Interactions Networks for Primary Heart Sarcomas

Styliani A. Geronikolou 1,2,3,* 1, Athanasia Pavlopoulou 4,5,  George P. Chrousos 1,2,3 and Dennis V. Cokkinos 1

1 Clinical, Translational and Experimental Surgery Research Centre, Biomedical Research Foundation Academy of Athens, 4, Soranou Ephesiou Str., 11527 Athens, Greece; chrousge@med.uoa.gr (G.P.C.);
dcokkinos@bioacademy.gr (D.V.C.)
2 University Research Institute of Maternal and Child Health & Precision Medicine, National and Kapodistrian University of Athens, Aghia Sophia Children’s Hospital, 11527 Athens, Greece
3 UNESCO Chair on Adolescent Health Care, National and Kapodistrian University of Athens, Aghia Sophia Children’s Hospital, 11527 Athens, Greece
4 Izmir Biomedicine and Genome Center (IBG), Balcova, Izmir 35340, Turkey; athanasia.pavlopoulou@ibg.edu.tr
5 Izmir International Biomedicine and Genome Institute, Balcova, Izmir 35340, Turkey
* Correspondence: sgeronik@bioacademy.gr

Simple Summary: Cardiac cancer represents a rare, largely understudied disease. The aim of this study was to elucidate the underlying pathophysiology of cardiac sarcomas by employing specific network-based methods. Focused interactomes comprised of heart- and tumor-associated gene/proteins were constructed. These networks allowed us to unfold the main pathways leading from heart sarcomas to cardiac diseases. The findings of this study could be utilized in the clinical setting for diagnostic and therapy decision-making.

Abstract: Personalized medicine incorporates genetic information into medical practice so as to optimize the management of chronic diseases. In rare diseases, such as heart cancer (incidence 0.0017–0.33%), this may be elusive. Ninety-five percent of the cases are due to secondary involvement with the neoplasm originating in the lungs, breasts, kidney, blood, or skin. The clinical manifestations of heart tumors (benign or malignant) include heart failure, hypertension, and cardiac arrhythmias of varying severity, frequently resulting in blood vessel emboli, including strokes. This study aims to explain the pathophysiology and contribute to a P4 medicine model for use by cardiologists, pathologists, and oncologists. We created six gene/protein heart-related and tumor-related targets high-confidence interactomes, which unfold the main pathways that may lead to cardiac diseases (heart failure, hypertension, coronary artery disease, arrhythmias), i.e., the sympathetic nervous system, the renin-angiotensin-aldosterone axis and the endothelin pathway, and excludes others, such as the K oxidase or cytochrome P450 pathways. We concluded that heart cancer patients could be affected by beta-adrenergic blockers, ACE inhibitors, QT-prolonging antiarrhythmic drugs, antibiotics, and antipsychotics. Interactomes may elucidate unknown pathways, adding to patient/survivor wellness during/after chemo- and/or radio-therapy.

Keywords: heart sarcoma; interactome; personalized medicine; heart failure treatment; primary heart cancer; case report

1. Introduction

Since 1999, when Wulff disputed Newton’s mechanistic point of view on ‘disease’, adopting the Aristotelian one (that an organism is a complex of qualities rather than quantities), complexity became an ongoing research subject in medicine and epidemiology [1]. Thus, the term ‘disease’ seems to be redefined by summarizing data from various directions (lifestyle, inherited predispositions, medical history, sensory data, imaging, all -omics) [2]. Noteworthy strides in the field have come from oncology, as well as from cardiology, where complexity and heterogeneity are recognized as dominant features. Most importantly,
both entities share the highest morbidity and mortality rates in Western societies, and the ongoing research in these fields strives to elucidate the implicated mechanisms and to search for potential diagnostic and/or therapeutic targets. Generally, cancer patients seldom share the same therapy, even if they are of the same gender, age, education, and lifestyle [3]. The complexity of such an attempt, as well as the treatment drug selection, are subjects of epidemiologic modeling. As the era of precision medicine evolves, epidemiology may profit from systems science, which concerns and encompasses translational research, traditional medicine, and -omics data, necessary to perform precise epidemiologic modeling [2–4].

Heart cancer is rarely encountered, as its incidence falls between 0.0017–0.33% [5], while heart sarcomas account roughly for one fourth of them [6], according to the Atlas of Tumor Pathology, published by the Armed Forces Institute of Pathology in the United States of America [7,8]. Importantly, cardiac sarcomas (angiosarcoma, rhabdomyosarcoma, leiomyosarcoma, undifferentiated pleomorphic sarcoma, myxofibrosarcoma, synovial sarcoma) are mostly primary cancers. Sarcomas’ prognosis is usually poor* [9], with metastases occurring both early and frequently. Moreover, metastases -relapses or distant-tumors in 45–75% of the cases may be manifested within 15 years, whilst overall survival is 12–17 months after initial diagnosis [10].

The clinical manifestations of heart tumors (benign or malignant) may include no or minor symptoms, such as the so-called medically unexplained symptoms (MUS)—including nausea, weight loss, fatigue, fever, dyspnea at rest, etc.—or serious problems, such as heart failure, hypertension, cardiac arrhythmia, peripheral emboli, or strokes. Cardiac sarcomas are mainly asymptomatic until reaching an advanced stage, when, chest pain, dyspnea, congestive heart failure secondary to blood flow obstruction, and systemic responses may be manifested. The relevant clinical manifestations in cardiac cancer are chest palpitations, chest pain (most common), cardiac tamponade (as the pericardium is often involved), and/or syncope [11].

The heart cancer diagnosis is usually made late, as it often starts after a stroke caused by a detached tumor tissue or thrombus. Echocardiography, CT scan and/or MRI are the main diagnostic tools in the clinician’s quiver. Unfortunately, no satisfactory published series of cases are available for the establishment of prognosis and treatment statistics.

While, chemotherapy is generally preferred for heart metastatic tumors, surgery is suggested in heart sarcomas, even though their underlying biology is still under-investigated. Heart failure induced by heart sarcomas is a major complication that warrants special attention, as, frequently, its underlying mechanisms are relatively unknown. Sparse published information challenges diagnosticians and therapists and begs for education and training. The rarity of the disease suggests personalized management and thoughtful treatment. The genetic profiles are unelucidated. More importantly, the rara avis itself and the location raise ethical issues urging for non-interventional research options. Thus, to explain the pathogenesis of cardiac sarcomas and their manifestations would be of value to cardiologists, pathologists, and oncologists, who normally deal with patients suffering from heart neoplasms.

2. Results

We constructed six different interaction networks—one for each type of primary heart sarcomas: (i) angiosarcoma, (ii) undifferentiated pleomorphic sarcoma, (iii) Rhabdomyosarcoma (iv) Leiomyosarcoma, (v) Myxofibrosarcoma, and (vi) Synovial sarcoma. The constructed interactomes (henceforth called CS1-6), which include nodes of gene/gene products of known and/or predicted interactions, are described in Table 1 and are illustrated in Figures 1–6. A confidence level > 0.7 was adopted. The names of all nodes are shown in the second column of Table 1. The NCBI RefSeq accession numbers [12] are added in a third column, while, in a fourth column, the specific interactome in which each gene is involved, is listed.
Table 1. Molecules included in the primary heart sarcomas interactions networks CS 1–6.

| Gene Symbol | Description | Accession Number \(^1\) | Interactome \(^2\) |
|-------------|-------------|--------------------------|------------------|
| ACE         | angiotensin I converting enzyme | NM_000789       | CS 1–6           |
| ACTA1       | actin alpha 1, skeletal muscle  | NM_001100       | CS 1–6           |
| ADD1        | adducin 1   | NM_0014189     | CS 5             |
| ADD3        | adducin 3   | NM_0019903     | CS 5             |
| ADSS        | adenylosuccinate synthase 2    | NM_001126       | CS 5             |
| ANXA1       | annexin A1  | NM_000700       | CS 5             |
| ASS1        | argininosuccinate synthase 1   | NM_000280       | CS 5             |
| CASP3       | caspase 3   | NM_004346       | CS 5             |
| CBX7        | chromobox 7 | NM_175709.5     | CS 1–6           |
| CCND1       | cyclin D1   | NM_053056.3     | CS 1–6           |
| CD34        | CD34 molecule | NM_001773     | CS 1–6           |
| CDC123      | cell division cycle 123       | NM_006023       | CS 1–6           |
| CDK4        | cyclin dependent kinase 4      | NM_000075       | CS 2             |
| CDKN2A      | Cyclin Dependent Kinase Inhibitor 2A | NM_001025109 | CS 1, 2          |
| CDKN2B      | Cyclin Dependent Kinase Inhibitor 2B | NM_006023 | CS 1             |
| CXCL1       | C-X-C motif chemokine ligand 1 | NM_001511       | CS 1–6           |
| CXCL8       | C-X-C motif chemokine ligand 8 | NM_000584       | CS 1–6           |
| CYB5A       | cytochrome b5 type A           | NM_001914       | CS 5             |
| DECR1       | 2,4-dienoyl-CoA reductase 1    | NM_001330575    | CS 5             |
| DNAH11      | dynein axonemal heavy chain 11 | NM_001277115    | CS 1–6           |
| DYNLL1      | dynein light chain LC8-type 1  | NM_001037494    | CS 1–6           |
| EDN1        | endothelin 1                        | NM_001955       | CS 1–6           |
| EEF2S3      | eukaryotic translation initiation factor 2 subunit gamma | NM_001415       | CS 1–6           |
| EGFR        | epidermal growth factor receptor  | NM_005228       | CS 2             |
| EP300       | E1A binding protein p300          | NM_001429       | CS 1             |
| ETV6        | ETS variant 6                      | NM_001987       | CS 1–6           |
| F8          | coagulation factor VIII            | NM_000132       | CS 1–6           |
| FBR5        | Fibroin                             | NM_001105079    | CS 1–6           |
| FGF2        | fibroblast growth factor 2         | NM_00361665     | CS 1–6           |
| FGF1        | fibroblast growth factor receptor 1 | NM_023110     | CS 1–6           |
| FIP1L1      | factor interacting with PAPOLA and CPSF1 | NM_030917     | CS 1–6           |
| GATA4       | GATA binding protein 4             | NM_00308093     | CS 1–6           |
| HAN1D1      | heart and neural crest derivatives expressed 1 | NM_004821     | CS 1–6           |
| HDAC2       | histone deacetylase 2              | NM_001527       | CS 1–6           |
| HLA-DQA1     | major histocompatibility complex, class II, DQ alpha 1 | NM_002122     | CS 1–6           |
| HLA-DRB1     | major histocompatibility complex, class II, DR beta 1 | NM_002124.4    | CS 1–6           |
| HMG2A       | high mobility group AT-hook 2      | NM_004543       | CS 2             |
| HRAS        | HRas proto-oncogene, GTPase      | NM_176795       | CS 4             |
| HSPB1       | heat shock protein family B (small) member 1 | NM_001540     | CS 5             |
| IFI6        | interferon alpha inducible protein 6 | NM_0022875    | CS 1             |
| IL6         | interleukin 6                      | NM_000600       | CS 1–6           |
| ISG15       | ISG15 ubiquitin like modifier     | NM_005101       | CS 5             |
| KDR         | kinase insert domain receptor     | NM_002253       | CS 1             |
| KIT         | KIT proto-oncogene, receptor tyrosine kinase | NM_000222     | CS 1             |
| KMT2D       | lysine methyltransferase 2        | NM_003482       | CS 1             |
| KRAS        | KRAS proto-oncogene, GTPase       | NM_033360       | CS 1, 2, 3       |
| LGALS3      | galectin 3                         | NM_002306       | CS 5             |
| MDM2        | MDM2 proto-oncogene                | NM_002392.6     | CS 2             |
| MEF2A       | myocyte enhancer factor 2A         | NM_00130926     | CS 1–6           |
| MMP1        | matrix metallopeptidase 1          | NM_002421       | CS 1–6           |
| MMP2        | matrix metallopeptidase 2          | NM_00127891     | CS 1–6           |
| MYC         | MYC proto-oncogene, bHLH transcription factor | NM_001354870 | CS 1             |
| MYH8        | myosin heavy chain 8               | NM_002472       | CS 1–6           |
| NBN         | nibrin                             | NM_00124688     | CS 1             |
| NGF         | nerve growth factor receptor       | NM_002507       | CS 5             |
| NKX2-5      | NK2 homeobox 5                     | NM_001166175    | CS 1–6           |
| NOTCH1      | notch 1                            | NM_017617       | CS 1–6           |
| Gene Symbol | Description | Accession Number | Interactome |
|-------------|-------------|-----------------|-------------|
| NRAS        | NRAS Proto-Oncogene, GTPase | NM_002524.5     | CS 1        |
| PCGF5       | polycomb group ring finger 5 | NM_032373       | CS 1–6      |
| PCNA        | proliferating cell nuclear antigen | NM_002592       | CS 1–6      |
| PDGFRA      | platelet derived growth factor receptor alpha | NM_006206       | CS 1–6      |
| PDGFRB      | platelet derived growth factor receptor beta | NM_002609       | CS 1–6      |
| PECAM1      | platelet and endothelial cell adhesion molecule 1 | NM_000442       | CS 1        |
| PIK3CA      | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha | NM_006218       | CS 2        |
| PLCG1       | phospholipase C gamma 1 | NM_182811       | CS 1        |
| POT1        | protection of telomeres 1 | NM_00104259     | CS 1        |
| POTEF       | POTE ankyrin domain family member F | NM_001099771    | CS 1        |
| PRKAR1A     | protein kinase cAMP-dependent type I regulatory subunit alpha | NM_001276289    | CS 1–6      |
| RHOB        | ras homolog family member B | NM_004040       | CS 5        |
| RFC2        | replication factor C subunit 2 | NM_181471       | CS 1–6      |
| RPL13A      | ribosomal protein L13a | NM_001270941    | CS 1–6      |
| RPLP0       | ribosomal protein lateral stalk subunit P0 | NM_053275       | CS 1–6      |
| SDC         | stearoyl-CoA desaturase | NM_005063       | CS 5        |
| SDC2        | syndecan 2 | NM_002998       | CS 1–6      |
| SMARCD3     | SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily d, member 3 | NM_001003801    | CS 1–6      |
| SMS         | spermine synthase | NM_004595       | CS 5        |
| SOX9        | SRY-box 9 | NM_000346       | CS 1–6      |
| SS18        | SS18 subunit of BAF chromatin remodeling complex | NM_001007559    | CS 6        |
| SSX2        | SSX family member 2 | NM_003147       | CS 6        |
| TIMP1       | TIMP metallopeptidase inhibitor 1 | NM_003254       | CS 1–6      |
| TNFRSF13B   | TNF receptor superfamily member 13B | NM_012452       | CS 1–6      |
| TP53        | tumor protein p53 | NM_000546       | CS 1        |
| VWF         | von Willebrand factor | NM_000552       | CS 1–6      |
| WWTR1       | WW domain containing transcription regulator 1 | NM_015472       | CS 5        |

1 NCBI’s RefSeq (https://www.ncbi.nlm.nih.gov/refseq/, accessed on 31 March 2021); 2 CS1: Angiosarcoma; CS2: Undifferentiated pleomorphic sarcoma; CS3: Rhabdomyosarcoma; CS4: Leiomyosarcoma; CS5: Myxofibrosarcoma; and CS6: Synovial sarcoma

2.1. Novelties

Eighteen novel intermediate nodes (histone deacetylase 2, cell division cycle 123, fibroblast growth factor 2, polycomb group ring finger 5, syndecan 2, dynein light chain LC8-type 1, POTE ankyrin domain family member F, proliferating cell nuclear antigen, platelet and endothelial cell adhesion molecule 1, nibrin, nerve growth factor receptor, adducin 1, adenylosuccinate synthase 2, cyclin dependent kinase 4, caspase 3, ISG15 ubiquitin like modifier, ISG15 ubiquitin like modifier, high mobility group AT-hook 2, E1A binding protein p300, 2,4-dienoyl-CoA reductase 1, E1A binding protein p300), are distributed in the six networks.

2.2. Major Hubs

In total, 18 highly connected nodes (cyclin D1, endothelin 1, matrix metallopeptidase 2, fibroblast growth factor 2, interleukin 8 (CXCL8), interleukin 6, G protein subunit beta 3,) were revealed.
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Figure 1. The heart angiosarcoma interactome.

Figure 2. The heart undifferentiated sarcoma interactome.

Figure 3. The heart rhabdomyosarcoma interactome.
Figure 2. The heart undifferentiated sarcoma interactome.

Figure 3. The heart rhabdomyosarcoma interactome.

Figure 4. The heart leiomyosarcoma interactome.

Figure 5. The heart myxofibrosarcoma interactome.
3. Discussion

Heart failure, coronary artery disease, and hypertension epidemics are major public health problems of high prevalence, whose pathophysiology has been insufficiently examined, especially when implicated in other diseases [13]. Heart cancer, on the other hand, is a rare neoplastic entity, that diagnosticians cannot decipher or even aptly treat, due to reasonable lack of familiarity [8]. The relevant research demands considerable costs and its effectiveness is time- and population size-dependent. Hence, in silico analysis as gene/gene products interactions networking (interactome construction) is a sine qua non cost/time-effective way to fill in gaps in knowledge in the little known and highly complex
field of heart cancer and its cardiological consequences [4]. The latter include heart failure, hypertension, and cardiac arrhythmias, leading to peripheral emboli or even strokes.

In a previous work, we had constructed the heart cancer interactions network (HFCC1) [14,15]. This work is an expansion of that preliminary work (HFCC1), as it is more focused (on sarcomas) and more specialized. It involves six different interaction networks, one for each heart sarcoma (CS 1–6) (Table 1).

Our constructed interactomes involve genes with their products that been implicated in various pathological mechanisms:

- oncogenesis (i.e., cyclin D1, CBX7, ETV6, KHDC3L, LINC00457, FGFR1, MMP1, and GRAMD1B) [16–21]
- heart failure (i.e., VWF, ACE2, EDN1, PDGFRB, GATA4, MEF2A, NOS3) [22–24]
- ischemia (NOS3, SCNS5A) [23]
- hypertension (i.e., ACE2, GNB3, EDN1, NOS3) [22,23,25]
- atrial fibrillation (i.e., GATA4, CD34) [26,27]
- atherogenesis (i.e., NOTCH1, F8, NOS3) [23,28]
- inflammation (i.e., IL6, IL8, CD34, VWF, HLA-DQA1),
- oxidative stress (i.e., MMP2) [29]
- renin angiotensin-aldosterone system (i.e., ACE) [22]
- endothelin system (EDN1) [25]
- α-adrenergic signaling (i.e., GNB3) [30]

Additional physiology mechanisms are also involved, influencing:

- cell survival (i.e., FGF2) [31]
- homeostasis (i.e., ACE2, GRAMD1B) [22]
- hemostasis (i.e., VWF) [32]
- hematopoiesis (i.e., CD34) [33]
- endocrine (i.e., autocrine CXCL1) [34]
- metabolism (i.e., GRAMD1B) [35]
- autonomic nervous system (i.e., ACE2, VWF, MMP2) [22,29]

More specifically, genes known [9,36,37] to be associated with each type of heart sarcomas are shown below:

(i) Angiosarcoma: (POT1, CDKN2A/B, PLCG1, KIT and KDR, MYC, TP53, KMT2D, NRAS or KRAS)
(ii) Undifferentiated pleomorphic sarcoma: (PDGFRB, FH and PIK3CA mutations KIT, PDGFRA/b, EGFR and MDM2 amplifications, CDKN2A deletion)
(iii) Rhabdomyosarcoma: (KRAS)
(iv) Leiomyosarcoma: (HRAS mutation)
(v) Myxofibrosarcoma: (IFI6, LGALS3, ANXA1 and ASS1 downregulation CYB5A, SCD, ADD3, HSPB1, SMS, WWTR1 and RHOB upregulation)
(vi) Synovial sarcoma: (SS18-SSX fusion)

The highly connected nodes (hubs) are cyclin D1, endothelin 1 (endothelin pathway), matrix metallopeptidase 2 (implicated in protein or RNA binding), fibroblast growth factor 2 (cell survival), interleukin-8, interleukin-6 (inflammation marker), G protein subunit beta 3 (involved in α-adrenergic signaling), nitric oxide synthase 3 (involved in cardiovascular disorders and hypertension).

Seventeen novel genes were detected:

1. histone deacetylase 2-implicated in tumorigenesis (HDAC2), chronic obstructive pulmonary disease, lung diseases [38]
2. fibroblast growth factor 2 (FGF2) implicated in cell survival and oncogenesis [38]
3. polycomb group ring finger 5 that is involved in oncogenesis [39]
4. syndecan 2 that has been associated to non-alcoholic fatty liver, hepatic fibrosis, post-traumatic stress disorder
5. dynein light chain LC8-type 1 that is implicated in prostate carcinoma in situ [39,40]
6. POTE ankyrin domain family member F, that has been related to dilated cardiomyopathy [41].
7. adducin 1 implicated in the cell volume homeostasis, cell morphogenesis and cellular response to calcium ions [42].
8. adenylosuccinate synthase 2 that is implicated in the de novo pathway and in the salvage pathway of purine nucleotide biosynthesis, it catalyzes the first committed step in the biosynthesis of AMP from IMP [43].
9. caspase 3, a canonical pro-apoptotic protein [43].
10. cyclin dependent kinase 4—a cell division protein encoded by the CDK4 gene—which is associated to tumorigenesis of variant cancers [44].
11. 2,4-dienoyl-CoA reductase 1 protein encoded by DECR1 gene participating in the beta-oxidation and metabolism of unsaturated fatty enoyl-CoA esters [45].
12. E1A binding protein p300, associated to various syndromes and epithelial cancers [46].
13. high mobility group AT-hook 2 which is a transcription factor related to malignancy and poor prognosis [47].
14. ISG15 ubiquitin like modifier—a small ribosomal subunit is a multi-modal unit implicated to immune response and more interestingly to cancer stem cells in a tumor [47].
15. nibrin, a protein involved in DNA damage repair [48], whilst its variants were shown to be associated with breast cancer [49].
16. nerve growth factor receptor—a neurotrophic factor involved in the regulation and survival of certain neurons and pancreatic beta cells [50].
17. platelet and endothelial cell adhesion molecule 1—a protein that removes aged neutrophils from the body, involving in leucocyte transmigration and angiogenesis [51].

Four non-mediating genes were recognized, namely: GRAM domain containing 1B (involved in cholesterol metabolism and oncogenesis), KH domain containing 3 like (involved in oncogenesis), subcortical maternal complex member (implicated in maternal effect of unknown exact function), unc-51 like kinase 4 (associated to bipolar disorder and schizophrenia).

The networks include oncogenes (i.e., cyclin D1), genes (i.e., EDN1, FGF2), enzymes (i.e., MMP2, HDAC2), ion channels (i.e., SCN5A), transcription factors (i.e., SOX9), proteins (i.e., IL-6, IL-8, POTE ankyrin domain family member F, G protein subunit beta 3), cancer cell apoptosis modulator (RHOB).

The created interactomes elucidate the main pathways leading to cardiac diseases (heart failure, hypertension, coronary artery disease, arrhythmias), such as the renin–angiotensin–aldosterone system (RAAS) and endothelin system, and excludes others, such as K oxidase or cytochrome P450 pathways in these patients. [52–55]: Based on the Mestroni et al. pharmacogenetics study, we noted that only EDN1 and ACE are included in the created interactomes. Although our study is preliminary, this finding is important for personalized medicine, but still needs to be validated in clinical settings in the future.

Angiosarcomas represent 40% of the cardiac sarcomas, are usually found in the right atrioventricular groove (Figure 7) [56], and often expand to the right atrial wall and pericardium. According to the 2015 WHO classification of tumors of the heart and pericardium, angiosarcomas ICD-O code is 9120/3 [56]. The mean prevalent age of heart sarcomas is 41 years, with angiosarcomas accounting for 37% of the total cardiac sarcomas.
The constructed interactome (henceforth called CS1) illustrated in Figure 1 involves 61 nodes. Its major hubs are IL-6, FGF2, TP53, KRAS, CCND1. The following genes are expressed exclusively in angiosarcomas and not in the rest sarcoma types: CDKN2A, CDKN2B, EP300, KIT, NRAS, POT1, NBN, KDR, KMT2D, PPLG1. Our study confirms the findings of literature references [57]. Notably, KRAS is expressed in angiosarcoma and rhabdomyosarcoma as well.

Connections coming through CXCL1, MMP1, TIMP1, CXCL8 connect to IL-6 and subsequently drive to SDC2, FGF2, CDKN2A, TP53. TP53 through MYC connects to KRAS. The latter connects to EP300 and KMTD2 and through CDKN2A to FGF2 and NRAS, KIT, PLCG1, and KDR.

We revealed novel not previously reported interactions in CS 1: platelet and endothelial cell adhesion molecule 1 (PECAM1) and nibrin (NBN).

Moreover, we identified one case of this extremely rara avis cancer entity (angiosarcoma) in the Onassis Cardiac Surgery Center in Athens, which is presented for the first time (Figure 7): a Greek woman < 41 years of age within the established in literature age range. Of note, our in silico study is not based on the individual data of this case.

The undifferentiated pleomorphic sarcoma is classified with the code number 8830/3 in the WHO classification of tumors of the heart and pericardium of 2015 [56].

The relevant interactome (as of now called CS2) is presented in Figure 2. CS2 consists of 51 nodes, of which IL-6, FGF2, EGFR, and CCND1 are the most interactant molecules (hubs). Five genes are expressed only in this type of sarcoma: PIK3CA, MDM2, HMGA2, EGFR, CDK, CDK4, while CDKN2A is implicated in angiosarcomas and undifferentiated pleomorphic sarcomas only (Table 1). In this subtype of sarcoma, CDKN2A firmly connects to MDM2, CCND1, PIK3CA, CDK4, CBX7, and less firmly to EGFR, and IL-6. More importantly, IL-6, FGF2, and PDGFRB form a triangle through which they connect to MDM2, CDKN2A and PIK3CA, CCND1, and CDK4, while they connect to PIK3CA, EDN1, ACE, etc. through PDGFRB, and EGFR.

Rhabdomyosarcoma classification number in the ICD-O Classification of Diseases for Oncology of 2015 is 8900/3 [56]. It is a tumor type routinely found in infants even fetuses, thus, assumed to be a congenital hamartoma. No sexual dimorphism has been reported, while it is usually localized in the ventricular myocardium or every so often project into the heart cavity. Homogenous echogenicity characterizes imaging of these tumors, whilst they incite arrhythmias. The rhabdomyosarcoma (hence called CS3) interactions network numbers 46 nodes, where IL-6 and FGF2 are its most connected nodes. CS3 is described in Figure 3. KRAS is involved both in angiosarcomas and rhabdomyosarcomas. It straightforward connects to PDGFR13, PDGFRB, FGF2, FGFR1, CCND1, and IL-6.

Leiomyosarcoma ICD-O code number in the ICD-O Classification of Diseases for Oncology of 2015 is 8890/3 [56]. This type of sarcoma is typically found in the left atrium, and has been characterized by specific tissue differentiation. The relevant interactome subsequently referred to as CS4 is shown in Figure 4 and contains only 46 nodes. It is the smallest network constructed herein, whilst its major hubs are IL-6, FGF2, and HRAS.
latter is expressed exclusively in this type of heart sarcoma, and, thus, may be assumed as typical of the entity. FGF2 interacts directly with IL-6 that interacts in its turn with HRAS. The latter connects directly to EDN1 or CCND1, FGFR1, MMP2, and VWF.

Myxofibrosarcoma is coded with the number 8811/3 in the ICD-O Classification of Diseases for Oncology of 2015 [56]. It was previously called malignant fibrous histiocytoma with at least one-quarter of the myxoid areas representing most of the left atrial sarcomas. The network created is henceforth called CS5 (Figure 5) and involves 62 nodes, while it is the most crowded network presented herein. Its major hubs are IL-6, FGF2, and MMP2.

This network is the only one that involves RHOB - a cancer cell apoptosis modulator and, currently a research target as a cancer therapeutic. As apoptotic factor, it decreases while tumors proliferate, whilst it has been identified in head and neck, lung, and brain cancers and in adenocarcinomas, as a poor prognosis indicator.

HSPB1, IFI6, WWTR1, SMS, NGFR, LGALS3, ISG15, SCD, CYB5A, DECR1, ADD1, ADD3, ADSS, ANXA1, ASS1, CASP3 are also expressed exclusively in CS 5. ADD1 and ADD3 are interconnected with CASP3 their only node. CASP3, in its turn, connects directly to IL-6, NGFR, SDC2, HSB1, ACTA1, and CCND1. DECR1 connects directly to CYB5A, EDN1, SDC2. NGFR interacts with FGF2 and RHOB only. ANXA1, in its turn, has three connections: EDN1, SDC2, CXCL8. LGALS3 interacts only with MMP1, MMP2. CYB5A is linked to SCD, except DECR1. ISG15 and IFI6 are directly linked together but through PCNA and then through CCND1 they connect indirectly to the common to all sarcomas’ major hubs FGF2 and IL-6. SMS connects to ASS1 which connects to ADSS and then to NKX2-5, which through GATA4 affects EDN1.

In keeping with the ICD-O Classification of Diseases for Oncology of 2015, the synovial sarcoma’s code number is 9040/3 [56]. The interactions network we have built (henceforward called CS6) includes 47 nodes and is shown in Figure 6. The high degree connections of this specific interactome are IL-6 and FGF2. Notably, HRAS, SS18, SSX2, MVP2 are uniquely expressed in synovial heart sarcoma. Of those, SSX2 and SS18 have been identified in histology-type investigations in the literature, whilst MVP2 function is little known, while HRAS is implicated in various types of cancers (i.e., salivary duct carcinoma [58], epithelial myoepithelial carcinoma [59], etc.

In sum, we observed that all cardiac sarcomas share

- forty-four common nodes
- two common hubs: IL-6 and FGF2, that may be assumed as typical of the overall entity (heart sarcomas)

All six interactions networks are presented in 3 basic color-specified units/clusters. Nodes in a given cluster are most closely connected to those nodes of the corresponding cluster, as compared to the other two clusters. Nodes in the same cluster module can be associated with similar/common biological functions. This information could be expanded to more complicated enriched clusters that represent cardiac sarcoma-related biological processes, in the future.

Finally, the wild-type gene inclusion is a limitation in this investigation.

4. Materials and Methods

The protocol followed is the established one in molecular networking [60,61] and is described in Figure 8.
Figure 8. Workflow chart representing the algorithm followed in this work.

An extensive search in literature (PUBMED, Scopus), databases (GeneCards, UniProt) and cancer official sites (https://www.aacr.org/, accessed on 31 March 2021, https://www.cancer.org/, accessed on 31 March 2021), was conducted in the period December 2018–January 2021, revealing 85 gene/protein heart sarcomas-related and tumor-related targets. The interactions among gene/gene products were studied through STRING v10 [62]. A relative high confidence interaction score of 0.7–0.97 was opted so as to extract relevant information from multiple and diverse sources, avoiding at the same time the inclusion of rather erroneous interactions (e.g., false positives). The average degree of connectivity (i.e., mean number of connections of a given node to its immediate neighbors) and $k$-means clustering in the constructed networks were computed with the usage of algorithms implemented in the STRING database. The nodes in the network were partitioned into three clusters, based on the shortest path (distance) between two given nodes. Intra-cluster edges are represented by solid lines, whereas inter-cluster edges are denoted by dashed lines.

Genes not previously published to be associated to the specific heart sarcoma type, thus, not been included in the initial set of molecules in String platform so as to be processed are described as ‘novel’ or ‘novelties’ in this text.

All six interaction networks are presented in three basic color-specified units/clusters. Nodes in a given cluster are most closely connected to those nodes of the corresponding cluster, as compared to the other two clusters. Nodes in the same cluster module can be associated with similar/common biological functions.

5. Conclusions

Cardiac sarcoma patients might profit from administration of beta-adrenergic blockers, ACE inhibitors, QT-prolonging antiarrhythmic drugs, antibiotics, and antipsychotics. Interactomes may elucidate unknown cardiac implications of cardiac malignancies and contribute to patient/survivors’ wellness during and after chemo and/or radio treatment.

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