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RNAi-Mediated Silencing of Polyamine Biosynthesis Genes for the Regulation of Oral and Breast Cancer Cell Proliferation

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Description

Cancer, also known as neoplasm in medical terms, is one of the world's most dangerous diseases, affecting the population. It was created using a mix of genetic, epigenetic, and pathogenic variables that advantage cancer cells exclusively over non-cancer cells. The causes of this sickness can be found in a wide range of places. It can appear in nearly every organ or tissue in the body, including the lungs, intestines, stomach, and skin. Breast cancer is the most frequent cancer in women worldwide, with over 1.3 million cases diagnosed each year and the highest fatality rate. Breast cancer is a condition that both men and women are susceptible to. Each year, over 13,000 males are diagnosed with breast cancer, which is unexpected yet accurate. Similarly, oral cancer is the 6th most common cancer worldwide, with an estimated annual incidence rate of approximately 275,000 [1]. India, Sri Lanka and Pakistan have reported the highest incidence of the disease, making it the most common cancer among men in these countries and, unlike other diseases, the number is rising.

There are eleven characteristics of cancer cells that help them survive in the face of adversity. They include proliferative signaling, growth inhibition, cell death inhibition, replication immortality, angiogenesis, attack and metastasis activation, energy metabolism regeneration, and mutation and genetics inhibition [2]. There are many ways to provide these symptoms specifically for cancer cells. Targeting pathways or molecules that interfere with one or more of these acquired abilities of cancer can lead to the development of effective cancer treatment [3]. Of particular interest is the fact that polyamines play an indispensable role in key cellular processes, such as growth, differentiation, and regulation of macrophage functions, such as molecules/molecules. Natural PAs are putrescine (put), spermidine (Spd) and sperm (Spm). These phases are catalyzed by amino propyl transferase, namely Spd and Spm syntheses, which attach propyl amino groups to putt and Spd, respectively, and make such propyl amino groups by decarboxylase sadenosylmethionine (dcS), (SAMDC), ODC and SAMDC, key enzymes in the biosynthesis of polyamines, are over-stressed in many human cancers. Elevated polyamines increase the malignancy of cancer cells and prevent the immune response. In fact, many inhibitors, such as α-difluoromythylelornitine, have been in clinical trials to control cancers by selective inhibition of polyamine biosynthesis. However, the toxicity of DFMO in its therapeutic concentrations prevented it from being commercialized. Therefore, there is a need to look for safer and robust alternatives to prevent the path of polyamine biosynthesis to make full use of this important goal. RNAi is one such strategy that has emerged as a potential tool for genetic silencing [4,5].

RNA interference (RNAi) is a process that demonstrates a sequence-specific degradation of RNA by a double-stranded RNA (dsRNA) with the intervention of RISC (RNA inducing silencing complex). RNAi has been well established for functional genomic studies to decipher the role of a particular gene in eukaryotic system. Along with loss-of function studies, RNAi has also found application in the arena of therapeutics. Utilizing this platform, a vast number of diseases including cancer, dominant genetic disorders, viral infections, etc. have been approached with a perspective of finding a safe and specific cure. Since its inception, it is widely used as a screening strategy for shortlisting cancer target. Using this tool, a plethora of factors has been rated to have a role in tumor biogenesis. Along with this, various individual genes have been targeted using RNAi technique in different tumor cells in vitro and in vivo. These genes include oncogenes/anti-apoptotic molecules, telomerase, growth factor receptor genes, signaling molecules and some other genes. However, the utility of RNAi as a means of gene silencing depends on several factors. These include the amount of gene silencing, the duration for which the gene remains silenced, the degree of recovery of gene function, and the response of the silencing process on general cell functions. Therefore, here carried out a compilation of suppression of ODC gene using small interfering nucleic acids (siNA) such as siRNA, LNA modified siRNA and si-Hybrids (RNA- DNA duplex) to control the growth of cancer cell lines and also examined the degree and duration up to which the RNAi effect persists in each case[6].

Despite the presence of enormous supporting preclinical data, daunting obstacles restricts its use in therapeutics. The main and foremost hurdle in the way of successful RNAi based drug is the delivery. It is very important to deliver these RNAi drugs specifically to the target organs/tissues along with a long, consistent and active stay to bring about an effective treatment. Thus, there is a need to find a safer, effective and targeted delivery approach to curb this obstacle. Nanoparticles (NPs) have come a long way in intracellular drug delivery scenario with much success. The important characteristics of a good NP carrier polymer are excellent endocytosis, passive tumor targeting, high encapsulation efficiency, and high stability. There has been a bulk of carrier polymers used, of which poly (D, L lactic-co-glycolic acid) (PLGA) is noteworthy in this regard. Being clinically validated biodegradable polyesters with the degradation products being lactic acid and glycolic acid, which are naturally occurring substances that further break down into water and carbon dioxide are apt for this purpose. For targeted delivery, the proteins overexpressed on cancer cell surface can be exploited. Among these, mucins, cell surface binding glycoproteins are used as tumor biomarkers. Aberrant glycoforms are associated with many epithelial cancer cells (breast,

ovary, colon, pancreas lungs and prostate). Targeting these glycoforms is a powerful approach because they are expressed only on cancer cells and are distinct from those expressed on normal cells [7,8].

In conclusion, the siRNAs designed to target the PA biosynthetic genes, ODC, SAMDC and SPDSYN the results will be shown in cell growth inhibition in oral (KB) and breast (MCF7 and MDA MB 231) cancer cell lines. One gene can silenced be simultaneously by siRNAs along with reduction in siRNA concentration. The mechanism of cell death was apoptosis. At molecular level, PA depletion leads to increased expression of pro-apoptotic and cell cycle inducing genes while the ant apoptotic and cell cycle inhibiters were down-regulated and also demonstrated that ASPN could encapsulate, protect and specifically deliver siRNA to MCF 7 cancer cells. This study will be prove that PA biosynthesis pathway plays an important role in the progression of oral and breast cancer, and silencing ODC, SAMDC and SPDSYN genes using RNAi technique may be a novel therapeutic option for abrogating cancer growth.

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