1 INTRODUCTION

DNA duplication has started from a vast range of sources which are triggered in either sequence of cells (in human or mouse cells, approximately 50,000 cells). There are several other possible roots in the genome which doesn't work in particular period by the cell. DNA duplication initialization at core is an extremely controlled procedure that begins with origin licensing, during which a multi-protein structure called the pre-replicative compound has been produced at the source of DNA duplication. A subgroup of such sources are then being initiated and duplication of DNA starts during the S stage from those origins. (look at review by Speck et al) In this study there is a concentration about the DNA

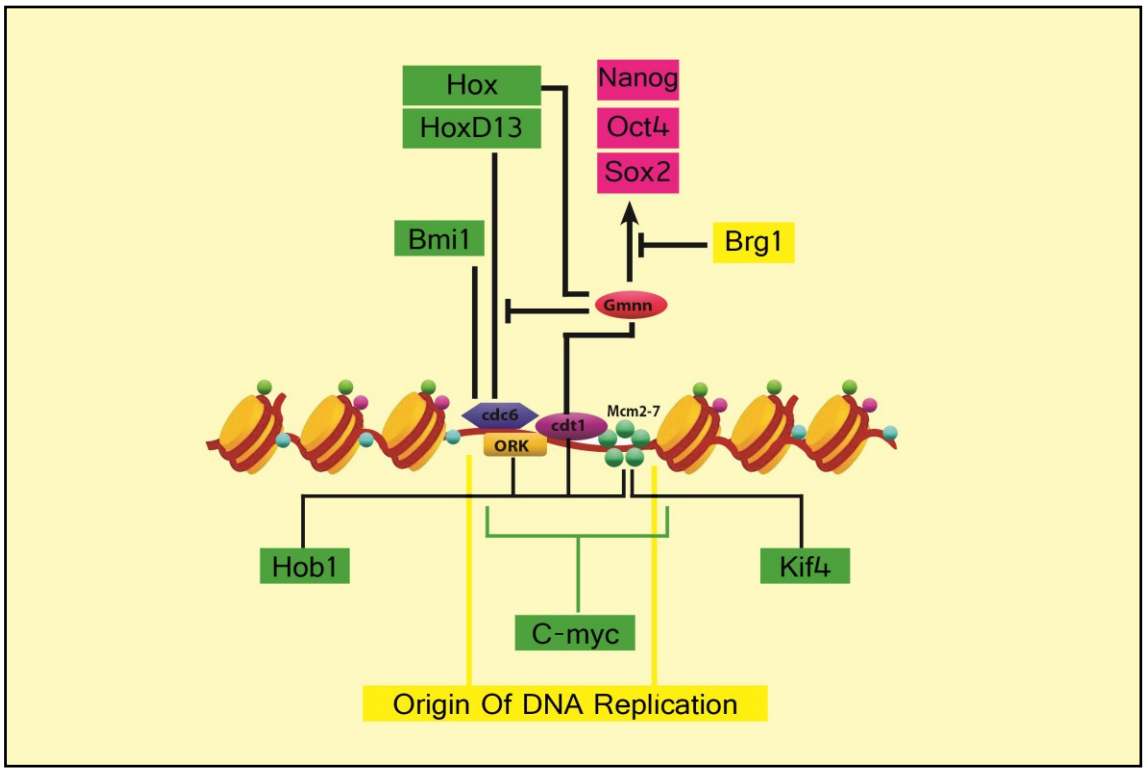

Figure 1; Interactions of the pre-replicative complex members (Cdc6, ORC, Mcm2-7and Cdt1), and the Cdt1 inhibitor, Gemini, with transcription factors and proteins participating in chromatin remodeling. Bmi1 interacts with Cdc6; Hbo1 with Cdt1,Orc1 and Mcm2; c-myc with MCM2-MCM7, ORC2, Cdt1 and Cdc6 whereas Klf4 has been reported to induce transcription of Mcm2. Antagonism between Geminin andBrg1 has been proposed to maintain expression of Oct4, Sox2 and Nanog. Gemini also interacts with Hox proteins and inhibits the interaction between HoxD13 andCdc6.

replication, which proteins involved in assembling the pre-replicative structure (pre-RC) in the basis is an important pace for starting duplication. Such a structure comprises of the origin recognition complex (ORC), Cdc6, Cdt1 and MCM proteins, and is interactively constructed onto chromatin. Ensuing source activation outcomes in pre-RC inactivation, as its sub-sections are adversely controlled by various procedures (Symeonidou et al., 2012). One of the main elements of the pre-duplicative structure is the protein Cdt1 that is liable for MCM proteins filling onto the duplication source. It has been adversely controlled by ubiquitin-dependent proteolysis and a minor protein blocker in metazoan called Gemini, which regulates the process very tightly. Moreover, growing pieces of evidence indicate that processes for DNA duplication have a far wider scope than formerly believed (Fig. 1). Flanagan and Peterson have mentioned this some yeast duplication sources rely on SWI / SNF structure for their basic functioning, when CDC6 has currently been used to engage with Bmi1, a part of the Poly comb protein family, in fetal fibroblasts of the mouse (MEF)(Agherbi et al., 2009). Most significantly, parts of the transcription factor group Hox, recognized for their function in growth, have been revealed to straightly engage human duplicative compounds and yeast. HoxA13 in human, HoxC10 and HoxC13 have been mainly detected on a one-hybrid yeast panel. Immediately,HoxC13 with HoxC10 have been demonstrated to engage in human sources, although changing the chromatin composition reduces the interfaces among origins and the HoxC13(Marchetti et al., 2010). But, unlike yeast, no standard nucleotide chain has been found in any metazoan reproduction source. The latter's DNA includes many likely sources but little some have been triggered throughout every single genome replication, a notion called like the Jesuit duplication prototype (Sequeira-Mendes *et al*., 2009).

While also, triggering of metazoan sources tends to be part of a multifaceted mechanism, involving epigenetic and transcriptional processes. In that aspect, this study concentrates about the interrelations involving DNA duplication, progression and pluripotency and in which way disruptions inside such “states” will cause to genomic changeability and tumor.

2 DEVELOPMENT AND DNA DUPLICATION LICENSING

2.1 . DNA duplication source description and development

Effective physiological modifications have been detected throughout growth, because stem and originator cells start fate modification systems and endure incurable specialization, thus retaining a population of auto-renewing characteristics. It has been theorized that these procedures are interconnected with alterations in transcription AL schemes and restructuring of chromatin and can affect the quality of origin, when a mutual regulation is indeed probable. MacAlpine et al are pioneers who used organized microarray method for revealing periodic duplication model associated with the active transcription rate, in Drosophila. Sequoia Mendes et al. then used fetal mouse stem cells to recognize 85% of the origins of duplication associated with transcriptional sections. In accordance with this, studies have proven currently that ORC1 genomic places, one of the major proteins controlling the specification of origin,

were linked with transcription starting locations of RNAs none-coding and coding, when their arrangement rates were connected with duplication scheduling (Dellino *et al*., 2013) . In fact, it was proposed that the sources of DNA duplication are structured in a high series composition. Knowing how the segmentation and selection of duplication origin happens through progression will put a spotlight on the interaction between selection of origin, transcriptional and chromatin arrangement. For the localization of effective duplication sources, an accessible chromatin structure is favored, while many histone amendments have been bound to aggregation, origin selection and targeting of pre-RC members (Almouzni and Cedar, 2016). Original existence associates with accessible chromatin verification connected to H3K4methylation when acetylating of the H4 and H3 histones will be required for a successful targeting of sources and consequently demonstrated the fact of H3K4 di-methylation lacking in yeast leads duplication faults, indicating that this sort of adjustment is essential for appropriate action of origin. In accordance with that, lysine K79 (H3K27Me2) dimethylation has been demonstrated to appear inside large proportion of human sources, beside proof indicating this it might be related with sequence and frequency of their releasing (Fu *et al*., 2013). In relation, increased rates of acetylating of nucleosome were indicated in effective origins at the time of Drosophila growth, displaying a statistical correlation between the previous and origin releasing activity. By comparison, rates of acetylation reduced as transcriptions were started and nearby sources were deactivated (Liu *et al*., 2012). It has been demonstrated that the histone acetyltransferase, Hbo1, interferes with Cdt1 and Orc1 connecting acetylating with chromatin entry and licencing of source. At lysine K20 histone H4 methylation was also involved with pre-RC gathering in sources of duplication (Chen *et al*., 2013). There are also many researches that illustrate the interaction between definition of origin

and transcription mechanism. A part of the pre-RC compound, Cdc6 can restrain transcription of CDH1via attaching its booster. This contributes to CTCF replacement, a repressor for transcription serving as a protector of chromosome, also the initiation of different duplication sources. Likewise, it has been revealed that linking on specific transcription causes, like c-Myc and GATA1, is correlated with action of DNA duplication source. Modifications in origin usage were also identified in the HoxB locus at the time of distinction of fetal carcinoma cells in the mouse, indicating that this system may have role in controlling the developmental production of HoxB genes (Sideridou *et al*., 2011).

2.2 . Pre-RC components developmental roles:

It has been proposed that pre-replicative structured constituents have different roles in many developmental procedures, with Gem-in being one of the most distinctive. In addition to its position in the controlling of the cell cycle, Geminin was originally recognized by its capacity in Xenopus embryos to extend the neural layer as over ex-pressed. Geminin is essential for controlling the self-restoration and transcription actions of neural progenitor cells through corticogenesis (Spella *et al.*, 2011), Although the growth of T cells in the thymus stays sun influenced by Geminin's disappearance In addition, it engages in axial layering via Poly comb regulated control of the Hox gene expression at the time of chick growth (Karamitros *et al*., 2010). Likewise, direct contact with the home obox, which contains the transcription factor Six3, regulates cell growth and distinction in Medaka fetal development during eye formation. Additionally, adversarial relations among Geminin and b-HLH transcription cause set elements to link the catalytic subgroup of SNF/ SWI

chromatin adjusting structure, Brg1. It was suggested to control the transfer from a nerve originator for a descended cell inside P19EC cells also xenopusembryos. Antagonism among Geminin and Brg1 was also suggested to regulate trophoectoderm label development and preserve transcription of main pluri-potency factors within embryonic base cells of the mouse. (Yang *et al*., 2011). It has been proposed in a new study by Kroll's team, the Geminin contradict bHLH expression genes which stimulate neurogenesis via preserving their developers' dual condition. It was shown by Lim et al. during the beginning stages of Xenopus embryogenesis Geminin limits endoderm, mesoderm and ectoderm involvement via the activation of Poly comb and Poly comb arbitrate depressive changes. nevertheless , neural status formation of ES cells, has been demonstrated to act as reliant on Geminin transcription that preserves nerve gene transcription and hyperacetylation (Lim *et al*., 2011) . The mechanistic method by which Geminin implements this function is not identified, and the findings of various researches frequently contrast each other, indicating that further investigations are required to determine Geminin's position and perhaps incorporate its function in controlling development and licencing. Geminin's partner, Cdt1, is formulated throughout embryogenesis in cortical progenitors; though, the involvement of Geminin is not presently obtainable. Two separate Cdc6 isoforms showed variable regulation throughout the foetus-genesis of Xenopus, connecting modifications in the structure of the cell cycle to growth (Yellajoshyula *et al*., 2011). MCM gene expression is an effective indicator for predicting development throughout embryogenesis and also for stem cells. Depleting MCM5 in zebrafish and particular mutations results in developmental deficiencies in some expanding tissues, when a hypomorphic mutation in mice is associated with deficiencies in stem cell species (Pruitt *et al*., 2007). Furthermore, some essential ORC subsections

were also noticed to control the formation of dendrites and dendritic spines in after-mitotic neurons. Though ORC3 has currently been shown to promote neuronal growth and development by preventing Rho in the controlled cerebellar granule cells. Likewise, ORC homologue, Drosophila homozygous deviants forlatheo, will not grow imaginary disks, and has too much restricted growth of CNS and die prematurely in the larvae period. (Chen *et al*., 2019). Both of these researches suggest morphogenetic functions for constituents of ORC, regardless of their position in the cell cycle. It is an interesting possibility and it needs further research to decide if it is a condition too, for different proteins involved with pre-RC group. Remarkably, variations in genes CDT1, CDC6, ORC4, ORC1 and ORC6, and have newly been identified with Meier Gorlin Disorder (MGS), an unusual autosomal recessive abnormality described as primordialdwarfism, hypoplasia, patellar aplasia and microtia. ORC1 has similarly been identified to include an area which interferes at lysine 20 (H4K20me2) with histoneH4 damp ethylised. Removal of this region has been shown to disable ORC1 activity as it has been stated that mutations have a vital role in MGS pathogenesis. Those researches indicate the fact which source licensing elements are necessary DNA duplication therefore mutations are supposed to cause growing deficiencies resulting to disrupted replication of cells and thus may decrease development broadly. Origins licensing of DNA duplication will be considered as an important procedure for DNA proliferation across growth, but further work is required to understand whether disordered cell replication and decreased development may occur from the involvement of pre-replicative complex constituents in other cellular activities in addition to DNA duplication. (Stiff *et al*., 2013).

3 PRE-RC MEMBER LINKS WITH

PLURIPOTENCY

The origins of duplication processes and also duplication structures tend to be related to the conservation of pluripotency in forms which have not yet clearly explained. Hiratani et al conducted the first genome-wide analysis to explore into this difficult problem, identifying certain segments of the chromosome in mouse ES cells which duplicated earlier in step S, whereas others duplicated later. This sequential structure of duplication was changed after depletion of pluripotence and differentiation, indicating that the duplication domain feature is cell-type relevant. These sequential profile alterations in cell culture versions from early to late epiblaststage were later reported by the researchers, correlating with alterations in chromatin prior to the actual defined germ level and the main pluripotency factors Oct4, Nanog and Sox2 were controlled (Hiratani et al., 2010). They have also shown that these tempo-ral duplication schemes are widely maintained in various organisms with related cell sorts. In the same way, Schultz studied human ES with micro-vascular endothelium cells utilizing one-molecule DNA replication testing method. He showed that the sources of duplication are substantially dissimilar between both the two types of cells inside a DNA section comprising the Oct4 gene, demonstrating the modifications that the replication system develops after the depletion of pluripotency. In accordance with this , new research of ES cells and modified fibroblasts suggested that some duplication regions may be replicated delayed after the depletion of such esBAF constituents such as Brg1, when different parts of the esBAF structure may alter replication duration in separate duplication domains(Takebayashi *et al*., 2013). Of

course, esBAF is a chromatin reshaping process that associates specifically with pluripotency genes and also, is necessary for pluripotency core occupancy. Importantly, it needs DNA duplication to enable pluripotency genes, when the cell phase is critical for somatic cell processing. Of note, esBAF is a chromatin remodeling complex that directly inter-acts with pluripotency factors and is essential for the main tenancy of pluripotency. Interestingly, DNA replication is required to activate pluripo-tency genes, while the cell cycle is important for thereprogramming of somatic cells. Likewise, it has been newly stated that DNA duplication in laboratory ESC-heterokaryons is an initial and critical process in theepigenetic reconditioning of somatic cells. Moreover, a large amount of publications offer proof in favor of Geminin pre-RC repressor also its function inside controlling pluripotency, auto-revival and development of stem cells. Mouse fetuses lacking the function of Geminin will not grow past the eight cell phase and not creating internal cell layer. Geminin transcription is then needed in mice ES cells via provoking SNF /SWI protein Brg1 to preserve the expression of the essential pluripotency factors , i.e. Sox2, Oct4 and Nanog. In connection with this, it has been currently discovered that SRR2, aSox2 improver, is enabled epigenetically in the existence of Gemi-nin but otherwise suppressed (Foshay et al., 2012). The following research stated that downregulation of Geminin activates the differentiation of mouse ES cells into mesendoderms, identified with low Sox2/ high Oct4 extents ; nevertheless, Yang et al, stated the fact of lacking Geminin leads in the variation into an excessive embryonic path. Furthermore, an other research analyzing Geminin's expression in mice ES cells revealed variance to the neural line if developed like a single-layer on the other hand distinction on the way to mesendodermin a tripple-dimensional culture (Slawny and O'Shea, 2013). Maybe the most unnoticed thing that connects pluripotency with DNA replication are the correlations with the latter of the major

pluripotency-connected expression causes. Utilizing gene transcription sampling and Gene Ontology (GO) study by Campbell et al stated the fact that in ES cells Oct4 is correlated with DNA duplication GO classes and arrangement, between others. Likewise, Nanog's overexpression, another essential ES cell pluripotency component, has been identified to control genes in mesenchymal stem cells relevant to cell phase regulation and DNA duplication, when also dedifferentiating them. with this direction, as examining the Sox2interactom inside ES cells, Gao et al. (Gao *et al*., 2012) noticed that such an element is correlated with the Polb, Rpa1,Rpa2 and Rpa3 DNA duplication system proteins. Moreover, more interestingly, there is a firmer correlation among pluripotency and c-myc and transcription aspects Klf4, their imposed transcription is considered to produce mediated pluripotent stem cells along with Sox2 and Oct4.i.e. diversified somatic cells modify again to pluripotence. Klf-4 has been described to attach in the uterine epithelium to the regulator of MCM2and activate its transcription, although Klf's transcription factor connectivity is essential for controlling immature stem cell self-revival that contains branches of the MCM group. However, cMyc was identified to foster DNA duplication through a non-transcriptional method, resulting to the targeting of defective origin and increased distribution of source. This factor has been demonstrated to connect closely with pre-RC system and to be co-refined to Cdc6,ORC2,Cdt1 and MCM2-MCM7. Its extirpation prevented duplication of DNA, at minimum partially according to non-transcriptional consequences, whereas its overexpression triggered greater duplication development (Srinivasan *et al*., 2013).

4 THE CANCER, PLURIPOTENCY AND DNA REPLICATION LICENSING.

4.1. Oncogenes and Pre-RC structures.

It is necessary a complete and accurate replication of the genetic content inside one cell phase; for the transfer of genetic data to daughter cells. It has been known the source licensing of DNA duplication regulated by pre-RC elements considered as an important method in purpose of preserving genetic stability, since high range -licensing and low range-licensing leads to abnormal DNA duplication (Dutta, 2007). Pre-RC protein transcription is raised in cancer due to excessive differentiation of the cells and duplication of DNA. Although, except their function as replication indicators, there has been significant proof that some of these proteins persist in their oncogenic dwellings and that their dysregulation may lead to genetic disruption. It was suggested that the abnormal control of Cdt1 facilitate the re-firing of the similar origins that cause genetic disorder and directly cause cells for dangerous mutation (Petropoulou *et al*., 2008). Most precisely, Cdc6 has also been demonstrated to be relatedto re-duplication in various tumorigenic cell strains and human samples, along with Cdt1. The transcription of Cdt1 and Cdc6 has been investigated in non-small cell pulmonary malignant tumor and their overexpression is proposed to cooperate in the mutation p53, causing cancer development, genetic disorder and associated with adverse diagnosis for these cases. In addition, it has been found in a corresponding analysis that mismanaged Cdc6 and Cdt1 transcription was detected at the beginning phases of hyperplasia and

dysplastic epithelial layer. Cdc6 and Cdt1 Inactivation in carcinogenesis cell groups stimulated re-duplication and created a reaction to DNA destruction, which triggered signals to trigger senescence and apoptosis. The cells which connect Cdt1 and Cdc6 inactivation with deficiencies in p53 process showed rather antagonistic characteristics also displayed epithelial to mesenchymal transfer characteristics, implying that inactivation of these factors may lead to intrusion and metastasis of cancer. More in laboratory proof of Cdt1's potential to stimulate tumorigenesis was given via Cdt1 extra-expression inside T cells which resulted in lymphomas and lymphoblastic developing due to p53 lack. Gonzalez et al. proposed an different method of how pre-RC components can lead to cancer development, as Cdc6 inactivation contributes to active transcription of INK4/ARF place, which is a type of very common human cancer cases. The method of transcriptional suppression regulated by Cdc6 encompasses heterochromatinization of chromatin via the activation of histoneedeacetylases, when the collaboration with other oncogenic signaling methods facilitates neoplastic differentiation. Additionally, the transcription of CDC6 and MCM5 in preventative pre-malignancy and tumor was stated to associate with the level of dysplasia. In accordance with this, many premalignancies and tumors like breast, renal, skin and esophageal were identified dysfunction of specific MCM proteins. In addition, a transformation of MCM4 called Chaos3 (randomly arising chromosome abnormalities 3) is a possible mutant and produces adenocarcinoma (Chuang *et al.*, 2010). Mouse with decreased MCM2 function usually grow but their life cycle is significantly shortened due to lymphomas [50]. There is a lack of cancer studies involving the ORC subgroups; although, a limited number of severe myeloid leukemia have detected removal of the ORC5L subgroup (Gough *et al.*, 2011). Remarkably, as merged into the nucleoporin 98 gene, HoxC13 and

Topoisomerase I and II, that doesn't include pre-RC constituents but member of the duplicative compound, develop bloodstream infections, probably because of their unregulated expression, as a consequence of the merging. Cdt1-inhibitor resection, Geminin, contributes to re-duplication. Researches on human cell chains and Xenopus stated that resection of Geminin causes in over-replication of the gene and disruption to the DNA. Additionally, Geminin down control was demonstrated to activate centrosome over replication and irregular division of chromosome (Chen et al., 2008). From another point of view, the condition tends to be rather complicated in the living organism ; while controlled knockout which miss Geminin inside lymphatic tissue region and basic neural organism are feasible without any indications of cancer progress ; Taraviras S, unpublished observations). Moreover, elevated extents of Geminin were noticed as correlated to CD133 development, a familiar tumor basic cell indicator, in a type of chest cancer (Chen *et al*., 2008), Potentially influencing the properties of stem cells in cancer cells.

4.2. Cancer and Pluripotency related factors.

Because of many current pioneering studies, the function of pluripotency-linked factors in disease studies self-restoration conditions and malignant tumor is getting much clearer. In this point (Kumar *et al*., 2012) demonstrated the fact which Oct4 will be necessary for preserving self-renovating characteristics of basic cell tumor (SCC)-like cells segregated from non-small cell pulmonary cancer cases. Rather interestingly, (Kumar et al., 2012) reported that imposed transcription of Oct4 within the cells of melanomata triggered their desperation to CSC-similar cells, although new evidence showed that Oct4 stimulates carcinogenesis and prevents cervical tumor programmed cell death (Wang *et al*., 2013). Likewise, it was

demonstrated that Sox2 promotes dedifferentiation in human pancreatic tumor cells thus increasing their cell differentiation and is also proposed to encourage pulmonary cancer cellular senescence by assigning CSC-similar characteristics to the cells. Accordingly, Nanog develops CSC-similar alleles in colon cancer (Ibrahim *et al*., 2012) in addition to the progress and metastasis of breast cancer. The c-myc, Klf4, Lin28 and Bmi1 expression factors, which are important for the prompted pluripotent stem cell deveopment, also provide similar functions along these sections. C-Myc is decontrolled in a number of human cancers like breast, colon, and prostate cancer, whereas its overexpression is found to maximize duplication source function and provoke DNA disruption.

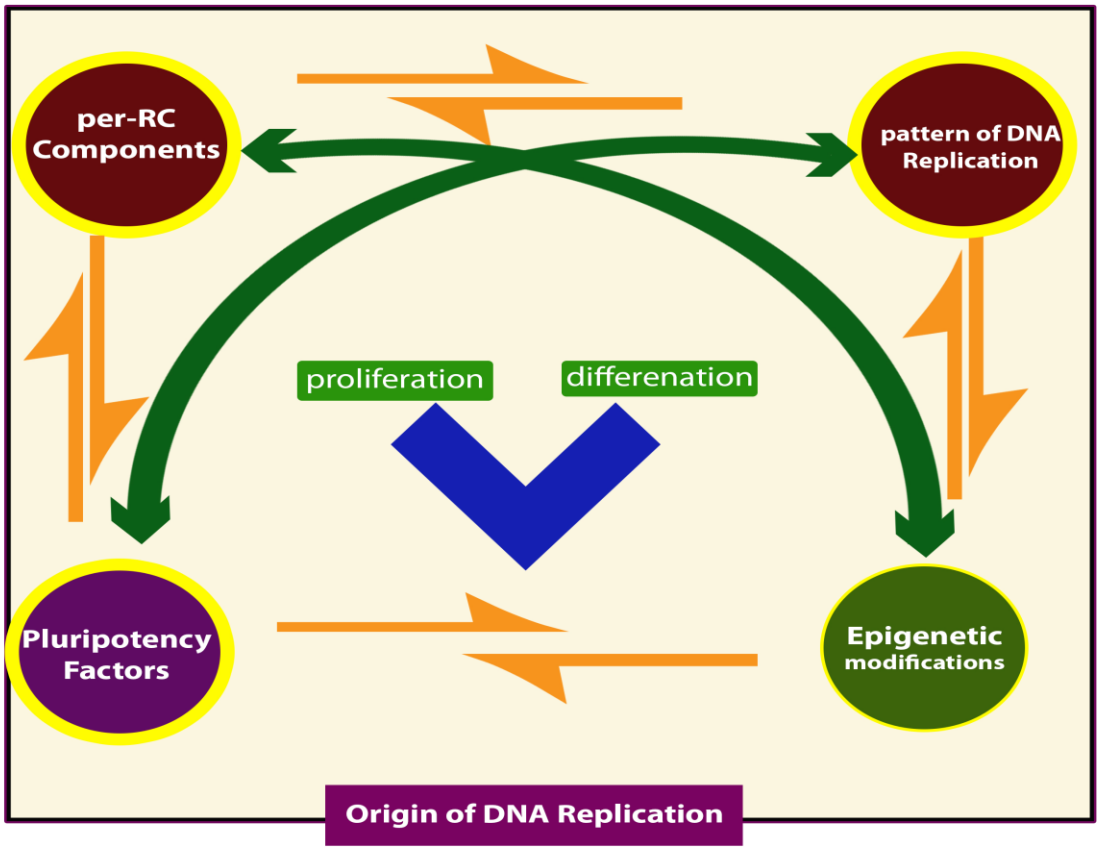

Figure 1 A general version illustrating the practical reciprocal connection among the pre-RC components, pluripotency genes , epigenetic variations with the design of DNA replication source releasing .

Likewise, it has been reported that Klf4 gives CSC-similar characteristics within colorectal tumor cells to promote a CSC group in vitro, and is proposed to have a crucial function in breast cancer growth and cell death (Leng *et al*., 2013). Finally, Bmi1 is required for cancer development in a glioma mouse model while Lin28 has been noted to foster differentiation in a cell chain of the mice lung cancer and its enhanced transcription is closely linked with progressed cancers (Viswanathan *et al*., 2009).

4.3. Epigenetics, cancer and DNA duplication.

Giving further aspect of complication, several Poly-comb family proteins are considered to be involved in differentiation actions and controlled by extended non-coding RNAs (ncRNAs) including some that arise as cancer promoting or restrictive genes as well. For instance, in most breast and colon cancer a longncRNA in the HoxC place called (Hox transcript antisense intergenic RNA) HOTAIR , it is upcontrolled and appears to impact on the role of the PRC2 Poly comb structure on a gene-wide range (Kogo *et al.*, 2011). Likewise, it is thought that the SWI / SNF structure is essential in oncogene inhibition, because many deactivating disruptions in its vertices have currently been reported in human tumors. In relation, Brg1, a part of SNF / SWI also Geminin's interconnected associate were stated to work like gene for tumor silencer (Wilson and Roberts, 2011). Likewise, CDC6 is recognized to connect with the Poly-comb protein category Bmi1, whereas c-Myc is demonstrated to control the transcription of the similar factor in a transcriptional manner. Surprisingly, Bmi1 was also resistant catalyzed with many ncRNAs. Further elucidation on this matter, CTP compound, a gene correlated with histone deacetylase (Ray et al., 2013) Demonstrated to be deregulated in most of several tumors, some ncRNAs are capable of encoding.

5 CONCLUSION

Duplication of DNA, cancer, growth and pluripotence tend to interrelated. Compound pre-RC proteins play different functions in growth, and their deregulation will lead genetic disruption and cancer. Of course, it has lately been found that, when compared to their non-cancer equivalents, cancerous cells get a greater range of effective duplication origins. In regard with this, Di Paola and Teammates recorded greater cancer cell origin development in comparison to non-transmuted cells, indicating larger stimulation of origin. Furthermore, expression elements correlated with pluripotency interfere with mechanisms for DNA duplication when their overexpression was closely linked to cancer. A comprehensive paradigm is suggested in this respect, in which the option of proliferation against segregation (the "seesaw of proliferation / differentiation") provides an unidirectional interaction with transcription of pre-RC parts, sequence of DNA duplication origin triggering also epigenetic changes. This study has been sponsored by the project "THALES: The function and techniques of symmetric cell separation throughout stem cell differentiation," co-funded by the European Social Fund (ESF) and Greek national funds via the National Strategic Reference Framework (NSFR) Functional Program "Education and Lifelong Learning."

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