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Review

Septin roles in tumorigenesis

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Abstract

Septins are a family of cytoskeleton related proteins consisting of 14 members that associate and interact with actin and tubulin. From yeast to humans, septins maintain a conserved role in cytokinesis and they are also involved in a variety of other cellular functions including chromosome segregation, DNA repair, migration and apoptosis. Tumorigenesis entails major alterations in these processes. A substantial body of literature reveals that septins are overexpressed, downregulated or generate chimeric proteins with MLL in a plethora of solid tumors and in hematological malignancies. Thus, members of this gene family are emerging as key players in tumorigenesis. The analysis of septins during cancer initiation and progression is challenged by the presence of many family members and by their potential to produce numerous isoforms. However, the development and application of advanced technologies is allowing for a more detailed analysis of septins during tumorigenesis. Specifically, such applications have led to the establishment and validation of *SEPT9* as a biomarker for the early detection of colorectal cancer. This review summarizes the current knowledge on the role of septins in tumorigenesis, emphasizing their significance and supporting their use as potential biomarkers in various cancer types.

Keywords: biomarkers; cancer; cytoskeleton; epigenetics; oncogenes; septins; tumor suppressor genes.

Introduction

Septins consist of a conserved family of GTP binding proteins that assemble into filaments and are associated with various processes in dividing and non-dividing cells. Septins were first identified in the early 1970s as mutants failing to undergo cytokinesis in budding yeast (Hartwell, 1971), where they were found to assemble into filamentous structures and rings located at the neck between the mother cell and the bud. Genetic and cytological studies revealed that septin rings might function as spatial landmarks to establish and maintain cell polarity acting as diffusion barriers to segregate cortical molecules between mother and bud and as scaffolds for anchoring other proteins or higher order subcellular structures (Fares et al., 1995; Dobbelaere and Barral, 2004; Versele and Thorner, 2004). Recent data suggest that the ability of yeast septins to form filaments is essential for survival. In fact, abrogating their ability to form filaments leads to improper localization to the plasma membrane and causes cell death (McMurray et al., 2011). Currently in mammals, 14 septin orthologous genes have been identified.

Septin genes share domains that are unique to this family (Hall and Russell, 2004; Pan et al., 2007). The central GTP-binding domain is highly conserved in all human septins with 58% similarity. Between the N-terminus and GTP-binding domain is a polybasic region conserved throughout eukaryotic phylogeny that might target septins to the plasma membrane by interaction with phosphoinositides (Garcia et al., 2006). A septin unique element maps between the GTPase domain and the C-terminus. Each septin is distinguished by their specific N-terminus and C-terminus sequences where long C-termini harbor coiled-coil domains that participate in septin-septin interactions to form hetero-oligomers (Sirajuddin et al., 2007). Based on the sequence homology among mammalian septins, four distinct groups have been defined (*SEPT2*, *SEPT3*, *SEPT6* and *SEPT7*).

In mammalian cells, septins have a much broader spectrum of cellular functions compared to those observed in yeast (Barral et al., 2000; Kinoshita, 2003; Kissel et al., 2005; Spiliotis et al., 2005; Kremer et al., 2007; Tada et al., 2007; Hu et al., 2010). A key characteristic of the septin gene family is its ability to form homo- and hetero-oligomer filament complexes. Specific combinations of septin monomers can oligomerize and form filaments *in vivo* and *in vitro* (Figure 1A) by mechanisms that are not yet fully characterized. Biochemical studies have isolated at least three complexes: *SEPT4/5/8* (Martinez et al., 2004), *SEPT7/9b/11* (Nagata et al., 2004) and *SEPT2/6/7* (Kinoshita et al., 2002; Sheffield et al., 2003; Low and Macara, 2006). The *SEPT2/6/7* complex has been characterized using X-ray crystallography and electron microscopy (Sirajuddin et al., 2007). This study revealed that a bipolar polymer building block containing a G domain forms filaments by generating interactions between nucleotide binding sites and/or the amino- and

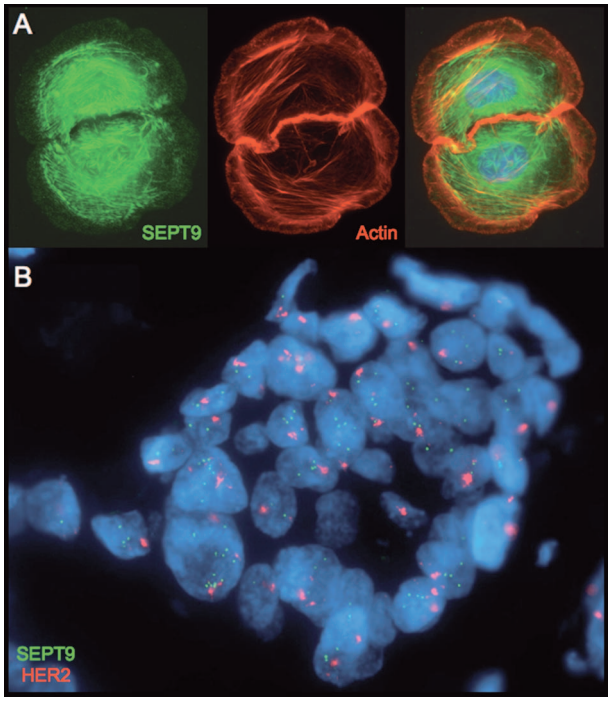


Figure 1 SEPT9 filaments and genomic amplification in breast cancer cells.
(A) Actin (red) and SEPT9 (green) filaments in SKBR3 cells. (B) Genomic amplification of the *SEPT9* locus (green) and *HER2* (red) observed in Ductal Carcinoma *in situ* in a human breast cancer patient.

carboxy-terminal extensions, whereas the predicted coiled coils have been shown to be unnecessary for complex and filament formation. An emerging feature of some septins are their intricate expression profiles of isoform variants (McDade et al., 2007) such as the one observed at the 17q25.3 genomic locus of *SEPT9*, which can express multiple isoform variants.

Because septins have been shown to maintain multiple roles in fundamental biological functions, it is not surprising that deregulation of members of this family has been found in a variety of tumors. However, due to the complexity of septin interactions and the lack of knowledge pertaining to the mechanisms by which they function, this field of investigation is only in its preliminary stages of development. In this review we summarize the body of literature that links septins to hematological malignancies and solid tumors with emphasis on the possible mechanisms that result in tumor promoting or tumor inhibiting properties.

Septins: oncogenes or tumor suppressor genes?

Numerous studies have found septins to be important in tumors of various tissue origin (summarized in Table 1). Findings in hematological malignancies where septins were found fused to the *mixed lineage leukemia (MLL)* gene (Megonigal et al., 1998; Osaka et al., 1999) provided the first link between septins and oncogenic function. The mechanisms by which chimeric proteins fuse to MLL and acquire tumor transforming properties remain largely unknown (Martens and Stunnenberg, 2010) but it is recognized that translocations leading to the formation of fusion proteins occurs with fusion partners that carry oncogenic properties. Fusion partners of *MLL* include transcription factors and genes that are mainly cytoplasmic and frequently associated with cytoskeleton dependent signal transduction (Zeisig et al., 2003). The implication of septins in hematological malignancies will be discussed in further detail in the next section.

At first glance, Table 1 would suggest that septins are altered in tumorigenesis as a consequence of genomic amplification (Figure 1B) or overexpression. This implies a gain of function and is consistent with acquiring oncogenic activity but we must also consider a loss of septin function, which can lead to improper cell division. Due to their essential role in cytokinesis and their requirement for complete cell division the main hypothesis for a tumor promoting function of septins is based on possible mechanisms that result in perturbation of cell division (Russell and Hall, 2005). SEPT2 localizes to the metaphase plate during mitosis and appears to have a critical role in controlling the proper attachment of chromosomes to the mitotic spindle by interacting with the checkpoint regulator centromere associated protein E (CENP-E) (Spiliotis et al., 2005; Zhu et al., 2008). This observation suggests that improper septin expression resulting in a loss of function in cytokinesis could potentially have deleterious consequences for the cell. Such consequences include chromosome mis-segregation, which can ultimately result in aneuploidy, a feature of cancer cells.

Several septins such as ARTS (apoptosis-related protein in the TGF-beta signaling pathway, the short isoform splice variant *SEPT4_v2*), *SEPT9* and *SEPT11* could possess tumor suppressor functionality. ARTS demonstrates unique proapoptotic activity and the ability to bind Inhibitor of Apoptosis Proteins (IAPs) (Larisch et al., 2000). Expression of ARTS is frequently lost in human leukemia (Elhasid et al., 2004) and the loss of *Sept4* function in mice promotes spontaneous leukemia or lymphoma (Garcia-Fernandez et al. 2010). These data support a tumor suppressor function for ARTS and raise the possibility of a dual function of tumor suppression and oncogenic activity for various members of the family.

The *SEPT9* gene has very unique characteristics and has been shown to act as an oncogene although tumor suppressor properties have been reported. *SEPT9* was first mapped to a region of loss of heterozygosity (LOH) in breast and ovarian tumors (Kalikin et al., 1996, 1997, 2000; Russell et al., 2000). Subsequently by retroviral insertion mutagenesis, a powerful tool for the identification of novel oncogenes (Uren et al., 2005), it was shown that *SEPT9* is a putative proto-oncogene involved in T-cell lymphomagenesis in mice (Sorensen et al., 2002; Suzuki et al., 2002). Soon after this discovery we reported that genomic amplification resulting in overexpression occurs in murine models for breast cancer

Table 1 Septin family members and their link to cancer.

Gene	Oncogenic function	Tumor suppressor function	Tumor type	References
SEPT1	Overexpression		Oral cancer	(Kato et al., 2007)
SEPT2	Overexpression		Brain	(Sakai et al., 2002; Kim et al., 2004; Khalil, 2007; Kumar et al., 2008)
	Gene fusion		AML	(Cerveira et al., 2006; van Binsbergen et al., 2007)
	Overexpression		Kidney	(Craven et al., 2006a,b)
		Downregulation	Glioma	(Khalil, 2007)
SEPT3	Overexpression		Medulloblastoma/ teratocarcinoma	(Methner et al., 2001; Kim et al., 2004)
SEPT4	Overexpression		Prostate cancer, renal cell carcinoma and bladder cancer	(Tanaka et al., 2003)
ARTS	Overexpression	Knockout mice Downregulation	Astrocytoma, leukemia	(Gottfried et al., 2004; Garcia-Fernandez et al., 2010), (Elhasid et al., 2004)
SEPT5	Overexpression		Pancreas	(Capurso et al., 2005)
	Gene fusion		AML	(Megonigal et al., 1998; Tatsumi et al., 2001; Santos et al., 2010a)
SEPT6	Gene fusion		AML	(Ono et al., 2002; Kadkol et al., 2006; Cerveira et al., 2008)
			Melanoma	(Jaeger et al., 2007)
SEPT7		Downregulation	Glioma	(Nagata et al., 2000; Jiang, 2002; Jiang, 2004; Jia et al., 2010; Tanaka et al., 2010)
SEPT8	None	None		None
SEPT9	Amplification/ overexpression		Breast	(Montagna et al., 2003; Scott et al., 2005; Gonzalez et al., 2007, 2009)
	Upregulation		Ovary	
	Gene fusion		AML, ALL	(Strehl et al., 2006; Gulten et al., 2009; Saito et al., 2010) (Santos et al., 2010a,b)
				(Osaka et al., 1999; Yamamoto et al., 2002; Strehl et al., 2006; Kreuziger et al., 2007)
		Hypermethylation	Colon and head and neck	(He et al., 2010; Tierling et al., 2010; Quyun et al., 2010) (Grutzmann et al., 2008; deVos et al., 2009) (Bennett et al., 2008; Lofton-Day et al., 2008; Stanbery et al., 2010)
		Deletion	Ovary, breast	(Kalikin et al., 2000; Russell et al., 2000)
			Hodgkin lymphoma	(Giefing et al., 2008)
SEPT10	None	None		
SEPT11	Gene fusion	Deletion	AML	(Santos et al., 2010b; Stevens et al., 2010)
		Deletion	Liver	(Huang et al., 2010)
SEPT12	None	None		
SEPT13	None	None		
SEPT14	None	None		

(Montagna et al., 2003) and the Russell group established that *SEPT9* overexpression occurs in various human tumors (Scott et al., 2005). The discovery of DNA hypermethylation at the promoter region of *SEPT9* in colorectal (deVos et al., 2009) and head and neck cancer patients (Bennett et al., 2008) complicated the conflicting data supporting this gene as either a tumor promoter or suppressor. Changes in human DNA methylation patterns are a major event in cancer initiation and progression (Esteller, 2008). Promoter hypermethylation of tumor suppressor genes is a hallmark of the cancer genome (Jones and Baylin, 2007) as it serves as one of the epigenetic mechanisms used to deregulate tumor suppressor gene activity. Based on the general assumption that hypermethylation can regulate tumor suppressor activity *via* gene silencing, one could speculate that *SEPT9* also maintains tumor suppressor functions.

Table 2 Known MLL fusion partners and their cellular functions (adapted from Krivtsov and Armstrong, 2007).

Group	% of all MLL rearrangements
Nuclear proteins	
AF4	>80%
AF9	
ENL	
AF10	
ELL	
Cytoplasm proteins	
EPS15	>10%
GAS7	
EEN	
AF6	
AFX	
Septin family	
SEPT2	>1%
SEPT5	
SEPT6	
SEPT9	
SEPT11	
Histone acetyltransferases	
CBP	>1%
P300	
MLL tandem duplication of exons 5–11	4–7%

It is clear that the mechanisms by which septin genes operate to promote or inhibit tumorigenesis cannot be oversimplified. Tumors that originate in different tissues might be affected by septin deregulation at various levels; alternatively, gene members of the septin family could simply interact with different partners and have various functions in different cell types. The fact that there are multiple septin isoforms raises the additional possibility that variants of these genes serve different if not opposite cellular functions. In the following sections we will outline implications of septins in various tumor types with a particular emphasis on their tumor suppressor and tumor promoting activity.

The role of septins in hematological malignancies

The first evidence for the involvement of septins in tumorigenesis came from studies of hematological malignancies (Megonigal et al., 1998; Osaka et al., 1999) where several members of the septin family were shown to fuse to *MLL*: *SEPT2, SEPT5, SEPT6, SEPT9* and *SEPT11*. The spectrum of diseases resulting from *MLL* rearrangements with septin genes includes acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) and acute lymphoblastic leukemia (ALL). In these tumors a gene fusion is generated by a chromosomal translocation, a frequent event in leukemias (Rabbitts, 1994; Look, 1997), where the most common breakpoint maps to 11q23, the genomic locus of *MLL* (Heim et al., 1987; Rowley, 1998). More than 50 different MLL fusion partners have been described (Ayton and Cleary, 2001) and they can be divided into five major groups: nuclear proteins, cytoplasmic proteins, the septin group, histone acetyltransferases and tandem duplications (Krivtsov and Armstrong, 2007, Table 2). The septin group accounts for approximately 1% of all MLL fusions observed and represents the protein family most frequently involved in MLL fusion events, suggesting that this phenomenon is anything but a random event. The mechanism by which *MLL* induces leukemogenesis has not been fully elucidated but the leading hypothesis implies that deregulation of *MLL* transcriptional activity results in the activation of genes of the *HOX* family and other crucial targets for cell differentiation (Krivtsov and Armstrong, 2007). The role that the fusion partners play in leukemogenesis is also unclear. It is highly debated whether fusion partners of MLL simply stabilize the chimeric protein or actively participate in tumor transforming events providing unique cellular functions. Nonetheless, truncation of *MLL* at the breakpoint resulting from translocation does not lead to the development of leukemia in mice, suggesting that the presence of a fusion partner is required for transformation (Corral et al., 1996).

In the septin group (Table 2), MLL-septin chimeric proteins always fuse to the septin N-terminal end and contain most of the septin sequence including the GTP-binding domain. Therefore, the generation of chimeric MLL-septin

Table 3 *MLL-SEPTIN 9* fusions and known break points.

MLL-SEPT9 fusion references	Breakpoint on *MLL*	Breakpoint on *SEPT9*
(Saito et al., 2010)	Exon 8	Exon 2
	Exon 9	Exon 2
(Gulten et al., 2009)	Not reported	Not reported
(Santos et al., 2010a)	Not reported	Not reported
(Santos et al., 2010b) coexistance	Exon 8	Exon 2
	Exon 8	Exon 3
(Kreuziger et al., 2007)	Exon 7	Exon 2
(Strehl et al., 2006)	Exon 8	Exon 2
	Exon 8	Exon 3
	Exon 7	Exon 2
(Yamamoto et al., 2002)	Exon 5	Exon 3
(Osaka et al., 1999)	Exon 8	Exon 3

proteins might disrupt septin-septin interactions and filament formation, enhancing MLL oligomerization (So et al., 2003; So and Cleary, 2004). Supporting this mechanism of transformation is that MLL fusion constructs resembling those found in human leukemia that always localize to the nucleus even when the fusion partner is a cytoplasmic protein (Yano et al., 1997; Dimartino and Cleary, 1999), affecting septin cellular interactions. Alternatively, the highly conserved septin GTP-binding motif might be crucial for transformation upon interaction with MLL. Despite these observations we cannot conclude the exact mechanisms by which the fusions between septins and MLL lead to leukemia.

MLL-SEPT9 fusion proteins are of particular interest because they support a significant role for SEPT9 in tumorigenesis of solid tumors. This member of the septin family is characterized by a large number of isoform splice variants including both amino and carboxyl variants (McIlhatton et al., 2001). The fusion proteins that have been reported so far (summarized in Table 3) result in the loss of exons one and two (Kreuziger et al., 2007). The outcome of these rearrangements is the loss of the variable region at the N-terminus of the protein that characterizes SEPT9 isoforms _v1 and _v2. Interestingly, although the function of SEPT9 isoform variants in tumorigenesis remains largely unknown, the evidence supporting an oncogenic role for _v1 seems quite compelling (Gonzalez et al., 2007; Amir et al., 2010). It is intriguing that the MLL fusion proteins lose the genomic region responsible for the genetic variation of the SEPT9_v1 isoform, which seems to be required for its oncogenic properties in solid tumors.

Additional speculations on the function of septins in leukemogenesis can be drawn from studies aiming to dissect the role of the MLL-SEPT6 fusion. Three separate studies report cases of pediatric AML patients carrying the MLL-SEPT6 fusion (Ono et al., 2002, Kadkol et al., 2006, Cerveira et al., 2008). Murine knockout models for *Sept6* alone do not exhibit a morphological phenotype and do not develop tumors (Ono et al., 2005). Thus, it is unclear if MLL-SEPT6 fusions are sufficient to promote tumorigenesis even though cases involving SEPT6 are quite rare. Translocations between MLL and SEPT11 have also been reported (Stevens et al., 2010), but their molecular and functional characterization has not been performed.

In conclusion, the exact function of MLL-SEPT fusions in both leukemogenesis and at the molecular level remains undefined. Comprehensive studies focused on the detailed mapping of septin breakpoints and the functional consequences of the rearrangement in *in vivo* models are required to understand the contribution of septins in hematological malignancies.

Septins and solid tumors

Although it has been established that septin filaments control basic and essential processes for cytokinesis and cell motility (Chacko et al., 2005; Tooley et al., 2009; Estey et al., 2010; Kim et al., 2010), their function in normal cells and the mechanisms by which they organize into heteropolymers and perform complex cellular functions remains largely unknown. It is therefore not surprising that deregulation of members of this gene family have been associated with a variety of solid tumors. Different septins are expressed at various levels in different tissues (Table 4). To date, septins have been found to exhibit altered expression or cellular localization in hormonally regulated tumors such as prostate (Amir et al., 2010), ovary (Burrows et al., 2003) and breast (Montagna et al., 2003; Gonzalez et al., 2007). The deregulation of septins has also been reported in oral/head and neck cancer (Kato et al., 2007; Bennett et al., 2008; Stanbery et al., 2010), melanoma (Jaeger et al., 2007), renal cell carcinoma (Craven et al., 2006a,b), gastrointestinal carcinoma (Kang et al., 2006), pancreatic tumors (Capurso et al., 2005) and hepatocellular carcinoma (Huang et al., 2010; Kakehashi et al., 2010).

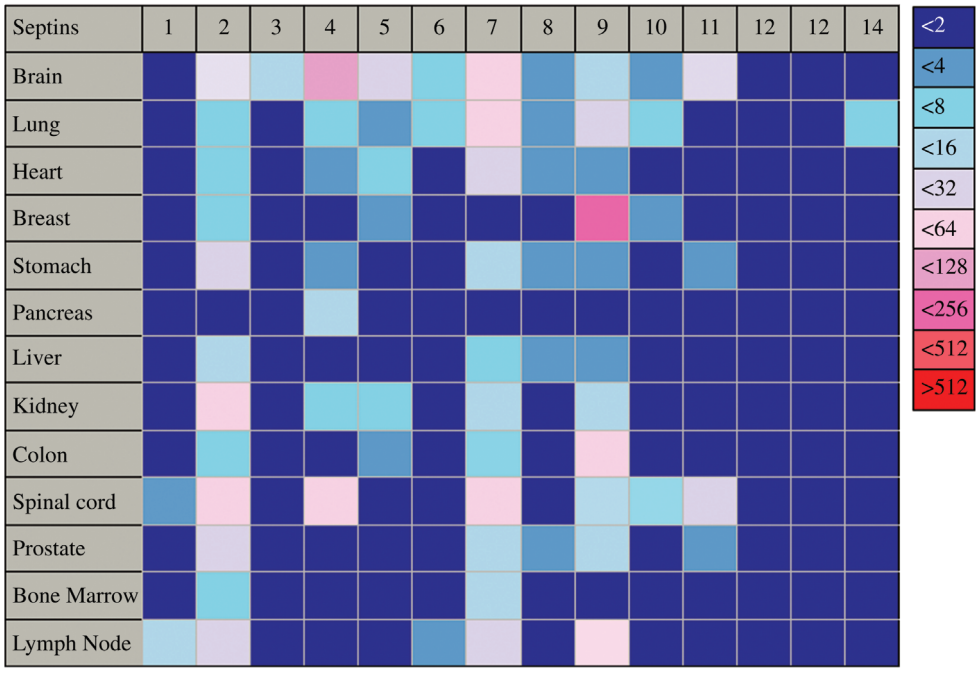
Hormonally regulated carcinomas and septins (prostate, ovarian and breast)

Several types of cancer have been correlated with hormonal regulation. Breast, ovarian and prostate cancer development may depend on the level of estrogen/androgens present in the body, or their receptor status in tumor cells. Such steroid hormones, in addition to signaling proteins, can modulate positive and negative regulators for the angiogenic switch in tumors. During tumorigenesis this angiogenic switch is frequently turned on enabling tumors to become progressively and increasingly vascularized by causing normal quiescent vasculature to develop new blood vessels (Hanahan and Folkman, 1996).

The hypoxia-inducible factor 1α subunit (HIF-1α) of the HIF-1 pathway is a transcription factor that is actively expressed in a hypoxic environment such as that of a solid tumor, whereas in a normal cell with normoxic conditions HIF-1α is typically hydroxylated and targeted for degradation. The increased and active expression of HIF-1α regulates the transcription of downstream target genes such as vascular endothelial growth factor A, which can help cells adapt to or survive in a stressful microenvironment, by increasing angiogenesis (Brahimi-Horn et al., 2007; Brahimi-Horn and Pouyssegur, 2007).

Several findings have indicated an underlying involvement of septins in hormonally regulated cancers. Breast, ovarian and endometrial cancers were first observed to exhibit overexpression of *SEPT9* mRNA in a microarray analysis looking at a large cohort of human tissue samples consisting of normal, non-tumor diseased and tumors (Scott et al., 2005). In addition, *SEPT9* has also been shown to be involved in prostate cancer, where the *SEPT9_v1* isoform is highly expressed in cancer samples compared to normal tissue. Specifically, SEPT9_v1 was found to bind and colocalize with HIF-1α in the nucleus of PC-3 prostate cancer cells (Amir et al., 2006). The overexpression of SEPT9_v1 both *in vitro* and *in vivo* is associated with increased transcriptional activity of the HIF-1α pathway by inhibiting the direct binding of receptor of activated protein kinase C1 (RACK1), the protein responsible for HIF-1α degradation, thus promoting its

Table 4 Expression levels of septin family members in a variety of human tissues.



Color Code indicates mRNA tags per 200 000. Data adapted from the SAGE anatomic viewer (tissue only) (Wheeler et al., 2000, 2001).

stabilization (Amir et al., 2009). The interaction of overexpressed SEPT9_v1 with HIF-1α in prostate cancer results in increased cell proliferation and tumor angiogenesis, whereas the knockdown of *SEPT9_v1* is associated with an increase in HIF-1α degradation, a decrease in HIF-1 transcriptional activity, cell proliferation and angiogenesis. Collectively, these findings suggest and support a significant role of this interaction in prostate tumor progression (Amir et al., 2006, 2010).

It has been established that HIF-1α is overexpressed in primary prostate cancers compared to normal prostate epithelium and that its upregulation is an early event in prostate carcinogenesis (Zhong et al., 1999, 2004). The use of the Transgenic Adenocarcinoma Mouse Prostate model for prostate cancer has further supported that HIF-1α overexpression in prostate tumorigenesis is an early event and acts as an angiogenic switch for tumorigenesis in the prostate (Huss et al., 2001; Kimbro and Simons, 2006) but how is it regulated?

In the past decade, many studies have shown a strong correlation between androgens and the modulation of HIF-1α in human prostate cancer where activated androgen receptors can interact with HIF-1 and in turn activate HIF-1 dependent gene expression (Mabjeesh et al., 2003; Sheflin et al., 2004; Boddy et al., 2005; Kimbro and Simons, 2006; Horii et al., 2007). Above we described that SEPT9_v1 plays a role in HIF-1α activation, so how do hormones, SEPT9 and HIF-1α all result in a tumorigenic phenotype? The gene fusion between the transmembrane protease serine 2 (TMPRSS2) and the v-ets erythroblastosis virus E26 oncogene (ERG) is found in a majority of prostate cancers and is associated with a more aggressive clinical phenotype relative to other prostate cancers (Demichelis and Rubin, 2007; Nam et al., 2007; Attard et al., 2008). Multiple studies have revealed that *SEPT9* is upregulated in tumors containing this chromosomal fusion (Setlur et al., 2008; Barwick et al., 2010). Of heightened interest was that Setlurs group also indicated that the TMPRSS2-ERG oncogene could be regulated by estrogen receptor (ER) dependent pathways, with ERα agonists stimulating its expression in this distinct class of prostate cancer. As Amir et al. (2009) mentioned, the SEPT9_v1 activation of HIF-1α in prostate tumorigenesis could be a downstream effect of the TMPRSS2-ERG fusion, all regulated by ER signaling.

In addition to prostate cancer, HIF-1α was also found to be overexpressed in breast and ovarian tumors compared to normal tissue, indicating that it might be an important transcription factor in these cancers (Zhong et al., 1999). Coincidentally, *SEPT9*, or at least one of its isoforms, has also been shown to be upregulated in these cancers (Burrows et al., 2003; Montagna et al., 2003; Scott et al., 2005, 2006; Gonzalez et al., 2007; Table 5). Altered expression of additional septin family members in breast and ovarian cancer has been recently reported. S*EPT4* was found to be significantly downregulated in five year relapsing estrogen positive breast carcinoma patients compared to patients with no relapse (Liu et al., 2010). This observation introduces a possible relationship between septin expression in the breast and ER signaling, as proposed with prostate cancer, thereby implying that hormones could potentially regulate septins

Table 5 Septin 9 overexpression in hormonally regulated cancers.

SEPT9 gene/isoform	Sample type	References
SEPT9	Mouse mammary gland adenocarcinomas; human breast cancer cell lines	(Montagna et al., 2003)
SEPT9 *SEPT9_v1*	Human breast cancer cell lines and breast tumors	(Gonzalez et al., 2007)
*SEPT9_v4**	Human ovarian tumors and ovarian tumor cell lines	(Burrows et al., 2003)
SEPT9 *SEPT9_v1* *SEPT9 v4**	Human ovarian tumors	(Scott et al., 2006)
SEPT9	Human tumors including breast and ovarian	(Scott et al., 2005)
SEPT9_v1	Prostate cancer cell lines and xenografts	(Amir et al., 2006)

and their cellular interactions and expression in cancer. However, despite the intriguing speculation of a connection between ER signaling and septin expression, a clear link has not yet been established.

Brain, liver, melanoma, head and neck, gastrointestinal and pancreatic cancers

During interphase of mitotically active and proliferating cells, septins form oligomers that assemble into filaments with the appearance of an array interacting and partially colocalizing with F-actin and microtubules (Nagata et al., 2003; Figure 1A). At the onset of mitosis, septin filaments disassemble and present a cytosolic diffuse pattern of expression in prophase. During anaphase, septins accumulate at the cleavage furrow where they aid in abscission of daughter cells (Estey et al., 2010). Knockdown of various septin genes in actively dividing cells results in multinucleated cells, cells that fail to properly carry out and complete cytokinesis and improper attachment of chromosomes to the spindle (Kinoshita et al., 1997; Nagata et al., 2003; Spiliotis et al., 2005; Estey et al., 2010). Based on these observations, it is tempting to speculate that the main mechanism by which altered gene expression leads to tumorigenesis is through septin downregulation or deletion, resulting in impairment of cell division leading to polyploidy or aneuploidy.

Despite these observations, few studies report loss of septin function or expression, with *SEPT9* in the breast and colon (Kalikin et al., 1997; Russell et al., 2000; Grutzmann et al., 2008), and *SEPT11* in hepatocellular carcinomas where patients with LOH of *SEPT11* have significantly lower survival than patients that do not show LOH (Huang et al., 2010).

The majority of cases have reported septins to be amplified and overexpressed in multiple cancers: *SEPT9* in breast cancer (Figure 1B) (Montagna et al., 2003; Gonzalez et al., 2007, 2009), ovarian carcinoma (Scott et al., 2006) and head and neck cancer (Stanbery et al., 2010); *SEPT1* in oral squamous cell carcinomas (Kato et al., 2007); *SEPT6* upregulation in invasive melanoma cell lines and metastasis (Kim et al., 2004; Jaeger et al., 2007); *SEPT2* overexpression and alteration of isoform expression in addition to overexpression of *SEPT11* in Von Hippel-Lindau (VHL) defective renal carcinoma cell lines and in renal cancer patients (Craven et al., 2006a,b); overexpression of *SEPT8* in gastrointestinal tumors carrying KIT mutations (Kang et al., 2006); overexpression of *Sept9* in rat hepatocellular carcinomas (Kakehashi et al., 2010).

How do we reconcile that septins are mainly upregulated in solid tumors with the evidence that the knockdown of septins might lead to aneuploidy? More in depth studies to broaden our knowledge of the mechanisms of septin function are required to answer this question but analysis of *SEPT9* implies that understanding the unique properties of various isoforms will be essential in determining the role in tumorigenesis. The most highly investigated of these isoforms is *SEPT9_v1*, whose overexpression in breast cancer cell lines leads to accelerated growth kinetics, increased cell motility and promoted invasion (Gonzalez et al., 2007). A working model for the increase in proliferation upon *SEPT9_v1* overexpression is that its potential binding to c-Jun N-terminal kinases leads to the transcriptional activation of proliferative pathways (Gonzalez et al., 2009). Less investigated are the mechanisms that link septin overexpression to increased migration; however, this function is most likely connected to the septins association with the microtubule and actin cytoskeleton (Surka et al., 2002; Nagata et al., 2003, 2004). Recently SEPT9 was found enriched in pseudopodes isolated from metastatic cancer cell lines and its downregulation induced a mesenchymal-epithelial transition (Shankar et al., 2010); however, the specific isoform leading to this phenomena was not characterized. Finally, the well established function of septins in maintaining cell polarity has been widely investigated in yeast and further supports an additional role for septins in tumorigenesis (Oh and Bi, 2011). Loss of cell-cell adhesion and cell polarity is commonly observed in tumors of epithelial origin and correlates with their invasion into adjacent tissues and formation of metastases. It remains unclear if septins play a functional role in epithelial polarity but SEPT2 appears to be required for efficient Golgi to plasma membrane transport and the morphogenesis of columnar shaped epithelial cells (Spiliotis et al., 2008).

Septins are not only expressed in highly proliferative tissues but also in the central nervous system, including neurons and glial cells (Kinoshita et al., 1998, 2000; Xue et al., 2004). They have been implicated in the process of exocytosis (Hsu et al., 1998; Beites et al., 2005; Son et al., 2005),

migration of neurons from the ventricular zone to the cortical plate (Shinoda et al., 2010) and in the formation of dendrite branching (Walikonis et al., 2000; Tada et al., 2007; Xie et al., 2007). Additionally, Septin 2, 3, 4, 5, 6, 7, 8, 9, 10 and 11 are all expressed in the brain making it the tissue with the widest expression of septin family members (Table 4).

Dendrite branching and spine formation determines the function of morphologically distinct and specialized neuronal subclasses. However, little is known about the programs leading to branching patterns in neurons. Sept7 is expressed at the base of dendritic protrusions in neurons and its overexpression results in increased branching, whereas knockdown led to reduced dendrite arborization and a greater proportion of immature protrusions (Tada et al., 2007). These data suggest that Sept7 is critical for spine morphogenesis and dendrite development during neuronal maturation. Kinoshita's group fine-mapped the localization of septins in the mouse brain (Kinoshita et al., 2000) where expression analysis of Sept5 (CDCrel-1), Sept6, Sept7 (CDC10) and Sept4 (H5) showed that Sept4 and Sept7 are strongly expressed in the Bergmann's glia with a very similar pattern of expression. This is particularly relevant because most brain tumors develop from cancerous glial cells (gliomas). SEPT7 is downregulated at the mRNA and protein levels in gliomas and its decreased expression negatively correlates with increased tumor grade. Overexpression of SEPT7 inhibits cell proliferation and arrests cell cycle progression in the G0/G1 phase both *in vitro* and *in vivo*. Complete depletion of Sept7 in glioma xenografts results in faster tumor growth compared with control tumors (Jia et al., 2010). SEPT2 is downregulated in gliomas (Khalil, 2007), whereas SEPT3 was reported to be upregulated in teratocarcinoma cells induced to undergo neuronal differentiation (Methner et al., 2001).

Septins as biomarkers

A biomarker can be defined as a predictive tool used for the detection and diagnosis of a disease, as a predictor of prognosis or as an indicator for targeted treatment therapy. Overall, when used in clinical practice, a biomarker must essentially improve the life expectancy or quality of life of a patient (Newton et al., 2010). Epigenetic events such as DNA methylation associated with cancer development and progression have recently become examples of such highly informative markers (Rodriguez-Paredes and Esteller, 2011). Decades ago, it was discovered that a high concentration of cell free circulating DNA (cfcDNA) from solid malignant tumors can be released into the blood and measured (Leon et al., 1977). Comparing the methylation pattern of cfcDNA from the blood of cancer patients to methylation patterns in non-malignant disease has enabled the identification of tumor specific changes and can therefore be used as a biomarker for many cancer types (Levenson, 2010). Colorectal cancer (CRC) is the third leading cause of cancer related deaths in the United States and over the past twenty years the death rate from this disease has been constantly declining. This is mainly due to the improvement of available diagnostic tools; accordingly, significant effort has been placed on the development of novel biomarkers for early detection.

In a study designed to identify potential blood-based epigenetic biomarkers for the early detection of colorectal cancer, it was found that plasma samples from colon cancer patients exhibited significantly high concentrations of methylated *SEPT9* DNA compared to other candidate markers. Specifically, methylation of *SEPT9_v2* demonstrated a sensitivity of 69% with a specificity of 86% for the detection of CRC in plasma samples (Lofton-Day et al., 2008). This finding was later validated in two independent case controlled studies: a training and a test series, with an overall reported sensitivity of 72% and specificity of 90% (Grutzmann et al., 2008). Collectively, these studies show that methylation of CpG sites in the *SEPT9_v2* promoter region is highly detectable in plasma from colorectal cancer patients and support its current and future use as a biomarker.

The *SEPT9* test had several limiting factors. Initially, the assays performance was affected by sporadic PCR inhibition during routine quality control (Grutzman et al., 2008). Additional issues typically associated with biomarker development and implementation also prevented the clinical use of the assay including adaptability for standard laboratory use, throughput, automation and cost. Therefore, a modified *SEPT9* assay retaining the performance presented in previous studies with an overall sensitivity of 70% and specificity of 91% across two independent case controlled studies has been developed to overcome these concerns. This group has reported the elimination of PCR inhibition, simplified and accelerated handling procedures, improved throughput, added automation potential and reduced costs (deVos et al., 2009). Although these issues appear to be resolved, the fact that specificity is only 91% implies that 9% of patients tested will be misdiagnosed and most likely need to undergo an unnecessary colonoscopy.

In heterogeneous diseases such as CRC, the detection of a single biomarker will most likely have less sensitivity compared to several markers used in conjunction. A test that incorporates multiple biomarkers achieves a better balance between sensitivity and specificity, as demonstrated by the multiplex MethyLight assay for the simultaneous detection of methylated genes in human CRC. This particular assay was able to detect and quantify the methylated DNA extracted from both tumor tissues and peripheral blood plasma for the genes *SEPT9*, *ALX4* and *TMEFF2*; each of which have previously been shown to be specifically methylated in CRC (He et al., 2010). Using similar methodology, the combined analysis of two of these methylated markers, *SEPT9* and *ALX4*, was capable of detecting advanced precancerous colorectal lesions (Tanzer et al., 2010). Not only do these studies further exemplify the significance of *SEPT*9 methylation status in distinguishing between cancer and non cancer samples but they also demonstrate that such highly sensitive techniques are paving the way for large scale non-invasive blood testing for early stage CRC.

To correlate the methylation profile of *SEPT9* with its expression Toth et al. measured mRNA and protein levels in

the different stages of colorectal cancer (adenoma-dysplasia-carcinoma, Toth et al., 2011). SEPT9 protein levels were found to decrease with increasing stages of tumorigenesis, corresponding to a possible increase in methylation levels. Moreover, demethylation of the HT29 colorectal adenocarcinoma grade II cell line with 5-aza-2-deoxycytidine (a DNA de-methylating agent) resulted in increased *SEPT9* mRNA and protein expression. This suggests that the increasing methylation of *SEPT9* during colorectal cancer progression is a mechanism responsible for decreasing mRNA and protein expression and its ability to be reversed by DNA methylation inhibitors makes *SEPT9* an ideal therapeutic target (Toth et al., 2011).

A genome-wide screen for promoter methylation status identified *SEPT9* to also be commonly methylated in head and neck squamous cell carcinomas. The methylation levels observed in these tumors did not significantly correspond to a decrease in mRNA expression levels in tumor samples compared to adjacent normal tissue (Bennett et al., 2008). Due to the ability of *SEPT9* to generate multiple transcripts, a limitation associated with these results is that methylation and expression analysis of *SEPT9* in tumors should be targeted to isoform specific levels instead of the entire gene. To address this concern a follow up study looking specifically at the expression of the SEPT9_v1 isoform was performed. Immunohistochemical analysis on tissue microarrays using an antibody specific to SEPT9_v1 indicated that this specific isoform is highly expressed in head and neck squamous cell carcinomas (HNSCC) compared to normal epithelium and furthermore the high expression levels correlate with poor clinical outcome and increasing stage. Interestingly, patients with high SEPT9_v1 expression show a poor response to chemotherapy compared to those with low expression, which in turn might relate to the poor outcome in patients with high SEPT9_v1 (Stanbery et al., 2010). These findings propose that SEPT9, primarily isoform _v1, could be utilized as a specific biomarker for HNSCC in addition to CRC.

Perspectives

Collectively septin expression status is altered in a wide range of human cancers, suggesting a highly significant and pivotal role in tumorigenesis. Although there are still many questions to be answered about septin cellular functions, it is clear that they sustain unique functions in various tissues, but is their altered expression a cause or consequence of tumorigenesis?

In hematological malignancies, the exact role of the MLL-septin fusion has yet to be defined, but it is unlikely that analysis of the fusion alone is sufficient to explain the specific functions of septins. Because of the technical challenge in visualizing the cytoskeletal network of cells in suspension, it is difficult to study the localization of non-fused septins in these cancer cells. However, the analysis of their expression levels and post-translational modifications is indeed feasible and may provide a basis for functional studies.

The role of septins in migration in relation to tumor metastasis and invasion, as illustrated by preliminary data on SEPT9 (Chacko et al., 2005; Gonzalez et al., 2007; Connolly et al., 2011), will require detailed functional analysis to establish the molecular mechanisms involved in this process including further investigation of the septin interactome in normal and cancer cells. Although septin localization along actin microfilaments and microtubules has been observed by several laboratories (Surka et al., 2002; Nagata et al., 2003; Spiliotis et al., 2005) little is known about its link to pro-migratory functions.

Potential specific functions of septins in early phases of cytokinesis or in the control of chromosome segregation (Spiliotis et al., 2005) and specifically SEPT9 in abscission (Estey et al., 2010) raise the question of how altered septin expression may induce genetic instability. Although these effects are a consequence of septin downregulation, it has also been suggested that septin overexpression could result in aberrant chromosome segregation (Gonzalez et al., 2007).

More broadly, there are still fundamental questions that remain unanswered: (i) what is the degree of redundancy of septin functions and what is their potential impact in tumor development? (ii) is there a distinct population of septin complexes with differential localization and dynamics? In respect to potential differences between septin isoforms, such as those observed for SEPT9, it appears that SEPT9_v1 has oncogenic properties compared to SEPT9_v3 or SEPT9_v4 but it is unknown how this relates to their respective levels of expression in tumors and to DNA methylation of CpG islands at the 17q25.3 locus. Ultimately, does the overexpression of SEPT9_v1 and/or downregulation of the other isoforms end up having similar tumorigenic effects?

For these reasons, it is extremely likely that some, if not each of the septin family members and/or their isoforms might prove to be useful biomarkers in cancer. In this regard *SEPT9* is the most thoroughly investigated candidate gene. DNA methylation affecting septin expression was first suggested during a study of *SEPT9* in ovarian cancer where expression of the *SEPT9_v4* transcript had little to no expression in a subset of the cancer cell lines analyzed, but could be re-expressed upon treatment of the cells with 5-azacytidine (Burrows et al., 2003). More recently, DNA hypermethylation of the *SEPT9* genomic locus in cancer patients has been identified in genome wide studies designed to discover biomarkers for colorectal cancer patients. The approach used unbiased genomic technologies and proposed *SEPT9* as a top candidate that was quickly tested in clinical trials and has been currently licensed to Abbot Molecular as an *In Vitro* Diagnostic Medical Device in the European market (Molecular Abbot, RealTime mS9 test).

This step represents a landmark for the development of septins as biomarkers. However, a few considerations need to be taken into account, such as the aforementioned issue concerning a specificity of only 91% leading to approximately 9% of misdiagnosed patients that will undergo unnecessary colonoscopy. Genome wide approaches for the identification of differentially methylated regions (DMRs) between tumors and non tumorigenic tissues are very

powerful for mapping regions of interest, yet they lack sensitivity and may not pinpoint the exact functional CpG sites. More sensitive techniques for the analysis of smaller fragments mapping to biologically relevant genomic sites, such as alternative promoters or transcription factor binding sites, could provide more useful information. In the case of *SEPT9* for instance, the altered expression of specific isoform variants might occur as a consequence of hypermethylation at alternative promoters. Identification of DMRs and a better understanding of the functional consequences resulting from altered isoform expression are crucial for the development of highly sensitive biomarkers.

The association of septins with the cytoskeleton and the oncogenic potential exhibited by some of the members suggest that septins could serve as targets for a new class of anticancer drugs. Although this field remains largely unexplored, a septin specific drug (forchlorfenuron) has recently been found to stabilize septin filaments in mammalian cells causing decreased cell migration and defects in mitosis (Hu et al., 2008). Because many septins are ubiquitously expressed in various organs, the outcome of treatments targeted to septins in regard to antitumoral vs. toxicological effects is unpredictable. Nevertheless, chemotherapeutics targeting microtubules such as paclitaxel present the same issues, thus further research on septin interactions should provide incentive to search for other specific inhibitors.

Due to the multiple roles of septins and their complex patterns of expression both comprehensive and multidisciplinary approaches are necessary at this point to make significant advances in our knowledge of septins and their involvement in tumorigenesis. Although there are multiple challenges in obtaining functional insight, research on mammalian septins is emerging and will provide new therapeutic targets and biomarkers for early detection of cancer.

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