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VEGF expression in pancreatic cancer and other malignancies: a review of the literature

M.I. COSTACHE[1,2], MIHAI IOANA[1,3], SEVASTIȚA IORDACHE[1], D. ENE[5,6], CORNELIA ALEXANDRA COSTACHE[7], A. SĂFTOIU[1,4]

[1]Gastroenterology Research Center of Gastroenterology and Hepatology, University of Medicine and Pharmacy Craiova, Romania
[2]Radiology Department, University Hospital, Craiova, Romania
[3]Nijmegen Institute for Infection, Inflammation and Immunity (N4i), Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands
[4]Gastrointestinal Unit, Copenhagen University Hospital Herlev, Denmark
[5]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[6]Surgery I Department, Floreasca Hospital, Bucharest, Romania
[7]Neurology Department, Neuropsychiatry Hospital, Craiova, Romania

Angiogenesis is a crucial event for tumor growth and it is regulated predominantly by several different growth factors. Vascular endothelial growth factor protein family (VEGF) and its receptors are probably the most important tissue factors responsible for angioblast differentiation and tube formation. VEGF protein family currently comprises several members: VEGF (or VEGF-A), VEGF-B, VEGF-C and VEGF-D , VEGF-F, placental growth factor (PlGF), and their receptors VEGFR-1, VEGFR-2 and VEGFR-3. VEGF is a key angiogenic growth factor and its level of expression is a critical marker for detection of the angiogenic diseases. The potent role of VEGF in tumor angiogenesis has been widely described in the past decade, being expressed in most types of nondigestive and digestive cancers. VEGF family members play an important role in the development of pancreatic cancer (especially VEGF-A, VEGF-C, VEGF-D, VEGFR-1 and VEGFR-2). VEGF-A is the most specific and prominent angiogenic factor among all family members and VEGFR-2 is the most important receptor in evaluating the angiogenesis in pancreatic cancer. Thus, VEGF overexpression may be considered as a diagnostic marker and as a poor prognostic factor of the disease.

Key words: Angiogenesis, VEGF, pancreatic cancer.

INTRODUCTION

All human cells need oxygen and nutrients to survive and to ensure proper growth and differentiation. Thus, the formation of the vascular system (***vasculogenesis***) by the differentiation of endothelial cell precursors [1] is crucial to provide efficient blood supply and organ specific vascular functions [2]. This system needs to be maintained through ***angiogenesis***, the process which summarizes a set of morphogenic events that expand and fine-tune the initial, more primitive, embryonic vascular network of arterioles, venules and highly branched capillaries [3]. The formation of new blood vessels occurs in normal circumstances (during wound healing, organ regeneration, and in the female reproductive system during ovulation, menstruation, and the formation of the placenta), but it is also an important factor in several ***pathological processes*** (tumor growth, rheumatoid arthritis, diabetic retinopathy, and psoriasis). Angiogenesis is tightly controlled by a ***physiological balance*** between the stimulatory (proangiogenic factors) and inhibitory (antiangiogenic factors) signals for blood vessel growth [1]. Angiogenesis and vasculogenesis are regulated predominantly by several different ***growth factors and their associated receptor tyrosine kinases***: vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF)-2, angiopoietins (Angs), transforming growth factor (TGF)-β, netrins, semaphorins, ephrin, Notch, survivin [4]. Probably, the most important tissue factors responsible for angioblast differentiation and tube formation are ***VEGF (vascular endothelial growth factor) protein family and VEGFRs (VEGF receptors)***. Established as the prime angiogenic molecule during organogenesis, as well as post-natal physiological and pathological angiogenesis, VEGF is the most potent stimulator

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of endothelial cell proliferation, sprouting, migration and tube formation and is also a powerful survival factor and permeability factor for endothelial cells [2].

VEGF PROTEIN FAMILY AND ITS RECEPTORS

Described for the first time in 1989 [5], the VEGF protein family currently comprises several members: VEGF (or VEGF-A), VEGF-B, VEGF-C and VEGF-D , VEGF-F, placental growth factor (PlGF), and their receptors VEGFR-1, VEGFR-2 and VEGFR-3 [6].

VEGF-A is a dimeric glycoprotein essential for many angiogenic processes in normal and abnormal states [4], being **the most specific and prominent angiogenic factor among all VEGF family members** [7]. It exists in at least nine homodimeric isoforms (with 121, 145, 148, 162, 165, 165b 183, 189, or 206 amino acids) [8]. In normal tissues, the highest levels of VEGF-A mRNA are found in adult lung, kidney, heart, and adrenal gland [1, 9, 10]. VEGF-A has the capacity to stimulate vascular endothelial cell proliferation and the ability to increase vascular permeability [11-14]. It also promotes the survival and migration of endothelial cells [4]. VEGF-A has become a center of interest due to its important role in physiological and pathological processes such as embryonic development, wound healing, female reproductive cycle, cancer, cardiovascular disease, etc. [15, 7]. Discovered in 1995, **VEGF-B** has a wide tissue distribution, but is abundantly expressed in the adult myocardium, skeletal muscle, and pancreas [16]. In adult tissues, **VEGF-C** is expressed most prominently in the heart, placenta, ovary, small intestine, and the thyroid gland [1]. It is the paracrine factor essential for lymphangiogenesis [4]. **VEGF-D** is found in adult tissues, particularly the lung, heart, skeletal muscle, colon, and small intestine [1, 17, 18].

Three VEGF tyrosine kinase receptors have been identified: VEGFR-1, VEGFR-2 and VEGFR-3 [17]. **VEGFR-1** (The fms-like tyrosine kinase, Flt-1) and **VEGFR-2** (the kinase domain region also referred to as fetal liver kinase, KDR/Flk-1) are expressed predominantly by vascular endothelial cells. They are present in tumor cells, where they are coexpressed with VEGF, and they are also expressed by smooth muscle cells, pancreatic beta cells, and osteoblasts [17]. But the**VEGFR-2** is the major mediator of the mitogenic, angiogenic and permeability-enhancing effects of VEGFA. Furthermore, recent studies have indicated that the activation of VEGFR-2 also promotes lymphangiogenesis [19]. **VEGFR-3** (Flt-4) is generally restricted to lymphatic endothelial cells, activation stimulates mitosis, migration, differentiation, and survival of these cells, being up-regulated in lymphangiogenic vessels, but not in angiogenic vessels [20]. **VEGFR2** is abundant in the tip cells of angiogenic sprouts, where VEGF/VEGFR2 functions upstream of the delta-like ligand 4 (DLL4)/Notch signal transduction pathway. **VEGFR3** is expressed in all endothelia and is indispensable for angiogenesis during early embryonic development. In adults, VEGFR3 is expressed in angiogenic blood vessels and some fenestrated endothelia. VEGFR2 is required independently of VEGFR3 for endothelial DLL4 up-regulation and angiogenic sprouting, and for VEGFR3 functions in angiogenesis [21].

VEGF EXPRESSION IN CANCER

VEGF is a key angiogenic growth factor and its level of expression is a critical marker for detection of the angiogenic diseases.The increase or decrease of angiogenesis is related to various diseases in different stages of life. Thus, we find a high level of VEGF expression in the diseases which show an increase in angiogenesis like cancers, atherosclerosis, haemangiona, diseases of the skin and mucosae, retinopathy, liver and kidney disease, inflammatory diseases.They are the pathological states which show reduction in angiogenesis where the expression of VEGF is low: ischemic disease, bone disorders, leukoencephalopathy, diseases of the brain, coronary artery disease, peripheral vascular disease [7]. The neovascularization of solid tumors facilitates their growth and metastasis by providing nutrient flow. The new blood vessels result by the proliferation and migration of endothelial cells from existing vasculature supplying the tumor bed in a complex process that involves the regulated interaction of several soluble mediators and their cognate receptors. The potent role of VEGF in tumor angiogenesis has been widely described in the last decade. VEGF is expressed in most

tumours and its expression correlates with tumour progression [22].

NON-DIGESTIVE CANCERS

Many meta-analysis and clinical studies demonstrated that VEGF expression and their receptors are implicated in most types of non-digestive cancer. Thus, overexpression of VEGF was found in ***head and neck cancer*** [23, 24]. By inducing proliferation of lymphatic endothelia cell and development of lymphatic vessels, **VEGF-C and VEGF-D** contributed to lymphatic metastasis of ***papillary thyroid carcinoma*** [25]. **VEGF** has important effects on the occurrence, development, and metastasis in ***non-small cell lung cancer*** (NSCLC) patients, which could be applied as the indicators to predict the malignancy and prognosis of this type of cancer [26-28]. **VEGF-C** expression is associated with poor prognosis for these patients, including patients with stage I NSCLC [29]. **VEGFR-1 and VEGF** expressions were significantly increased in ***breast cancer*** in relation to surrounding tissue and the VEGF expression was significantly increased in lymph node positive breast cancer patients [30]. **VEGF** could impact ***ovarian cancer's*** malignant progression [31]. **VEGFR2** is significantly related to ovarian metastasis and invasion [32]. TheVEGF-receptor status as a molecular biomarker for monitoring tumor cell spread to the bone marrow and, particularly, revealing prognostic significance of **VEGF-R1** [33]. **VEGF** is an important proangiogenic factor in neoangiogenesis in precancerous and cancerous changes in the ***cervix*** [34**]**. Detection of VEGF-C mRNA has clinical potential as a predictor for identifying patients with pN0 cervical cancer at high risk of lymph node recurrence and poor prognosis [35]. An increased expression of **VEGF-A, VEGFR2 and VEGFR-3** was seen in ***endometrial cancers*** compared with normal endometrium. VEGFR3 was significantly correlated with tumor stage, with a trend towards poorer disease free survival [36]. **VEGF** expression has an important impact on overall survival in patients with ***osteosarcoma*** and high VEGF expression is associated with poorer overall survival [37, 38]. Activation of **VEGFR-1 by VEGF-A** within the carcinoma, and activation of lymphatic endothelial cell **VEGFR-3 by VEGF-D** within the adjacent benign stroma may be important signaling mechanisms involved in the progression and subsequent metastatic spread of ***prostate cancer*** [39]. Alterations in the expression of VEGF and VEGF receptors are associated with disease stage and recurrence in ***bladder cancer*** patients [40]. **VEGF** expression may be strongly correlated with pathological characteristics of ***diffuse large B cell lymphoma (DLBCL)*** [41]. **VEGF** plays a significant role in the pathogenesis and tumor angiogenesis of ***ocular adnexal lymphoma*** [42]. Both **VEGFR-2 and VEGFR-3** can serve as markers for prognosis of ***papillary renal cell carcinoma***. Differently, VEGFR-3 is a predictor of lymph node metastasis, increased VEGFR-2 expression could be used to predict a potential blood dissemination [43].

DIGESTIVE CANCERS

In the field of gastroenterology, VEGF family expression has been extensively studied.

Gingival and oral cancer

A meta-analysis of 17 studies that evaluated the correlation between VEGF overexpression detected by immunohistochemistry and survival in patients with ***oral cancer*** demonstrated that VEGF overexpression had an unfavorable impact on overall and disease-free survival in patients with oral cancer. VEGF overexpression indicates a poor prognosis for patients with oral squamous cell carcinoma (OSCC), adenoid cystic carcinoma and mucoepidermoid carcinoma of the salivary glands [44]. The VEGF-C may be a predictive factor for oral squamous cell carcinoma cancer outcome, lymph node metastasis, and recurrence. Moreover, VEGF-C may be an important factor in the development of new therapies for OSCC patients [45]. The serum VEGF level may be a reliable biomarker and may be a potential target for development of chemopreventive and chemotherapeutic strategies for patients with tobacco-related oral carcinoma [46]. The increased expression of VEGF was positively correlated to recurrence and lymph node metastasis in ***gingival cancer*** [47].

Esophageal cancer

Lymph node metastasis is one of the most important prognostic factors in ***esophageal squamous cell carcinoma (ESCC)***. Positive expression of VEGF-C was found to correlate significantly with depth of tumor invasion, lymphatic invasion and lymph node [48]. Both **VEGF-C** and **VEGF-D** are highly expressed in esophageal squamous cell cancer tissue, which may be related to the lymph

node metastasis of cancer cells. Hence, VEGF-C and VEGF-D can be clinically considered as important reference indexes of lymph node metastasis [49]. Moreover, the expression of **VEGF-C** was positively correlated with tumor status and poor clinical prognosis **[**50]. There was also a significantly increased risk for patients with **VEGF** overexpression to have an advanced stage of the disease (III and IV). Additionally, patients with VEGF overexpression had a 2.03-fold increased risk for distant metastasis and shorter overall survival [51]. In ***resectable esophageal squamous cell carcinoma*** patients, the expression of **VEGF** is a predictor of distant metastasis, overall survival, and distant metastasis-free survival. Using a combination of VEGF expression, tumor stages, and tumor cell grade, identification of patients with increased risk of postoperative metastases may become possible [52].

Gastric cancer

It was demonstrated the importance of angiogenetic factors in serum and tumor tissue in ***gastric cancer*** for prognosis and treatment response [53]. Increased expression of VEGF-C may play a significant role in the carcinogenesis and progression of gastric adenocarcinoma [54]. Moreover, VEGF-C overexpression indicates a poor prognosis for overall survival at patients with gastric cancer [55]. VEGF-A andVEGF-D are also unfavorable indicators of overall survival and disease free survivalin patients with gastric cancer [56, 57].

Colorectal cancer

In ***colorectal cancer***, the VEGF expression significantly correlated with advanced stage, unfavorable survival and an increase in the rate of invasion and distant metastases [58, 59]. Over expression of VEGFA has been associated with a high TNM stage, the degree of cell differentiation and patient death as a result of disease being a prognostic molecular biomarker for patients with resected colorectal cancer liver metastasis [60, 61]. The expression VEGF-C serves also as a significant index for evaluating the degree of malignancy, clinical stages, lymph nodes, and distant metastasis of colorectal adenocarcinoma [62, 63].

Liver cancer

VEGF-C overexpression and VEGF-C gene polymorphisms are associated with susceptibility to ***hepatocellular carcinoma***. It might be a predictive factor for advanced-stage disease [64]. **VEGF-A** is highly expressed in ***gallbladder carcinoma*** and correlates with poor prognosis, suggesting that VEGF-A expression could be used as a biomarker for predicting malignant behavior and for identifying a subset of patients who may benefit from anti-VEGF-A therapies [65]. VEGF-D plays, also, an important role in ***gallbladder cancer*** progression [66].

Pancreatic cancer

Many studies in literature show the importance of VEGF proteins family and their receptors in pancreatic tumors. Most of these evaluate the expression of VEGF using postoperative samples and mice models or the level of VEGF in blood or bile.

The pancreatic endocrine tumor is the first human tumor entity in which VEGF-C-related intratumoral lymphangiogenesis has been demonstrated. The upregulation of VEGF-C may be involved in the progression and metastases. Examination of the VEGF-C-specific receptors VEGFR-2 and VEGFR-3 demonstrated intense endothelial immunoreactivity for VEGFR-2, as well as VEGFR-2 and VEGFR-3 expression on the majority of neoplastic cells, suggesting a possible role in autocrine/paracrine neoplastic growth regulation [67, 68].

Mucinous pancreatic cysts (intraductal papillary mucinous neoplasm and mucinous cystic neoplasm) have the potential to progress to invasive pancreatic adenocarcinoma. VEGF, VEGF-A,VEGF-C, VEGFR-2 and VEGFR-3 are overexpressed in these types of tumours. Having a high sensitivity and specificity VEGF-A is a good biomarker for early detection, prevention, and cure for the serous cystic neoplasms of the pancreas [69-71].

VEGF plays an important role in the development of pancreatic cancer [72]. Compared with normal pancreas and chronic pancreatitis, **VEGF** and its receptors were overexpressed in pancreatic cancer [73]. Seo Y *et al*. demonstrated that 93% of ***ductal pancreatic adenocarcinomas*** were positive for **VEGF** protein [74]. A recent study shows a positive expression rate of VEGF 77% in pancreatic cancer tissues and 15% in adjacent normal pancreatic tissues [75]. The lymphangiogenesis can be considered an early event that enables the dissemination of metastases. VEGF expression and low lymphatic vessel density

can be considered as poor prognostic factors as tumors with this profile are fast growing and highly aggressive [76]. VEG Foverexpression was found to be associated with high microvascular density and emerged as adverse prognostic factors in terms of patient survival in pancreatic ductal adenocarcinoma [77]. The expression of VEGF is also significantly ***correlated with TNM*** stage and lymph node metastasis. VEGF may play an important role in the occurrence, development, and metastasis of pancreatic cancer [75]. Moreover, multivariate logistic regression analysis indicated a significant association between high VEGF expression and liver metastasis [74]. A recent meta-analysis revealed that the immunohistochemical expression of VEGF representing a significant and reproducible marker of adverse prognosis in ***resected pancreatic cancer*** [78], but most consistently reproducible molecular marker with prognostic value in resected pancreatic adenocarcinoma is considered to be the fibroblast activation protein [79]. *In vitro*, most pancreatic ductal carcinomas show a distinct VEGF related angiogenic potential, as demonstrated by 2- and 3-D endothelial cell proliferation, which may be promoted by severe hypoxia. Surprisingly, perinecrotic tumor areas, which are supposed to be hypoxic, only rarely showed the expected increase in microvessel density and VEGF expression [80]. ***VEGF-A*** gene locus analysis across 80 human tumour types reveals VEGF-A gene alterations were predominantly observed in hepatocarcinomas, adenocarcinomas of the pancreas and intestine, large cell carcinoma of the lung and in endometrium serous carcinoma [81]. Immunohistochemical analysis of 50 pancreatic cancer tissue samples revealed the presence of VEGF-A immunoreactivity in 50% of the cancer tissue samples. The presence of VEGF-A in these cells was associated with larger tumor size and enhanced local spread but it was not associated with decreased patient survival [82]. VEGF-A significantly increased the motility of pancreas cancer cells playing an important role in inducing invasion and migration of pancreatic cancer cells [83]. The prognosis for VEGF-A-positive patients was significantly poor [84]. UICC stage III pancreatic carcinoma patients with **VEGF165** (a type of VEGF-A) negative tumor cells had a significantly better outcome after surgery compared to UICC stage III patients with VEGF165-positive tumor cells (median survival time 19 months *vs*. 9 months respectively [85]. We can summarise that ***VEGF-A expression is an important predictor for both distant metastasis and poor prognosis*** in ductal pancreatic adenocarcinoma.

In the cancer samples, ***VEGF-C*** mRNA transcript increases approximately 2.2-fold, compared with the normal pancreas. Immunohistochemical analysis confirmed the expression of VEGF-C and its receptor (VEGFR-3) in the cancer cells within the tumor mass. VEGF-C expression was positive in approximately 80% of pancreatic cancers [86, 84]. VEGF-C was abundantly expressed in pancreatic cancer tissue and cell lines and VEGFR-3 was expressed in cancer stromal cells. These results suggest that active lymphangiogenesis is not required for lymphovascular spread of pancreatic cancer. VEGF-C may promote local tumor growth via paracrine signaling to stromal cells expressing VEGFR-3 and support the entry of cancer cells into peritumoral lymphatics [87]. VEGF-C expression was correlated with invasion of lymphatic vessels around the tumor [88]. Moreover, in human pancreatic cancer and nude mice model, the expression of VEGF-C on lymphatic metastasis was higher than in primary tumor [89]. The presence of VEGF-C in the cancer cells was associated with increased lymph node metastasis, but it was not associated with decreased patient survival [86, 82].

VEGF-D plays a pivotal role in stimulating lymphangiogenesis and lymphatic metastasis in human ductal pancreatic cancer [90]. VEGF-D expression was positive in 36% of pancreatic cancers [84]. VEGF-D expression in tumor cells in the marginal portion of the tumor significantly associated with lymphatic metastasis and prognosis in patients with pancreatic head cancer [91].

Vascular endothelial growth factor receptors are mainly expressed by endothelial cells, but they are also expressed in pancreatic cancer cells. Compared with normal pancreas and chronic pancreatitis, **VEGF receptors** were overexpressed in pancreatic cancer [73]. VEGF and its 3 principal receptors (VEGFR-1,VEGFR-2 and VEGFR-3) were expressed to varying degrees in tumors of the pancreas. Overexpression of VEGF in tumors may activate tumor cells bearing VEGFR-1 via an autocrine pathway [92]. ***VEGFR-1*** plays a role in tumor progression in pancreatic cancer through the induction of epithelial to mesenchymal transition [93]. ***VEGFR-1*** appears to be expressed ubiquitously in pancreatic carcinoma cell lines, in which it induces signaling and promotes migration and invasion. But, a significant association was

found between low expression of VEGFR-1 and both poor prognosis and advanced stage, suggesting that tumor expression of this VEGF receptor is a marker of less aggressive disease [94]. Compared to normal human pancreas, cancer tissue showed overexpression of ***VEGFR-3*** in conjunction with a high lymphatic vascularization [90]. Nevertheless, ***VEGFR-2*** is the most important receptor in evaluating the angiogenesis in pancreatic cancer. A recent study shows that VEGFR-2 were positive in 69% of pancreatic cancers. In contrast, VEGFR-1 and VEGFR-3 expression was only observed 12% and 14% of pancreatic. VEGFR-2 expression in cancer cells correlates significantly with invasion into the surrounding tissues as well as with poor prognosis of pancreatic cancer. The 5-year survival of patients with VEGFR-2-positive tumors was 0% in comparison to 21% for patients with negative tumors. A multivariate analysis showed VEGFR-2 to be an independent predictive factor of prognosis in pancreatic cancer especially at clinical stage IIA [84].

VEGF was also, recently, studied using samples collected by **endoscopic ultrasound-guided fine needle aspiration (EUS-FNA)**. A study of thirty-five patients who had undergone endoscopic ultrasonography followed by EUS-FNA of focal pancreatic masses showed that VEGF and EGFR mRNA expression in EUS-FNA samples may be used as a diagnostic marker associated with invasiveness in patients with pancreatic adenocarcinoma [95].

CONCLUSIONS

Angiogenesis is a crucial event in tumor growth process. It is regulated predominantly by several different growth factors and their associated receptor tyrosine kinases of which vascular endothelial growth factor is the most potent stimulator of endothelial cell proliferation, sprouting, migration and tube formation and it is also a powerful survival factor and a permeability factor for endothelial cells. In the field of gastroenterology, VEGF family expression has been extensively studied and its expression was correlated with: oral cancer, gingival cancer, esophageal cancer, gastric cancer, colorectal cancer, liver and gallbladder cancer. Many studies in literature show the importance of VEGF proteins family and their receptors in pancreatic tumors. VEGF family members over-expression was correlated with the presence of pancreatic adenocarcinoma, with the increase of the invasion and migration of pancreatic cancer cells, with larger tumor size , with TNM stage and lymph node metastasis, with distant metastasis and the poor prognosis of the disease. Therefore, VEGF represents a novel therapeutic target for this devastating type of cancer.

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Angiogeneza este un eveniment crucial în creşterea şi dezvoltarea tumorală şi este controlată de o serie de factori de creştere. VEGF (factorul de creştere a endoteliului vascular) este, probabil, cel mai important factor tisular, implicat în diferenţierea angioblastelor şi în formarea reţelelor vasculare. Familia proteinei VEGF cuprinde în prezent mai mulţi membri: VEGF (sau VEGF-A), VEGF-B, VEGF-C şi VEGF-D, VEGF-F, factor de creştere placentar (PlGF) şi receptorii lor VEGFR-1, VEGFR-2 şi VEGFR-3. VEGF este un factor de creştere cheie, iar expresia sa este un marker critic pentru aprecierea bolilor angiogenice. Rolul decisiv al VEGF în angiogeneza tumorală a fost descris pe larg în ultimul deceniu, acesta fiind exprimat în majoritatea tipurilor de cancere non-digestive şi digestive. Membrii familiei VEGF joacă un rol esenţial în dezvoltarea cancerului pancreatic (în special VEGF-A, VEGF-C, VEGF-D, VEGFR-1 şi VEGFR-2). Dintre aceştia, nivelurile tisulare ale VEGF-A şi ale VEGFR-2 sunt cele mai specifice şi mai evidente în ceea ce priveşte utilitatea în evaluarea angiogenezei în cancerul pancreatic. Expresia genetică crescută a VEGF poate fi, astfel, considerată un important marker diagnostic dar şi un indice de prognostic nefavorabil al patologiei neoplazice pancreatice.

Corresponding author: Madalin Ionut Costache, 11A Rovinari str., Craiova, Dolj, 200533, Romania
Tel: + 40765790960
E-mail: costache_madalin_ionut@yahoo.com

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