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Role and hallmarks of Sp1 in promoting ovarian cancer

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ABSTRACT

Ovarian cancer has a poor prognosis especially due to late diagnosis, intrinsic resistance to some therapeutic drugs, increased interest in finding novel DNA – binding and transcription factor agents as a probable chemotherapy in treating ovarian the gynecological cancer. Based on many previous reports it is evident that the expression of various cellular genes are been regulated by Sp1 the transcription factor, but still a better understanding is required, about its role in developing and progressing the human cancer. Sp1 is been found playing dual role such as the activation as well as suppression of the cellular genes either converting into an oncogene or performing biological activity such as proliferation, differentiation, DNA damage response, apoptosis and angiogenesis. There are even proofs, which suggest that Sp1 has homologous forms of proteins named as Sp2 and Sp3, which also support Sp1 in contributing the progression of tumor cells. These typical characters of Sp1 and its interesting facts related to biological functions are yet to be explained clearly. Thus, in this current review, we briefly explain the role, characters and proteins associated with Sp1 family of transcription factor do contribute as a "hallmarks of cancer". We also review the evidence suggesting that Sp1 is highly over – expressing the genes, which pay ways in promoting ovarian cancer. Thus, we conclude that targeting Sp1 one of the best diagnostic tool to detect ovarian cancer in early stages or promoting Sp1 as best therapeutic agent would be a best resolution to reduce the incidence of ovarian cancer.

1. Introduction

Ovarian cancer is one of the most lethal gynecological cancers, especially among older women.[1] Ovarian cancer is been ranked in the sixth position as the most common cancer and as the causative agent of cancer death in seventh position among women throughout the world.[2] The over-all 5 year of survival rate for women diagnosed with later stages of ovarian cancer is only 27%.[3] Among the gynecological cancer's, cancer of ovary has the most unfavorable prognosis. Ovarian cancer is a malignant cancer described with invasion in the surrounding stroma, distant metastasis, anticancer drug resistance and angiogenesis.[1] Many studies have revealed that, many genes have been over – expressed or activated by Sp1 and/or by other transcription factors in ovarian cancer cells, resulting in to tumor development[4–9]. Thus by using the potential role of transcription factors in ovarian cancer, a novel therapeutic target will be developed to treat this cancer in early stages.

Some of the biomarkers which is currently been used to detect ovarian cancer are human epididymis protein 4, carrion - embryonic antigen, legumain, mesothelin, osteopontin and vitamin E – binding plasma protein.[10] Some of the promising inhibitor therapies which are been used to treat ovarian cancer are polyadenosine diphosphate - ribose polymerase inhibitors and angiogenesis inhibitors.[1] However, these treatments are only effective in the initial stages of the ovarian cancer. Hence, we can say that detection of ovarian cancer in the early stages is difficult. Thus, a better knowledge about the molecular biology of the ovarian cancer is an immediate need to rescue the patients affected with this deadliest cancer. A combined genomic analysis in ovarian cancer is been carried out,[11] through which an exact link between survival rate, response to treatment and the role of transcription in ovarian cancer is been tried to understand.[12,13] Thus, it is clear that the classification of transcription factors for tumorigenesis as well as for progression of cancer will result in creating appropriate treatments to treat ovarian cancer.[14,15]

One of the most common transcription factors, which are been associated with ovarian cancer progression, is the Specificity Protein 1 (Sp1)[4–9]. Sp1 protein belongs to the family of Sp/Kruppel –

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like factors, which is highly indulged in basal regulations of transcription in various genes.[16,17] In the beginning, Sp1 was been identified as an important promoter – specific binding factor for transcription of SV40 gene.[18,19] Sp1 normally binds with GC – rich double – stranded DNA through zinc fingers and thus managing the transcription of many housekeeping genes and thus lending its contribution in various biological functions such as metabolism, cell cycle and cell death[20–23]. In a recent article is has been established that in an entire human genome, approximately Sp1 has 12,000 binding sites, thus providing an evidence that Sp1 does plays major role in promoting cancer by regulating functions of innumerable cellular genes such as induction and inhibition of transcription[16,17,24].

The current review investigates the potential role of Sp1 in progression of ovarian cancer by revealing the over – expression of cellular genes by transcription especially regulated by Sp1. Moreover, decoding of the molecular footings of ovarian cancer will greatly contribute to the better understanding of the invasion and prognosis of the deadliest gynecological cancer in women. Furthermore, this review will provide a base to create Sp1 as a future best diagnostic tool to detect ovarian cancer in the early stages itself.

2. Symptomatic overview of ovarian cancer

Ovarian cancer is one of the foremost causes of death due to malignancy in the reproductive organ. It is described by the presence of dissemination in the peritoneal cavity with a rare occurrence of visceral metastases.[25] Women with perimenopausal stage are at higher risk of getting ovarian cancer. Based on the previous reports it is pretty much clear that ovarian cancer affected subjects have no particular symptoms to diagnose in the early stages.[26] Until now, there is a lack of availability of knowledge about the exact symptoms in advance and effective diagnosis for ovarian cancer. Some of the wide range of symptoms which is been observed in ovarian cancer are diffuse abdominal complaint's, Tympanites or meteorism, sudden weight and appetite loss, changes in bowel habits and abdominal swelling.[26] Possible symptoms linked with early stages of ovarian cancer are pelvic and abdominal pain, increased abdominal size, bloating, and difficulty in eating.[27] While the symptoms for later – stages of ovarian cancer include gastrointestinal problems such as nausea and vomiting, constipation and diarrhea.[28]

3. Characterization of Sp1

Transcription factor Sp1 also referred as specificity protein 1 encoded by SP1 gene in humans. Sp1 protein is the first eukaryotic transactivator identified with multiple functions towards the cellular genes. According to a previous study by Veena et al. (1998) pointed out that purified Sp1 has 778 amino acid single polypeptide chains with a molecular mass of 105 kDa.[29] It has a dual role of both activation and inhibition of genes through gene expression regulation, thus affecting the affinity of DNA - binding, rate of Sp1 protein synthesis and nuclear translocation.[30] According to the previous reporting it can be stated that the reasons behind the defaults in gene expression is may be due to modifications in the post - translations in the Sp1 protein.[31] Many studies have reported that Sp1 post - translational changes include phosphorylation, acetylation and glycosylation.

The transcription factor from Sp family mostly binds with GC rich domain for the purpose of regulation of genes, which is familiar with three-conserved Cys2His Zinc fingers DNA binding domain.[20] Through this Sp1 and GC-rich domain binding, the mRNA synthesis is been activated in the genes, which contains the functional recognition sites in the genes. Sp1 plays a major role in regulating the expression of various genes by various mechanism such as either by GC- rich motifs binding with high affinity[21–23] or by modulating the expression of TATA absent and/or present genes through interactions with other transcription factors like c-myc,[32] c-Jun[33] or Stat1[34] or protein - protein interactions.[35] Kadonaga et al., in (1986) provided with an evidence about the characteristic binding site of Sp1, which is a decanucleotide consensus sequence such as **5′-G(T)GGGCGGG(A)G(A)C(T)-3′**.[23] In any form of location of the binding site of Sp1 is functional in most of the cellular genes. Another interesting fact about the Sp1 factor is that they can also bind to the GT-rich sequences.[36,37] In many genes the promoter region is been activated by the formation of connection between a series of Sp1 binding sites.[29]

4. Proteins associated with Sp1

There are evidences, which suggest that there is existence of proteins analogous to Sp1 thus making the Sp1 even more complicated to understand.[37] The other two proteins similar to Sp1 were evolved during an experiment of T-cell antigen receptor promoter, where GT-rich elements were able to bind Sp1 along with other two proteins.[37] The two new proteins similar to Sp1 is been encoded by two different genes such as Sp2 (~80 kDa) and Sp3 (~100 kDa) with a similar kind of protein structure to that of Sp1[29]. All the three proteins Sp1, Sp2 and Sp3 sequence analysis with cDNA clones revealed that the proteins were encoded with many transactivation domains along with a wide-ranging homology of Zinc finer DNA binding domain to that of Sp1 protein.[37] The Sp2 protein has following transactivation domain's such a serine/threonine – rich region, glutamine – rich domain, highly charged domain and three Zinc fingers. Whereas Sp3 ha two homologous glutamine – rich regions, a serine/threonine – rich region, three zinc fingers, highly charged domain and a C-terminal domai. When it comes to the binding affinity of the Sp proteins it is been observed that Sp2 protein has a lower affinity to bind with GT box motif and no affinity to bind with GC – rich domain. On the other hand, Sp3 has a high binding affinity towards both GT – rich and GC-rich motifs.[29] Thus, from the above references it is clear that all the three Sp proteins that is SP1, Sp2 and Sp3 create a novel Sp1 multigene family.

5. Role of Sp1 in promoting cancer

Sp1 the transcription factor plays a major role in various cellular processes which also includes development and progression of tumor cells. Many recent and earlier reports suggest that Sp1 promotes the cancer cells by manipulating the pathways related to transcription. According to an earlier study, abnormality in Sp1 leads to deregulation of cell survival, growth and angiogenesis, resulting into formation and progression of gastric cancer.[38] Thus based on many previous studies it has been made relevant that Sp1 is been over expressed in breast, thyroid, hepatocellular, prostrate, pancreatic, gastric, lung and ovarian cancers. In a pre-clinical study, where a small molecule of Sp1 was been inhibited, which further resulted that there was a successful reduction in tumor burden.[39] Another study, it was found that specific Sp1 binding sites in mouse FGF21 promoter region, Sp1 positively regulates the transcription of FGF21 in HepG2 cells.[40] Another interesting study showed that, there is an increase in epithelial tumors due to Sp1 mRNA and Sp3 DNA binding process when compared to papillomas in skin.[41] In a previous study it was been established that Sp1 is consistently been over functioning in human pancreatic cancer.[42]

The tolfenamic acid (TA) connected with the degradation of Sp1 transcription factor results in to anti-cancer activity in the normal

cells.[43] Many studies have showed that Sp1 is also up regulated and linked with aggressiveness and poor prognosis in cancer cells[44–46]. Vascular Endothelial Growth Factor (VEGF) is one of the prime agents linked with angiogenesis process.[47,48] According to the transcriptional pathways, it is clear, that Sp1 has a major support role in regulating VEFG during tumor angiogenesis process. Another most important gene, which is involved in cancer development, is the BRAC1 gene. Based on a previous report, BRAC1 and Sp1 has a direct communication via amino acids 260–802 which is stimulated by IGF – 1 gene.[49–51] Thus, we can say that from the above reports an abnormal Sp1 has a major role in progression the normal cell in to cancer cells.

6. Role of Sp1 in ovarian cancer

Sp1 had been appointed as the top applicant among the transcriptional factor when it comes to ovarian cancer. In ovarian cancer, the inhibition of cell cycle and growth resulting into cell death due to apoptosis is because of the down-regulation of Sp1 protein induced by TA[52]. In recent study, the association of Sp1 and surviving in epithelial ovarian cancer cells can be targeted with the help of tolfenamic acid a potential sensitiser in epithelial ovarian cancer cell lines.[53] In a previous study, it has been established that in ovarian cancer cell lines the transcriptional regulation of CLDN4 gene, where Sp1 is a crucial for its promoter activity. Further the authors described that epigenetic modifications such as DNA methylation and histone modification plays a major roles in regulation of Sp1 expression of CLDN4 gene.[54] In a prior study it has been observed that, the CpGs located around −230 within the Sp1 binding sites were methylated in EpCAM-negative ovarian cell lines and unmethylated in the EpCAM-positive lines was also reported for several other types of tumors.[55] In an earlier study, it was been found that MDM2 SNP309T > G promoter polymorphism enhances the Sp1 binding and results into cancer risk whereas MDM2 promoter polymorphism SNP285C dismisses SP1 transcription factor binding and reduced the risk of breast and ovarian cancer among the Caucasians.[56] Another study revealed that a critical role of ZFAS1/miR-150–5p/Sp1 axis in promoting proliferation rate, migration activity, and development of chemoresistance in epithelial ovarian cance.[57] Another study investigated that, whether Sp1 phosphorylation is involved in the regulation of CD147 expression and the effect of association of Sp1 and CD147 on invasion ability of ovarian cancer. These study results suggested that, Sp1-CD147 positive feedback plays a vital role in the invasion ability of ovarian cancer cells [30]. In a previous study the results established that the Sp1's activity and expression regulates the expression levels of CD147 directly in lung cancer.[58] Thus, the association between CD147 expression regulated by Sp1 can be used for the exact and early detection of the ovarian cancer proving as boon for the female population.

7. Future prospects

There is still a lot of debate about the precise relationship between Sp1 protein family and ovarian cancer. Are these Sp1 transcription factor variations driving disease, involved in disease progression or implicated in treatment response and adaptation to treatment? Or are they merely passenger observations? Thus, through this review we can say that Sp1 can both damage as well as can survive a normal gene being converted into oncogenes either by activating or by suppressing. Creating novel FISH probes for Sp1 gene will be more useful to detect ovarian cancer not only in genomic but also in chromosomal levels. As Sp1, have both positive and negative effect on a cellular gene, a more deeper molecular level understanding of its activities on different promoters and under different conditions is essential before it may be exploited as a target for cancer treatment. Thus, based on a future research and progressive knowledge about the role of Sp1 in ovarian cancer, we can establish a better understanding about the ovarian cancer initiation as well as progression and finally resulting in to improvement in the early prognosis and treatment of ovarian cancer affected patients.

8. Concluding remarks

The chapters that are discussed in this review, focuses mainly on the role of Sp1 in ovarian cancer, which eventually projects clearly that Sp1 is the prime agent in regulating the transcription and proper gene expression which can ultimately pay ways as “hallmarks of cancer”. It is expected that the next chapter will cover some novel discoveries, which will act as an inhibitor to stop some of the risky functions of Sp1.

Conflicts of interest

The authors declared no conflicts of interest.

Authors contribution

Conception and Design: Iyer Mahalaxmi, K·S. Santhy.
Provision of Study materials: Iyer Mahalaxmi.
Manuscript writing: Iyer Mahalaxmi.
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