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Two Anti-sense Non-coding RNAs Regulate their Sense Gene mRNAs: OXCT1–SCOT for Ketolysis and FGF 14 an Anti-proliferation Factor, in Cancer

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ABSTRACT

In spite of an increased uptake of glucose by tumour cells, the last steps of glycolysis and entry in oxidative glycolysis are blocked in tumours, impairing the glycolytic supply of mitochondrial Acetyl- CoA. Since mitotic cells have to synthetize fatty acid to form new membranes, the degradation of fatty acids automatically stops, which interrupts the fatty acid Acetyl-CoA supply. Hence, tumour cells become dependent on ketone bodies and SCOT, the specific ketolytic enzyme, transcribed from the sense OXCT1 gene, for synthetizing their mitochondrial Acetyl-CoA. A non-coding Anti-sense RNA is also transcribed from the OXCT1 gene (OXCT1-AS). It activates gene promoters supporting regenerative processes, cell proliferation, anti-apoptotic effects and induces a ketolytic metabolism as for "embryonic cell". OXCT1-AS was studied in heart recovery after an infarct, the anti-sense transcript is also named SARRAH. In tumour cells, the OXCT1-AS "sponges" micro RNAs, which interrupts their inhibitory effects on cell cycle pro-mitotic proteins, or neutralizes micro RNAs inhibiting proliferation. Thus, the OXCT1-AS regulation will aggravate tumour progression, while the OXCT1 sense gene product SCOT provides Acetyl-CoA supporting tumour cell growth. In parallel, we discuss the situation for another gene: FGF14, which codes for an anti-proliferation factor: FGF14. The non–coding anti-sense FGF 14-AS transcript for this gene is able to "sponge", a micro RNA inhibiting FGF14 expression, which restores FGF14, thereby inhibiting tumour proliferation. FGF14-AS also sponges another micro RNA inhibiting a transcription factor: E2F1. In this case, the effect of FGF14-AS sponging, depends on the concentration reached for E2F1, only high levels blocking the tumour.

Keywords: OXCT1- SCOT, lncRNA, OXCT1- AS, FGF14, FGF14 -AS, Micro RNAs Mirs

INTRODUCTION

We have in previous works implicated the enzyme Succinyl-CoA: 3 oxoacid CoA transferase (SCOT) in the metabolism of tumour cells that greatly depend on this enzyme for producing their mitochondrial Acetyl-CoA. This enzyme is the limiting step in ketolysis and its inhibition should affect the development of tumour cells, while normal cells are able to use the glycolytic

and fatty acid supplies of mitochondrial Acetyl-CoA. This difference between tumour cells and normal cells results from the observation that Pyruvate kinase and Pyruvate dehydrogenase at the end of glycolysis and entry in oxidative metabolism, remain inhibited by a persistent phosphorylation, as if a "dephosphorylation switch" that normally operates when moving from catabolism to anabolism, was inactivated in tumour cells [1]. We even considered the possibility that this anomaly could be linked to the endocrine pancreas able to switch off catabolic glucagon when anabolic insulin release is active, a mechanism controlled by GABA, co-released with insulin [2]. The double bottle neck at the end of glycolysis and entry in the citric acid cycle, explains the release of lactic acid by tumour cells. The ketolytic dependency of tumour cells is exacerbated by the fact that mitotic tumour cells need to synthetize fatty acids and new lipid membranes, in this condition, citrate exits the mitochondria and is processed in the cytosol by ATP citrate lyase and Acetyl-CoA carboxylase, along the fatty acid synthesis pathway. The malonyl- CoA produced by the carboxylase, turns off the fatty acid carnityl driven transporter, and entry of fatty acids in mitochondria, suppressing their degradation by beta- oxidation, when fatty acid synthesis is active. This explains that ketone bodies and SCOT become essential for supplying mitochondrial Acetyl-CoA to tumours. Two salvage pathways produce Acetyl-CoA if SCOT does not receive its substrates, first branched chain ketogenic amino acids (BCAA) and second, exogenous acetate feeding directly Acetyl-CoA synthetase, and the cytosolic fatty acid synthesis pathway [3]. The role of Oxct1 and SCOT in cancer was reconsidered when it was found that a long non-coding RNA (lncRNA) OXCT1 anti-sense (OXCT1-AS1) was transcribed from the anti-sense strand of the SCOT gene. This anti-sense RNA also named SARRAH for (SCOT–antisense RNA regulated during aging) was studied in the infarcted heart recovery, by Trembinski et al., 2020 [4]. The SARRAH locus overlaps with the SCOT gene, its start site on the anti-sense strand, is situated within the first OXCT1 intron. SARRAH was shown to regulate the heart repair process and recovery from an acute myocardial infarction. Moreover, the regulatory role of the OXCT1- AS in cancer appeared to be essential. The discovery of many more non-coding LncRNAs (longer than 200bp) with regulatory effects on coding gene transcripts opened an immense new field of research, in which a great part of DNA would be transcribed into lncRNAs able to regulate the coding genome. The discovery of micro RNAs (Mirs), their maturation and traffic from the nucleus to the cytoplasm led to a mechanism of action, in which the Mirs bind the 3'UTR untranslated end of mRNAs and suppress translation. The finding that lncRNAs could act as competing RNAs (CeRNA) able to "sponge" specific Mirs and cancel their inhibitory role on protein translating mRNAs, oriented an experimental approach in a variety of cancers [5]. The OXCT1 sense and anti-sense non coding lncRNA and Mirs that are sponged, were here reviewed, in parallel to another gene, FGF14 (a growth factor known to be mutated in a late onset form of cerebellar ataxia with GAA repeats). This gene FGF14, displays anti-proliferative properties regulated, by the anti-sense lncRNA: FGF 14- AS, able to sponge several Mirs, in various tumours. Our attempt was to draw a helpful comparison between the two genes and their anti-sense transcript and Mirs that are sponged, in a variety of cancers.

LESSONS FROM SARRAH (OXCT1-AS) STUDIES ON INFARCTED HEART REPAIR

SARRAH (OXCT1- AS) silencing, or it's down regulation with age, or in infarcted hearts, elicits apoptosis. On the contrary, SARRAH (OXCT1 -AS) over expression in mice, is anti-apoptotic improving the recovery of the infarcted heart. This, is associated to the induction of genes such as NRF2 (an anti-oxidant and anti-apoptotic transcription factor). SARRAH inhibits caspase - mediated apoptosis, while stimulating VEGF an endothelial growth factor and Crip 2

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transcription. It was suggested that SARRAH facilitates gene expression by forming triple helices, at gene promoters to be activated for supporting heart recovery [5]. The SARRAH binding site, also recruits transcription factors such as P300 (acetyl transferase). We know that the acetylation of histones elicits the expression of genes active in the course of development. The recovery of cardiomyocyte is sustained by a ketolytic metabolism dependent on SCOT-OXCT1. The ketone body, Betahydroxybutyrate (BHB) is incorporated and metabolised. In parallel, BHB inhibits histone deacetylase (HDAC), strengthening the effect of P300 acetyl transferase recruited by SARRAH, bound to promotors of activated recovery genes. The survival of cardiomyocytes will then stimulate in a paracrine manner the proliferation of endothelial cells. The recruitment of Crip2 on the promoter sites activated by SARRAH requires a comment. SARRAH facilitates the survival of myocytes that trigger the proliferation of endothelial cells. Presumably, a population of mitotic stem cells supports the process, it is then necessary to keep the mitotic situation under control, in order to avoid a possible transformation of mitotic cells into tumour cells. Crip 2 is the cysteine rich intestinal protein 2, it was shown that it represses the binding of NFkB to promoters of pro-angiogenic cytokines (IL6) and VEGF. Repression of NFkB by Crip2 will set a limit to the proliferation process triggered by SARRAH and to the mitosis of endothelial stem cells elicited by the recovery of cardiomyocytes. Crip 2 suppresses tumorigenesis, by helping the differentiation of new daughter cells. Keeping in mind that NFkB transcription is a hallmark in cancer, its repression by Crip2 avoids that a mitotic repair process becomes a tumour.

EFFECTS OF THE LncRNA: OXCT-AS (SARRAH), IN DIFFERENT CANCERS

The OXCT1-AS non-coding lncRNA studied in osteosarcoma was shown to inhibit the maturation of a micro RNA: Mir 886, by sponging premature Mir886. Since Mir 886 suppresses cell proliferation in osteosarcoma, OXCT1-AS will promote osteosarcoma cell proliferation by sponging Mir 886, which is unfavourable. In addition, it was found that the direct effect of SARRAH (OXCT1- AS) was anti-apoptotic by blocking caspase a protease that supports apoptosis, which aggravates osteosarcoma [6}. The situation is different In cervical cancer, where it was found that that Mir 886 down regulates the expression of the apoptotic Bax protein, thus if OXCT- AS sponges Mir 886 it should favour Bax and apoptosis, counteracting the direct anti- apoptotic effect of OXCT1- AS, it is presumably a defence mechanism against anti-apoptotic OXCT1-AS (SARRAH) and proliferation [7]. Other examples indicate that OXCT1-AS supports the aggressiveness of tumours, this is the case of bladder cancer, in which the lncRNA OXCT1- AS sponges Mir 455- 5p, which cancels the inhibition of JAK signalling by this Mir, thereby enhancing the JAK signal supporting proliferation [8]. A similar situation concerns glioblastoma. Here, OXCT1-AS sponges Mir 195, cancelling the inhibition by Mir 195 of CDC25A, a phosphatase controlling the mitotic cell cycle and mitosis, which enhances proliferation and glioma progression [9]. In addition to these mostly unfavourable effects, of OXCT1- AS on tumour progression, the sense coding OXCT1 gene supports via SCOT the nutrition of tumour cells, shown to be vulnerable to SCOT and ketolysis inhibition [10, 11]. One would then gain to knock-down the anti-sense OXCT1-AS, (SARRAH), which sponges the indicated Mirs that boost the tumour progression Figure 1.

FGF14-AS NON-CODING LncRNA AND FGF14 GENE TRANSCRIPTION IN CANCER

FGF 14 is a growth factor protein, the gene was previously studied in a neuropathological context. The identified disease, is a late onset form of a cerebellar ataxia, in which a GAA repeat expansion is found in the first intron of the FGF14 gene, impairing the expression of the protein

[12]. The observation that FGF14 had anti- proliferation properties, regulated by the anti-sense (FGF14- AS) non-coding lncRNA, via the sponging of several Mirs in cancer, led us to gather part of this information summarized figure 1, in parallel to the OXCT1 sense and anti-sense description cited above.

A good example to put forward is colorectal cancer, in which FGF 14 is down regulated, this was a consequence of its promotor methylation decreasing the expression of the gene, which stimulated proliferation. FGF14 could then be restored after a demethylation treatment with (5-aza-2 deoxycytidine) an inhibitor of DNA methyltransferase. Restored FGF 14 acted as a tumour suppressor inducing apoptosis, via the inhibition of PI3K/AKT /mTOR signalling [13]. The role of the anti-sense FGF14- AS non coding RNA was also studied in breast cancer [14] and shown to sponge a microRNA: Mir 370-3p, cancelling the inhibitory effect of this Mir on the expression of FGF14 sense transcription. The resulting increase of FGF14 inhibited proliferation and tumour progression. These two examples show that FGF 14 is a tumour suppressor, and that the anti-sense non-coding FGF14-AS2 helps the expression of the sense FGF14 protein, (by removing the inhibitory Mir 370 from the 3' UTR mRNA). In contrast to OXCT1- AS, studied above, the FGF 14- AS, has an anti-tumour effect. However, the role of FGF14- AS is more complicated in glioma, since it accelerates tumorigenesis [15]. This deserves a further analysis, in relation to another micro RNA (Mir 320a) also sponged by FGF14- AS, which inhibits the expression of a transcription factor E2F1. It was earlier shown that this transcription factor E2F1, promotes at low doses cell proliferation, at moderate doses of E2F1, the mitotic cell cycle stops and at higher doses E2F1 triggers apoptosis [16]. Well, in glioblastoma, FGF14-AS sponges Mir-320a and cancels the inhibition of E2F1 by Mir320, this increases E2F1, which binds to the promoter of FGF14-AS and increases its expression. In glioblastoma the feedback loop studied promotes proliferation. Presumably one fails to reach a range of moderate or higher concentrations E2F1that would block proliferation or trigger apoptosis. Probably, sponging Mir320 is maximal but E2F1 still remained in a range of low concentrations that stimulate proliferation. There are indications that the proteasome hydrolysis of E2F1 keeps it in the lower concentration range, increasing proliferation. It was indeed found that a proteasome inhibitor (NLM2238) tested on a lung cancer cell line resulted in E2F1 dependent mitotic arrest, suggesting that in glioblastoma, a proteasome hydrolysis of E2F1 maintains it low, which elicits proliferation. An inhibitor of the proteasome could then be added in this particular case, if this fails, one might then try to neutralise FGF14- AS. However, note that the increase of FGF14-AS was able to sponge the other Mir such as Mir 370 3p, increasing FGF14 and its anti-proliferation action, Figure 1.

CONCLUSION

We already suggested to inhibit tumour ketolysis using SCOT inhibitors (acetylhydroxamate), and to interrupt tumour ketolysis at all possible levels: the entry of BHB into the cell (syrosingopin, epigallocatechin), the SCOT inhibition (acetylhydroxamate, lithothamnium, Pimozide and others) at ACAT1 production of Acetyl-CoA (Vitamin C a butenolide) arecoline and melatonine would inhibit ACAT1. Then to inhibit the exit of citrate from mitochondria, and to block ATP citrate lyase and ACC carboxylase, for decreasing the fatty acid synthesis necessary for synthesizing the lipid membranes for mitotic cells, (lipoic acid hydroxyl citrate). Intracellular BHB helps tumour growth and supports the embryonic phenotype of mitotic cells. On the other hand, extracellular BHB activates the HCA2 receptors triggering anti-inflammatory, beneficial effects that can be preserved by niacin, instead of BHB see [1-17}. In

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general, all conditions that decrease the supply of succinyl-CoA to SCOT and acetoacetate its other substrate, will have an anti- tumour effects. This is the case for an inhibition of glutamine and glutamate sources of succinyl–CoA. Presumably, the anti-helminthic effect of fenbendazol, which blocks fumarate reductase, decreases succinate, which then pulls the conversion of succinyl- CoA into succinate and increases succinic-dehydrogenase (SDH) activity; which deprives SCOT of succinyl-CoA. A situation also found when the respiratory Complex II is activated [17]. Remember that the opposite situation (SDH) mutation is carcinogen (Carney triad tumours) the mutation increases the succinyl- CoA supply to SCOT [18]. As other carcinogenic mutations (Ferro chelatase) in the Protoporphyrin pathway, which leaves more succinyl–CoA for SCOT, while the aminolevilinic reaction of succinyl- CoA and glycine decreases.

In sum, a pharmacological inhibition of SCOT and ketolysis, should affect tumour growth. Particularly if the salvage pathways coming from Branched chain amino acids are blocked at the transaminase level [3] (cycloserine, aspulvinone and others) and if the exogenous acetate supply is cut by inhibiting Acetyl-CoA synthetase with allicine. There are also the effects of OXCT1 – AS (SARRAH) to block, while boosting the Mirs that are inhibited by OXCT1-AS (such as Mir 886). Presumably, a down regulation of OXCT1-AS could be tried with an adequate RNA probe. For the OXCT1 SCOT gene product a pharmacological approach seems more reasonable, in combination with neutralisation of its non- coding anti- sense RNA transcript; while providing the Mirs discussed for each case. For FGF14, the expression of the gene and protein has anti- proliferation effects that should be helped, as well as its FGF14- AS, in tumours in which it sponges Mir 370. In other tumours where it sponges Mir 320, acting on E2F1 transcription, one might try a proteasome inhibitor for reaching elevated concentrations of E2F1 able to block the mitotic cycle, since low E2F1 concentration increase mitosis, and aggravate the tumour.

Having reached these conclusions, we measure the amount of experiments that remain to be done, before improving cancer treatments, 69 years after Warburg's publication [19].

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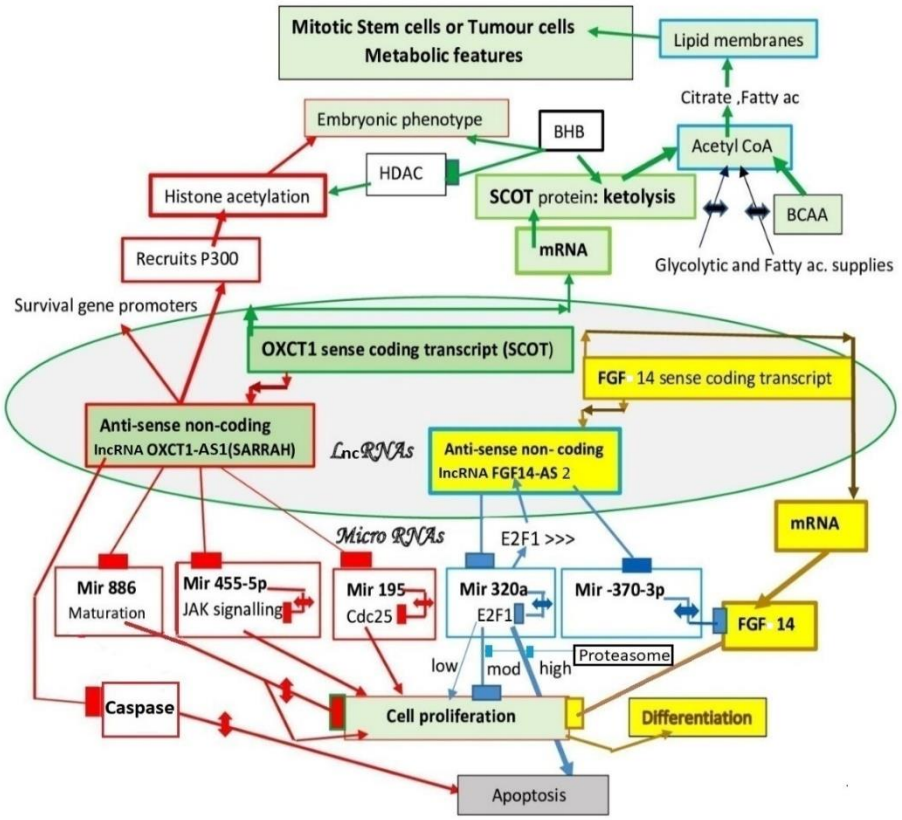

Figure 1: OXCT1 and FGF14 Sense mRNAs and their anti-sense non- coding lncRNA regulators.

The two selected genes OXCT1 and FGF14, code respectively for SCOT the specific ketolytic enzyme and FGF14. They were chosen for the implication of their sense mRNA coding transcripts (SCOT, FGF14) in cell proliferation, and for the regulatory role of their anti-sense non coding long RNAs (lncRNA) in cancer, respectively: lncRNA-AS 1 (SARRAH) for OXCT1 and lncRNA FGF14- AS 2 for FGF14. In tumour cells the glycolytic Acetyl-CoA supply is interrupted at Pyruvate kinase and Pyruvate dehydrogenase steps, giving rise to lactate release. The Fatty acid Acetyl-CoA formed by beta oxidation also stops, since fatty acid synthesis operates in mitotic cells, producing malonyl-CoA, which blocks the mitochondrial transporter of fatty acids and their degradation in mitochondria. Thus, tumour cells depend on ketolysis by SCOT, and of Betahydoxbutyrate (BHB) supply for making Acetyl-CoA. Ketogenic branched chain amino acids (BCAA), and exogenous acetate ensure salvage supplies of Acetyl-CoA and the survival of tumour cells. In parallel, BHB blocks histone deacetylase, supporting the acetylation of histones, and the expression of genes operating in development. This regulation is strengthened by lncRNA OXCT1- AS 1 named SARRAH, it was studied in infarcted heart repair. The anti-sense transcript stimulates survival gene promoters, recruits transcription factors, and Histone acetylase P 300, operating in parallel to BHB, for supporting repair, mitosis, and inhibit apoptotic proteins such as caspase in cells harbouring a ketolytic metabolism. Above all, lncRNAs are competing RNAs (ceRNA) able to sponge and cancel the effects of a set of microRNAs (Mirs) that usually inhibit mRNAs after binding the 3'UTR untranslated end. A few examples are shown in figure. OXCT1- AS1 "sponges," premature Mir 886 a proliferation inhibitor as observed in osteosarcoma, this will then stimulate proliferation, in a situation where the sense gene (OXCT1- SCOT) supports tumour cell nutrition, this is certainly not

favourable. OXCT1-AS1 also sponges Mir 455-5p, a JAK signalling inhibitor, and Mir 195, a Cdc25 inhibitor, in both cases, proliferation is stimulated, an effect to avoid in cancer. It might then be useful to neutralise OXCT1 AS1, while boosting the Mirs that inhibit proliferation such as Mir 886 and those that inhibit proteins supporting mitosis (Mir 455-5p and Mir 195). In parallel, a pharmacological inhibition of SCOT, and the salvage BCAA and acetate supplies of Acetyl-CoA could be tried, by compounds previously indicated. The FGF14 gene and coded growth factor, has an interesting anti-proliferative effect that should be boosted by suppressing its inhibition by Mir 370 that can be sponged by FGFI4- AS, in this case the anti-sense can fight the tumour. Another Mir, (Mir320a) is more difficult to handle, apparently the E2F1 transcription factor stimulates LncRNA FGF14-AS2 transcription, but Mir 320a inhibits E2F1. Here, LncRNA FGF14-AS2 sponges Mir 320a, and cancels the inhibition of Mir 320a over E2F1, which should increase FGF 14-AS2 and E2F1. Other works indicate that low doses of E2F1 stimulate proliferation, while moderate (mod) doses, stop the mitotic cycle and high doses give apoptosis. One might then try to increase FGF14-AS, and to sponge Mir 320a, for increasing E2F1, until reaching the anti-proliferative range of E2F1, this does not seem to occur in glioblastoma, presumably an elevated proteasome activity decreases E2FI, cancelling its increase after sponging Mir 320a. On the other hand, elevated levels of FGF14- AS2 will also sponge the other Mir 370 3P, which preserves the anti-proliferative action of FGF14. In sum, one would gain to attenuate OXCT1 AS1, and SCOT ketolysis, while stimulating the FGF14- AS2 and FGF 14 sense gene, a proteasome inhibition might be necessary for increasing E2F1, and get a mitotic arrest in glioblastoma.

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