ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 09, Issue, 11, pp. 31893-31899, November, 2019

RESEARCH ARTICLE OPEN ACCESS

TUMOR DORMANCY IN POPULATION OF CANCER STEM CELLS: GENE INTERACTIONS BY BIOINFORMATICS

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ARTICLE INFO

Article History:
Received 27th August, 2019
Received in revised form
03rd September, 2019
Accepted 03rd October, 2019
Published online 30th November, 2019

Key Words:

Tumor stem cells; Quiescence, Biomarkers, gene interaction network, Genomic map.

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ABSTRACT

Introduction: Cancer stem cells (CSC) correspond to a small population of cells tumor with the ability to remain hidden. This contributes strongly to the resistance to antitumor therapies, the occurrence of relapse and metastasis. **Objective**: Inter relate the gene interactions networks of tumor dormancy (TD) and CSC. **Methods**: Genetic interaction networks of CSC and DT were identified in the Gene Cards® database. The maps of genomic interactions were performed using the software STRING 10.0. The cluster analysis of the genes was performed in the SPSS® Statistic 18.0.DT network genes present in the CSC were identified. Dormancy markers were analyzed for the interactions performed in both networks. **Results**: 386 and42genes belonging to the CSC and TD networks, respectively, were identified. TP53, MYC, AKT1, CTNNB1, JUN andSTAT3 genes were considered the leading of the CSC. The leading genes of TD were AKT1,CDK2, MAP2K4, PCNA, VEGFA and MCM2. The dormancy presented 12 genes common to CSC, with prominence for AKT1, considered leader in both conditions. All of the dormancy markers were identified in the CSC network, with between 8and 13 interactions performed per gene. **Conclusion**: Twelve genes common to the TD and CSC networksratify the interrelation between them.

Citation: João Vitor da Silva Rodrigues, Franciele Ornelas Cunha, Daniela Oliveira Lima Magalhães *et al.* 2019. "Tumor dormancy in population of cancer stem cells: gene interactions by bioinformatics", *International Journal of Development Research*, 09, (11), 31893-31899.

INTRODUCTION

Cancerous Stem Cells (CSC) correspond to a small population of tumor cells capable of self-renewal and differentiate into all tumor cell types. These cells do not actively proliferate and are demonstrably resistant to various cytotoxic treatments targeting cells in mitotic activity. In the treatment of patientswith cancer, the presence of tumor cells in the state of dormancy diminishes the effectiveness of the therapeutic response and allows them to remain undetectable for long periods, favoring the occurrence of recurrences and metastases (Dean, 2005; Yang *et al*., 2016). CSC were first identified in human acute myeloid leukemia and later in several solid tumors, such as breast, brain, lung, liver, pancreas, melanoma, prostate, colon, stomach, ovary, head and neck cancer, among others (Singh, 2013). The plasticity of CSCs gives them the potential for survival in an unknown environment, which is largely due to the increase in their genetic instabilities. When the epithelial tumor cell spreads towards the mesenchyme, in the epithelial-mesenchymal transition phenomenon, the epithelial cell undergoes biochemical, molecular and morphological changes that confers to it a mesenchymal cell phenotype. This process is facilitated by the tumor microenvironment, but is a behavior strongly present in the CSC phenotype (Pascussi*et al*., 2016; Konrad *et al*., 2017). It is also proposed that a population known as Metastatic Cancer Stem Cells (mCSC) and its progenies manipulate the tumor microenvironment and influence the biology of the metastatic niches.

Table 1. Genes common to the networks of gene interaction of tumoral dormancy and cancer stem cells

Genes	Descriptions *
AKT1	AKT Serine / Threonine Kinase 1, also referred to as kinase B, is known as an oncogene. It participates in the regulation of several cellular processes, including metabolism, proliferation, cell survival, growth and angiogenesis.
CD82	Themolecule*CD82* is a membrane glycoprotein related to the reduction of the tumor progression of human cancers.
CXCR4	C-X-C MotifChemokine Receptor 4 acts as a receptor for extracellular ubiquitin; participates in the events of hematopoiesis.
DLL4	Delta Like Canonical NotchLigand 4 is involved in the Notch signaling pathway, which includes events related to cell proliferation, death and differentiation, and angiogenesis.
MAPK14	Mitogen-ActivatedProteinKinase14 is a kinase which acts as an essential component of the MAP kinase signal transduction pathway. MAPK14 plays an important role in the cascades of cellular responses leading to the direct activation of transcription factors.
MTOR	Mechanistic Target ofRapamycinKinase is a serine / threonine protein kinase that is a central regulator of cell metabolism, growth, and survival.
NOTCH3	NeurogenicLocusNotchHomologProtein 3 is a receptor for membrane bound ligands Jagged1, Jagged2 and Delta1 to regulate the determination of cell fate and is involved in the implementation of differentiation, proliferation and apoptosis programs.
NOTCH4	NeurogenicLocusNotchHomologProtein 4 is a receptor for membrane bound ligands Jagged1, Jagged2 and Delta1 to regulate the determination of cell fate and is involved in the implementation of differentiation, proliferation and apoptosis programs.
PTK2	Protein TyrosineKinase 2 is a protein kinase that plays a key role in regulating cell migration, adhesion, scattering, cytoskeletal reorganization, formation and disassembly of focal adhesions and cell protrusions, cell cycle progression, and apoptosis.
SOX2	Sex DeterminingRegion Y-Box 2 is a transcription factor that forms a trimeric complex with OCT4 in DNA and controls the expression of several genes involved in embryonic development, such as YES1, FGF4, UTF1 and ZFP206.
SPP1	SecretedPhosphoprotein 1 acts as a cytokine involved in increased production of interferon-gamma and interleukin-12, and reduced production of interleukin-10, being essential in type I immunity.
VEGFA	Vascular Endothelial Growth Factor A is an active growth factor in angiogenesis, vasculogenesis and endothelial cell growth. It promotes cell migration, inhibits apoptosis, and induces permeabilization of blood vessels.

* Genesinformation were obtained from the Genecards database.

In the new site, mCSCs may actively proliferate or become dormant, and niche stimulating factors may lead to CSC reactivation and metastatic lesion formation (Li *et al*., 2007). Many of the factors that maintain dormant cells also influence CSC behavior. It is believed that three mechanisms are involved in the dormancy of cancer cells, such astumor microenvironment factors that maintain the cells in the G0 phase of the cell cycle, the low vascularization around the tumor and the marked immune response against tumor cells (Evans and Lin, 2015). Immune quiescence and escape are hallmarks of some CSCs (Kleffels and Schattont, 2013). From these evidences, it is understood that new methodologies that contribute to the understanding of the biology of the tumor, and especially the CSC, need to be explored. Biomarkers are fundamental in this process, and are commonly used in many applications (Califf, 2018). In this scenario, bioinformatics tools have received considerable attention in the interpretation and understanding of large volumes of data in the health sciences, being relevant to the knowledge of a series of events related to a wide range of diseases (Santos *et al*., 2017; Marco-Ramell *et al*., 2018). Computational tools can be exploited to better understand the intrinsic characteristics of cancer stem cells and tumor dormancy. Therefore, the objective of this study was to identify and analyze the networks of gene interaction of cancer stem cells and tumor dormancy, as well as to evaluate the gene interactions carried out by genes related to tumor dormancy in the cancer stem cell network.

METHODS

Identification of the genes: The identification of the genes involved with the CSC and TD conditions was carried out through searches in the Gene Cardshuman genetics database® during the period of January, 2018. The official nomenclature for human genes was used *Human Genoma Organization*(HUGO). The descriptors were used in English language and defined according to the medical *Subject Headings* "(MeSH). The descriptors "*cancerstemcells"* and "*dormancy"* and "*cancer*" were used for the CSC and TD, respectively. All the genes studied had a confidence level above 0.9 provided by the Gene Cards® database.

Construction and analysis of maps of genomic interaction

After selecting all the genes belonging to each biological condition, a genomic map of each situation was constructed using the software STRING *(*Szklarczyk *et al*., 2015), using all sources of active interactions in the species *Homo sapiens* (text mining, experiments, database, co-expression, neighborhood, fusion of genes and co-occurrence) that had a confidence level above 0.9. Gene network mapping analysis in the STRING database resulted in afile *Text Output* containing the scores for all associations made by each gene in the study network. Thus, such scores were tabulated in Excel 2013 program, together with the associations of each gene in the network under consideration and multiplied by 1000, in order to meet a single score, the weighted number of connections*(Weighted Number of Links* (WNL)) (Poswar*et al*., 2015). In this study, we also calculated the overall *score* of genes called significant global connectivity *(significant global connectivity* (TIS)). TIS was calculated by adding the values of each gene associations in all available networks obtained in the global interaction file *Protein Network Data* STRING software (Pereira, 2016). The WNL / TIS ratio represents the most influential genes within the network under study Genes that did not interact with the selected genes in the network were identified as orphan genes (Poswar *et al*., 2015; Pereira, 2016; Santos *et al.*, 2016). The genes of the genomic map were grouped according to their WNL values by the *K-means algorithm,* analyzed in the statistical program SPSS® PASS Statistic 18.0. Analysis of variance (ANOVA) and post-test of Tukey Kramer were used to evaluate the difference between groups, whose statistical significance was set at *p*value <0.001. Genes that presented higher WNL values were considered as leading genes (Santos *et al.,* 2016).Genes common to the TD and CSC network were also identified.

Interactions Performed by Tumor Dormancy Markers : The markers were chosen based on a research conducted in scientific articles published in theonline database Pubmed, available from the Medical Literature Analysis andRelay System Online, MEDLINE. The main tumor dormancy markers mentioned in the articles were registered and, as a criterion of inclusion in the research, the markers mentioned in the articles were selected and were present in the gene network

of tumor dormancy provided by the GeneCards database. Subsequently, the interactions performed by each dormancy marker gene in the CSC and TD conditions were evaluated. The graph representing the number of interactions was constructed in the program GraphPadPrisma® 5.0. Genes interacting with tumor dormancy markers were also defined.

RESULTS

Comparative analyzes between CSC and TD gene interaction maps: The gene interaction networks of CSC (Figure 1A) and TD (Figure 1B) were composed of 386 and 42 genes, respectively. 341 (88%) perform interaction in the CSC network and 25 (63%) in the TD network. 45 (12%) and 17 (37%) genes were considered orphans of the CSC and TD networks, respectively. Statistical analysis of the weighted number of links (WNL) ranked the 341 genes related to the cancer stem cell network in groups from 1 to 14. Those who performed the most interactions in the study network received higher WNL values and were classified in group 1. *STAT3* (Signal Transducer and Transcriptional Activator 3) (n = 64 interactions) were the ones that presented the best combinations of high WNL and low TIS, therefore considered to be leading genes for cancer stem cells (Figure 2A) . The distribution of genes per group can be seen in figure 2B. Statistical analysis of the WNL values by group revealed that there was a statistically significant difference between them ($p < 0.001$). The 25 genes related to the tumor dormancy network were classified into groups of 1 to 4 ($p < 0.001$). The major genes were *AKT1* (AKT Serine / threonine kinase 1) (n = 6 interactions), *CDK2* (n = 4 interactions), *MAP2K4* (Mitogen-Activated Protein Kinase 4) (n = 3 interactions), *PCNA* (Proliferating Cell Nuclear Antigen) (n = 3 interactions), *VEGFA* (Vascular Endothelial Growth Factor A) (n = 4 interactions) and *MCM2* (Microsome 2 maintenance) (Figure 2C and D). In both conditions studied (CSC and TD), all leading genes were above the regressive trend line (linear R^2). 28,6% (12) genes of the TD network were present in the CSC network: *AKT1*, *CD82*(Molecule CD82), *CXCR4*(CXC motif 4), *DLL4*(Delta As Canonical Notch Ligand 4), *MAPK14*

Table 2. Interactions performed by tumoral dormancy markers in cancer stem cell networks and tumor dormancy

Markers	Condition	Number of interactions	Genes interacting with tumor dormancy markers
CXCR4	CSCs	11	*CCL5, CDC42, CXCL12, CXCR1, CXCR6, HIF1A, IL8, JAK2, RAC1, S1PR3, STAT3*
	Dormancy	2	*CXCL2, OH*
DLL4	CSCs	8	*DLL1, HEY1, JAG1, NCSTN, NOTCH1, NOTCH3, NOTCH4, VEGFA*
	Dormancy	2	*NOTCH3, NOTCH4*
NOTCH3	CSCs	11	*ADAM17, DLL1, DLL4, EGFR, HEY, JAG1, NCSTN, NOTCH1, NOTCH4, NUMB, POGLUT1*
	Dormancy	2	*DLL4, NOTCH4*
NOTCH4	CSCs	10	*DLL1, DLL4, FBXW7, JAG1, JUN, NCSTN, NOTCH1, NOTCH3, NUMB, POGLUT1*
	Dormancy	2	*DLL4, NOTCH3*
SOX2	CSCs	13	*ATOH1, CDX1, CDX2, FGF2, KLF4, LIN28A, NANOG, POU5F1, POU5F1B, PROM1, STAT3, TDGF1, TWIST1*
	Numbness	0	

* Interaction gene networks were provided by the GeneCards database.

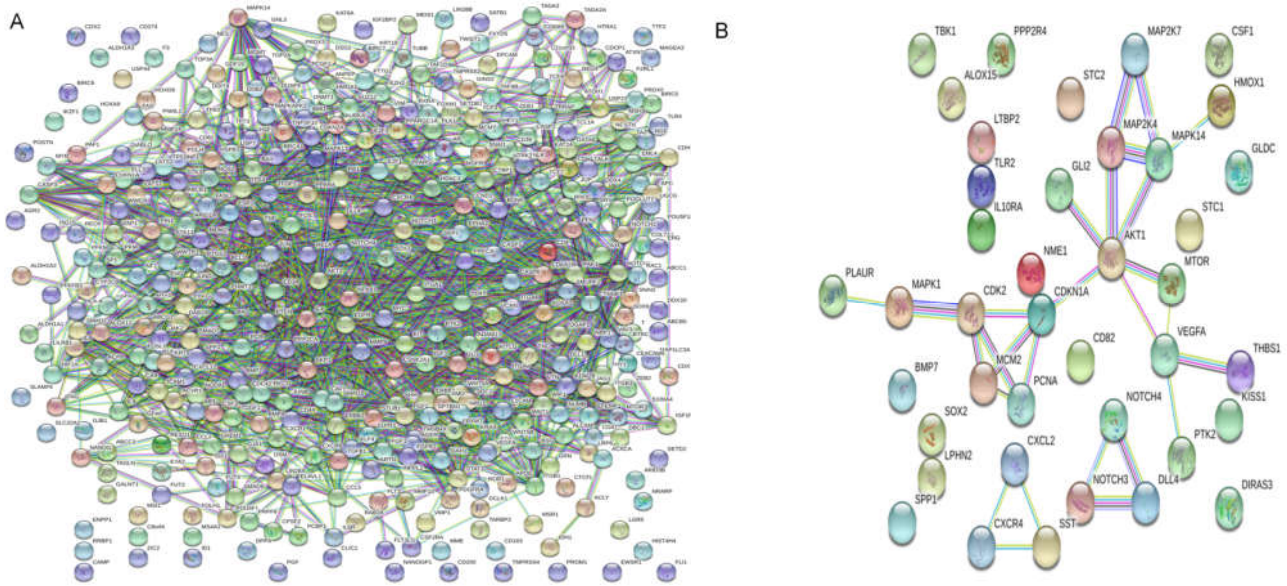

Figure 1. Gene interaction network of cancerous stem cells (a) and tumor dormancy (b). Red association indicates gene fusion; green: neighboring genes; dark blue: co-occurrence of genes; purple: protein homology; pink: experimentally determined relationship; yellow: relationship determined by studies of text mining; light blue: relationship from a curated database; black: gene co-expression. Orphan genes do not interact with other genes in the network

In contrast, the genes that performed the least interactions within the network were allocated in group 14. Thus, *TP53* (Tumor Suppressor Protein p53) (n = 108 interactions), *MYC*(Proto-Oncogene MYC, BHLH transcription factor) (n=77 interactions), *AKT1*(AKT Serine / threonine kinase 1) (n = 79 interactions), *CTNNB1* (Beta catenin 1) (n = 73 interactions), *JUN* (Proto-oncogene Jun, = 62 interactions) and (Mitogen Activated Kinase Protein 14), Kinase *MTOR Mechanism* (Rapamycin Target), *NOTCH3*, *NOTCH4* (Notch 4 neurogenic locus), *PTK2*protein (Protein Tyrosine Kinase 2), *SOX2* (Region determinant of sex Y-Box 2), *SPP1* (Secret Phosphoprotein 1) and *VEGFA*.*AKT1* is highlighted, which is present as a leader gene in both conditions(Table 1). It has 79 interactions in the CSC network and 6 in the TD network.

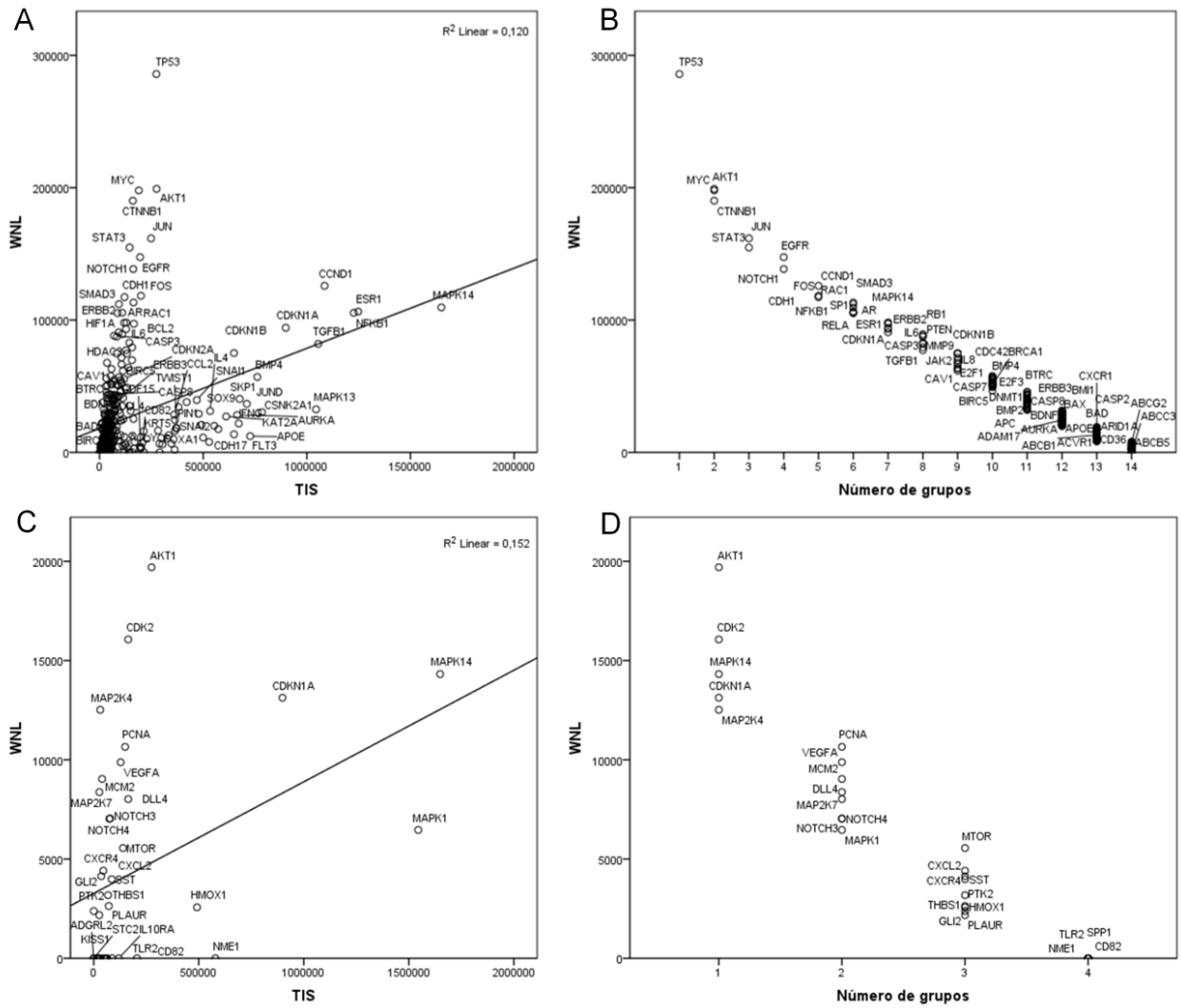

Figure 2. Distribution of cancerous stem cell (a and b) and tumor dormancy (c) genes as a function of the WNL (weighted number of connections) and TIS (a and c) and cluster analysis (b and d)

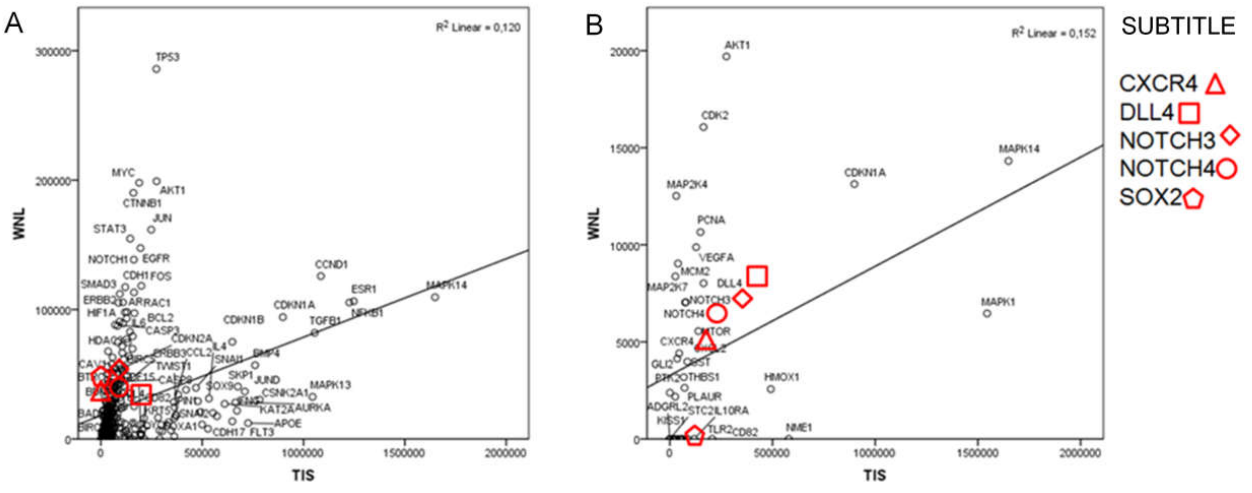

Figure 3. Representation of tumor dormancy markers as a function of WNL (Weighted Number of Links) and TIS (Significant Global Connectivity) in cancer stem cell networks (a) and tumor dormancy (b)

VEGFA is one of the leading genes of TD that has also been shown in the CSC network. Table 2 also shows brief descriptions of the functions of these genes in relation to the events of dormancy and stem cell characteristics.

Interactions by dormancy markers in CSC and TD: From the inclusion criteria adopted in the study, the *DLL4*, *NOTCH3*, *NOTCH4*, *CXCR4* and *SOX2* genes were considered the genes markers of tumor dormancy. It can be seen in the TD network that they presented high values of WNL and low values of TIS, being, as a function of the WNL, only the leading genes, with the exception of*SOX2*, which has no interaction in this specific network (WNL value equal to 0, considered an orphan gene in this condition) (Figure 3A).

All dormancy markers were present in the CSC network, presenting lower WNL and TIS values in relation to other genes present in the network (Figure 3 B). However, all markers were above the regressive trend line. Table 2 shows the dormant markersgenes, the number of interactions performed by each marker gene, and genes who are interacting in each condition (CSC and TD). It is noted that *SOX2* was the marker gene to tumor dormancy made larger number of interactions (13) in the CSC network. Surprisingly, he did not perform any interaction in the tumor dormancy network. The other tumor dormancy markers showed interactions with 8 to 13 genes in the CSC network and with 2 genes / marker in the condition of tumor dormancy. In the latter, *DDL4*, *NOTCH3* and *NOTCH4* interact with each other. CSC analysis of the network revealed that *DLL1*, *NCSTN*, *JAG1* and *NOTHC1* are common binders to *DDL4*markers, *NOTCH3* and *NOTCH4. CXCR4* and *SOX2* have only one ligand gene common to both genes (*STAT3*) and no ligand common to the *DDL4*, *NOTCH3* and *NOTCH4* genes.

DISCUSSION

Considerable progress has been made to understand the behavior of tumor cells, to understand how they evade to cell proliferation control mechanisms, their interactions with cells and blood plasma components with metastatic sites, and what factors may determine whether these cells will survive, remain dormant, or become metastatic (Carceri *et al*., 2017). The discovery of Cancer Stem Cells (CSCs) challenges our understanding of tumor spread, relapse, drug resistance, metastasis, and how cells leave dormancy for malignancy (Patel and Chen, 2012). Many biological mechanisms involved in controlling the state of tumor dormancy may also govern the behavior of tumor stem cells (Kleffel *et al*., 2013). We proposed in the present study to establish, by computational approach, a parallel between the genes of the networks of tumor dormancy and cancer stem cells. The networks of gene interaction of cancer stem cells and tumor dormancy presented a total of 428 genes related to several cellular events, with the presence of genes involved with hypoxia, proliferation, differentiation, transcription, apoptosis, angiogenesis, among other relevant events in the progression of various diseases. The CSC network presented 386 genes, 6 of them considered leaders of the network due to their high interaction within the network and low interaction in other global networks. Among them, the gene *TP53* was the most important gene in the network, followed by *MYC*, *AKT1*, *CTNNB1*, *JUN* and *STAT3*. In the genome's guardian function, the p53 protein prevents the differentiation and propagation of stem cells with abnormalities. Many studies have associated p53 with the regulation of the quiescence of these cells, since it is essential to restrict entry into the cycle and inhibit stem cell transcription factors such as Oct4, Sox2 and Nanog.

The loss of p53 activates the epithelial-mesenchymal transition increases the number of CSCs (Golubovskaya, 2013; Olivos and Mayo, 2016; Lim *et al.,* 2005). The proto-oncogene *MYC,* the second gene with the largest interactions in the CSC network, is a transcription factor with critical functions in the self-renewal of stem cells. It has been shown to be a critical regulator of malignant transformation in the early stages of various types of cancer (Aravalli *et al*., 2015). The MYC gene, which is already considered a marker of CSC associated with tumorigenesis and resistance to therapies, is also a good target for therapeutic interventions due to the high number of gene interactions performed by *MYC* in the CSC network in the present study and to the reports of elevated expression of that gene in that cell type (Wang *et al.,* 2008; Ninomiya *et al.*, 2017). Serine/Threonine Kinase 1 (*AKT1*) was the third gene in number of interactions performed in the CSC network and the first gene leader in the tumor dormancy group. It is part of the family of kinases known as key regulators in biological processes. Proliferation, survival, growth, metabolism, angiogenesis and resistance are processes in which there is central participation of the AKT1 protein (Sahlberg *et al*., 2014). Its low expression in cancer cells is directly related to the state of dormancy (Alves *et al*., 2018). In CSC, inhibition of AKT produces a decrease in survival, reduction in the generation and growth of CSC (Gargini *et al*., 2015). These cells can also by means of β-catenin regenerate AKT1 to reactivate AKT signaling, immediately returning to the cell cycle and producing offspring (Alves *et al*., 2018). The gene *CTNNB1*, also known as β-catenin1, plays two crucial roles for cellular homeostasis as a component of cell-cell adhesion structures and also is a key member in the Wnt/β-catenin signaling pathway (Nakayama *et al*., 2014). Wnt binds to several cellular receptors, which promote stabilization and accumulation of β-catenin in the nucleus and subsequent transcriptional activation of Wnt target genes (Zhang *et al*., 2017). The Wnt/β-catenin pathway is associated with the progression and development of cancer and the maintenance of the cancer stem cell population (Wu *et al*., 2015; Moon *et al*., 2014).

As the genes described above, *JUN* was also one of the leading genes in the CSC network. JUN protein is also involved in important pathways in tumor progression. In colorectal cancer, JUNcan promote the adoption of a stem cell phenotype in the population of colorectal cancer cells by activating the *NANOG* gene promoter (Kuo *et al*., 2016). JUNand β-catenin are regulators of *NANOG* transcription, conferring self-renewal ability to these cells (Ibrahim *et al*., 2012). *STAT3* was considered the sixth gene leader of the CSC group. It is a member of a family of proteins that are involved in the mediation of cellular responses to cytokines. It acts on the growth and invasion of tumors and its activation occurs by the phosphorylation of a tyrosine residue mediated by JAK (Santoni *et al*., 2015). Studies indicate that the signal transduction pathway and activation of the *JAK/STAT* transcript (Janus kinase/signal transducer and transcriptional activator) plays an important role in regulating the self-renewal of CSC and is constitutively activated in various types of human cancers. Some cancer stem cell factors, such as Nanog, are well-known targets of the STAT3 signaling pathway, further elucidating the regulatory role of STAT3 signaling in CSC maintenance. Among the leading tumor dormancy genes *AKT1*, *CDK2*, *MAPK2K4*, *PCNA*, *VEGFA* and *MCM2*, the *AKT1* gene was also considered a leader in cancer stem cells, demonstrating the importance of this gene for the phenotype of dormancy in CSC populations. Data suggest that cells with low expression of *AKT1* express other markers characteristic of quiescent cells, and yet cells with this profile exhibit many properties attributed to cancer stem cells, including increased tumor initiation capacity and epigenetic plasticity (Kabraji*et al*., 2017). The second leading gene associated with dormancy was CDK2, which is part of a network of Cyclin-Dependent Kinases (CDKS) that act directly on the G1, S, G2 and M phases of the cell cycle (Gerard and Goldbeter, 2012). The gene encoding mitogen-activated protein kinase4 (*MAP2K4*), also considered one of the leading genes of TD, also has

implications for cell cycle blockade, differentiation and apoptosis (Osisami and Keller, 2013). The low expression of *AKT1*, *MCM2* and *CDK2* is related to a state of cellular dormancy (Spencer *et al*., 2013). MAP2K4 has mechanisms of action associated with p21, inducing cell cycle block and tumor cell dormancy (Horak *et al*., 2008). Other studies have shown that activation of p38 by MAP2K4 is involved in pro-metastatic phenotypes, specifically in the transition from epithelial cells for mesenchymal cells (Pavese *et al*., 2014). Another leading gene for tumor dormancy was Proliferating Cell Nuclear Antigen (*PCNA*). It is known that the protein encoded by the PCNA gene is directly involved in the replication and repair of DNA and, consequently, in the progression of the cell cycle. It is unclear how PCNA is involved in dormancy, but Yao and contributors, 2015report that there is a declining expression of statistically significant PCNA in quiescent prostate cancer cells. Vascular Endothelial Growth Factor A (*VEGFA*) has also been one of the leading genes associated with dormancy. VEGFA is one of the regulatory proteins of the angiogenesis process, and its low expression, as well as other pro-angiogenic proteins, has had an implication on the disability to induce neovascularization, and consequent promotion of angiogenic dormancy. Pharmacological disturbance of the balance between antior pro-angiogenic molecules may induce tumors into a dormant state or potentially prevent them from leaving this state (Kang and Watnick, 2008).

CDKN1A and *MAPK14* also had high interactions in the dormancy network compared to the other genes in the network, but these genes were not considered leaders due to their high number of interactions in other networks. Interestingly, among the 42 genes in the dormancy network, 12 were common to cancer stem cell genes, two of them leading genes (*AKT1* and *VEGFA*). Among the tumor dormancy markers *DLL4*, *CXCR4*, *NOTCH3*, *NOTCH4* and *SOX2* indicated by the literature, only *SOX2* does not interact with genes in the network. As a result, SOX2, a transcription factor related to pluripotency, would not be a good target to promote injury to dormant cells, although it is a marker used to identify them (Boix*et al*., 2016). All other marker genes are commonly used for this purpose, and are still critical to the network of tumor cell dormancy interactions because they present WNL and TIS very similar to those of the leading genes. *DLL4* and *NOTCH3* are some of the genes that control angiogenic dormancy and are important regulators of cancer stem cells. The output of the dormancy state is controlled by the DLL4/NOTCH3 and DLL4/NOTCH4 signaling pathway proteins, which explains the occurrence of links between DDL4, NOTCH3 and NOTCH4 and the high number of binding genes common to these 3 genes (Stremitzer *et al*., 2015). *CXCR4* and *SOX2* present only 1 common linker gene (*STAT3*) and no ligand common to the *DDL4*, *NOTCH3* and *NOTCH4* genes in CSC. *CXCR4* is a member of the CXC chemokine receptor family. Nobutani *et al.,* 2015found that there are changes in the expression of CXCR4 in breast cancer cells in the processes of entry and exit of dormancy. Thus, it is suggested that the attack on tumor dormancy marker genes is important to promote damage to dormant cells, and additionally interfere in the gene interactions of CSC, although there are other better targets for the inactivation of these cells, such as the reported leading genes.

Conclusion

We conclude, therefore, by means of computational tools, that the genes *TP53, MYC, AKT1, CTNNB1, JUN* and *STAT3* are leading genes of cancer stem cells and that *AKT1, CDK2, MAP2K4, PCNA, VEGFA* and *MCM2* are leaders of tumor dormancy. The dormancy, which is considered one of the phenotypic characteristics of the cancer stem cells, present 12 genes common to the CSC network (*AKT1, CD82, CXCR4, DLL4, MAPK14, MTOR, NOTCH3, NOTCH4, PTK2, SOX2, SPP1* and *VEGFA*), which are considered the leading genes for both conditions. The dormancy markers *DLL4, NOTCH3, NOTCH4* and CXCR4 perform high interactions within the tumor dormancy network and few interactions in other networks. However, in the cancer stem cell network, these marker genes perform less gene interactions compared to other genes.

Conflict of interest: The authors declare that there is no conflict of interest that could influencethe impartiality of the research reported.

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