SOCIETÀ ITALIANA DI FARMACOLOGIA

MODELLO PER INVIO RELAZIONE DI METÀ E FINE PERIODO

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TIPOLOGIA DI BORSA RICEVUTA: Borsa SIF brevi periodi all´estero

TIPOLOGIA DI RELAZIONE (es.: metà periodo o finale): Relazione di metà periodo

TITOLO DELLA RELAZIONE: *HDL and cholesterol homeostasis in prostate cancer cell*

RELAZIONE:

Introduction

Prostate cancer (PCa) is one of the most frequently diagnosed tumors and a major cause of death among men in the developed world. The best therapeutic option is represented by androgen deprivation therapy (ADT) that efficiently lead to death of androgen-dependent tumor cells [1]. However, these cells can frequently evolve to a castration-resistant phenotype (CRPC), characterized by a highly proliferative, angiogenetic and metastatic potential. Since therapeutic options for CRPC are limited and its prognosis is poor, new therapeutic targets are needed.

Tumor cells and normal cells coexist within the so-called "tumor microenvironment" and their interactions can affect proliferation, metabolism and cell growth, angiogenesis, hypoxia and immune response [2]. Since tumor microenvironment has been shown to play a role in the progression of tumor itself [3], it could represent a source of novel targets for the treatment and prevention of cancer. In particular, the presence of oxidative stress, pro-inflammatory molecules and sources of cholesterol can favor tumor cell proliferation.

Cholesterol metabolism is known to take part in cancer progression: cells need cholesterol to proliferate as structural component of cell membranes and as substrate for intra-tumoral synthesis of hormones in the case of hormone-dependent tumors, as PCa [4]. Generally, in tumor cells cholesterol synthesis is upregulated with a loss of by-product inhibition [5]. The uptake of extracellular cholesterol from lipoproteins is also increased through the overexpression of the LDL-receptor (LDL-R) and the scavenger receptor type BI (SR-BI), with a concomitant decreased expression of transporters mediating cholesterol efflux from the cells, as the ATP-binding cassette (ABC) transporter family [6].

Moreover, dysregulations of cholesterol metabolism in cancer cells can contribute to increase the oxysterols. Oxysterols regulate cholesterol homeostasis and can exert potent effects on several biological processes. These metabolites are cholesterol oxidation products, generated by enzymatic and self-oxidation processes. The enzymatic pathways are mediated by enzymes from the cytochrome P450 (CYP) family and cholesterol-25-hydroxylase (CH25H). These endogenous oxysterols include 22(R)-hydroxycholesterol [22(R)-HC]; 25-hydroxycholesterol (25-HC), 27-hydroxycholesterol (27-HC) [7]. Conversely, ring oxysterols are generated by non-enzymatic oxidation mediated by reactive oxygen species, some of these are 6-hydroxycholesterol (6-HC), 7α/β-hydroxycholesterol (7α/β-HC), 7-ketocholesterol (7-KC). Oxysterols are generally present in low concentrations compared to cholesterol [8]. However, these metabolites could be involved in cancerogenesis and tumor progression, in fact 27-hydroxycholesterol for example could contribute to tumor growth, also in prostate cancer [9]. Some evidences suggest that oxysterols play a role in malignancies such as breast, prostate, colon, and bile duct cancer [10].
High density lipoproteins (HDL) are well known for their atheroprotective functions, that are mainly due to their ability to reduce cell cholesterol content and to exert anti-inflammatory and antioxidant activities. Through the same mechanisms, HDL could also exert an antitumoral role. Epidemiological and experimental evidences support the antitumoral role of HDL.

Work in progress

For experimental procedure, LNCaP and PC-3 cells were used as androgen-dependent and castration-resistant prostate cancer cells, respectively. These cells were compared to non tumor prostate cell lines PNT2. HDL are the main actors of the reverse cholesterol transport (RCT), a process by which cholesterol is carried from peripheral tissues to the liver and then it is eliminated through the bile [11]. Cholesterol efflux is a specific process that is regulated by different intracellular transporters, such as ATP binding cassette transporter proteins A1 (ABCA1) and G1 (ABCG1) and scavenger receptor type B1 [12].To evaluate the ability of HDL to modulate cell cholesterol content in ABCA1-dependent way, the expression of this protein was first assessed in the three cell lines by immunofluorescence. In PCa cells, ABCA1 expression is reduced compared to PNT2 cells. Then, to evaluate the possible involvement of ABCA1 in the regulation of cell cholesterol content, PCa cells will be treated with Probucol. Probucol causes not only inactivation of ABCA1, but also inhibits its degradation [13]. Moreover, Probucol impairs the translocation of ABCA1 from intracellular compartments to the plasma membrane [14, 15]. The results that will be obtained could confirm that the HDL activity is ABCA1-dependent in cells treated with Probucol and it could represent a novel target for the treatment of prostate cancer.
Moreover, PCa cells could contain different oxysterols and when PCa cells will be treated with HDL there could be a change in oxysterols content. Since the oxysterols content could contribute to carcinogenesis, it will be interesting investigate the differences in LNCaP and PC-3 cells, treated and untreated.

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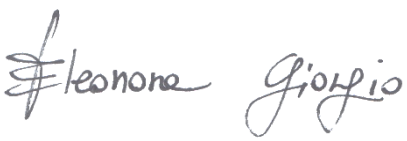
Data 30-3-2020 Firma 

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