AXIN1 and AXIN2 variants in gastrointestinal cancers

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A B S T R A C T

Mutations in the APC (adenomatous polyposis coli) gene, which encodes a multi-functional protein with a well-defined role in the canonical Wnt pathway, underlie familial adenomatous polyposis, a rare, inherited form of colorectal cancer (CRC) and contribute to the majority of sporadic CRCs. However, not all sporadic and familial CRCs can be explained by mutations in APC or other genes with well-established roles in CRC. The AXIN1 and AXIN2 proteins function in the canonical Wnt pathway and AXIN1/2 alterations have been proposed as key defects in some cancers. Here, we review AXIN1 and AXIN2 sequence alterations reported in gastrointestinal cancers, with the goal of vetting the evidence that some of the variants may have key functional roles in cancer development.

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Introduction

Somatic mutations in genes functioning in the canonical, or β-catenin-dependent, Wnt pathway are found in approximately 90% of colorectal cancers (CRCs) [1]. These mutations contribute to CRC development by stabilizing the “free” signaling pool of β-catenin via disruption of the “β-catenin destruction complex”, which includes the APC (adenomatous polyposis coli) [2–4], AXIN1 [5–7], AXIN2 [8,9], and GSK3β proteins [10,11]. The most common destruction complex defects in CRCs are loss of function mutations in the APC tumor suppressor gene, although a subset of CRCs have CTNNB1 mutations encoding a mutant β-catenin protein that is likely resistant to regulation by the destruction complex [12,13]. While APC is the most frequently mutated Wnt pathway tumor suppressor gene, both germline and somatic mutations in the AXIN1 or AXIN2 genes have been identified in a subset of CRCs and in several other cancer types. Since the first reports of AXIN1/2 mutations in cancer, other studies have been completed and AXIN1/2 sequence polymorphisms in the general population have been better defined. The purpose of this review is to offer a comprehensive update of the reported constitutional and somatic AXIN1 and AXIN2 sequence variants described thus far. Previous publications addressing AXIN1/2 mutations have reviewed selected variants and have sometimes used different AXIN1/2 reference sequences, making it difficult to compare mutations in a comprehensive fashion. Additionally, since the time of some prior publications, germline sequence variation in control populations has been described in more detail [14]. In-depth evaluation of previously reported and recently reported AXIN1/2 mutations with reference to consistently annotated AXIN1/2 amino acid sequences and the current list of known polymorphisms will lead to a better understanding of which AXIN1/2 sequence variants may confer functional consequences for cancer development. While this review specifically addresses AXIN1/2 mutations in gastrointestinal (GI) cancers, a comprehensive table of AXIN1/2 sequence alterations reported in non-GI cancers is shown in Appendix: Supplementary Table S1.

The Wnt/β-catenin pathway

The canonical Wnt pathway regulates cell fate during development and cellular homeostasis in adult tissues, and Wnt pathway dysregulation is seen in many cancer types (reviewed in Anastas and Moon) [15]. The canonical Wnt pathway transmits extracellular Wnt signals to the nucleus via effects on β-catenin levels and localization [16]. In the absence of an activating Wnt ligand, a protein complex assembles to phosphorylate β-catenin at multiple residues in its amino-terminal domain [12,13,17,18]. The phosphorylated β-catenin is then recognized by a ubiquitin ligation protein complex and subsequently targeted for degradation by the proteasome [19]. The APC, AXIN1, and AXIN2 proteins are thought to function in the assembly of a β-catenin destruction complex. When an activating Wnt ligand is present, the destruction complex is inhibited and the free, signaling pool of β-catenin can translocate to the nucleus, where β-catenin binds to TCF/LEF transcription factors to modulate the expression of target genes [16,20–22].
AXIN1/2 protein function

There are two AXIN proteins: AXIN1 and AXIN2. In the case of AXIN2, the mouse protein is also known as Axil. Axin1 was initially identified as the locus responsible for a series of dominant “kinky” tail mouse phenotypes, all resulting from spontaneous transposon insertions into an exon of Axin1 [23]. When co-injected with Wnt pathway components into the ventral side of Xenopus embryos, Axin1 mRNA inhibits ectopic axis formation, identifying the protein as a negative regulator of Wnt signaling [24]. A primary function of AXIN1 in the Wnt pathway is in the assembly of the β-catenin destruction complex, thus inhibiting the expression of Wnt- and β-catenin-dependent target genes. Abrupt activation of the Wnt pathway is widely presumed to be a main driver of CRC. Hence, in part because AXIN1 is a negative regulator of β-catenin levels and localization, AXIN1 has been classically thought of as a tumor suppressor protein.

AXIN2 was initially identified based on its yeast-two-hybrid interactions with β-catenin and GSK3β and named for its homology to AXIN1 [8,9]. AXIN2, like AXIN1, acts as a scaffold to help assemble the β-catenin destruction complex, and the two proteins show high similarity to one another in several domains: the Tankyrase binding domain which regulates AXIN protein stability via PARsylation [25]; the RGS domain, which mediates binding to APC [8]; the β-catenin-binding domain [8,9]; and the DIX domain, a dimerization domain named for proteins which share this motif – Disheveled and AXIN1 [8,26–29]. Similar to AXIN1, AXIN2 negatively regulates β-catenin-dependent Wnt signaling. Injection of Axil cDNA in Xenopus shows the axis induction axis caused by activated Wnt signaling, and dorsal cDNA injection results in ventralized embryos [9]. These two AXIN proteins are considered functionally equivalent, as an Axin2 cDNA rescues the Axin1-null lethality in the mouse [30]. However, while the Axin1 knockout mouse is lethal in embryogenesis at e9.5 [31,32], mice carrying homozygous null mutations in Axin2 are viable and fertile, with only a mild skull abnormality [33], providing proof that the two genes are not redundant in vivo. This difference in phenotype is likely due to the differential expression of the two genes [33]. The expression of AXIN1 is ubiquitous in various tissues [24], while AXIN2 shows a more restricted developmental and cell-type-specific expression pattern [9,24]. Uniquely, AXIN2, but not AXIN1, is a transcriptional target of β-catenin-dependent Wnt signaling [34–36], and AXIN2 expression is elevated in cancers with activating Wnt pathway mutations. Because of AXIN2’s positive regulation by upstream Wnt- and β-catenin-dependent signals and because the AXIN proteins are the least abundant members of the destruction complex, changes in AXIN2 protein levels could be a key negative feedback mechanism for the regulation of Wnt/β-catenin signaling in cells [37].

Colorectal cancer – germline mutations in AXIN1/2

Inactivating mutations in the APC gene are the most frequent mechanism for activating the Wnt pathway in CRCs, with about 80% of CRCs harboring somatic APC mutations [1]. About 0.5–1.0% of CRCs arise in individuals with familial adenomatous polyposis (FAP), who carry an inactivating germline APC mutation [38]. Colon and rectal adenomas and CRCs arise in those with FAP; in part, due to somatic genetic or epigenetic inactivation of the remaining wild type APC allele, leading to outgrowth of cells with no functional APC alleles and dysregulated β-catenin levels. However, germline APC mutations only account for a subset of the CRC cases with a hereditary component. Axin1 was analyzed as a candidate gene that might harbor CRC-associated germline mutations in a set of 124 UK CRC patients [39]. Several silent mutations were identified as well as seven heterozygous, missense mutations in various exons. Four of these mutations were found only in patients, while the other three were also found in controls, but at lower frequencies. One of the patient-specific mutations has also been described in CRC cell lines [40] and is suggested to interfere with the interaction of AXIN1 and GSK3β [41]. The four patient-specific mutations have since been added to dbSNP, indicating that the variants are found in the general population.

There are only three reported germline mutations in AXIN2 that have been associated with CRC risk (see Table 1 for more detailed information). The first is a premature stop codon in exon 7 that was found in a family with oligodontia (the absence of multiple adult teeth) and a strong history of CRC [54]. The CRC phenotype in this family was variable, and the age at CRC diagnosis for carriers ranged from 27 to 64 years. A second report of a family with oligodontia and a CRC risk found another premature stop codon, also in exon 7 (see Fig. 1) [55]. This family also had a variable cancer phenotype including one case of early-onset breast cancer. A third germline

### Table 1

<table>
<thead>
<tr>
<th>Sequence alteration identified</th>
<th>Cancer type</th>
<th>Reference</th>
<th>Notes</th>
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<td>[44]</td>
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<td>CRC</td>
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<td>CRC, GC</td>
<td>[45]</td>
<td>[46], [44], [47]</td>
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<td>CRC</td>
<td>[45]</td>
<td>[46], [44], MSI</td>
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<td>[55]</td>
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</table>

* Nucleotide and amino acid numbering modified to match modern sequences: NM_004655.3, NP_004646.3.
† These two mutations were found in the same individual, References [49] and [45] respectively.
‡ These variants are now listed in dbSNP (http://www.ncbi.nlm.nih.gov/SNP).
AXIN2 mutation was found in a family with an apparently milder form of familial polyposis, known as attenuated FAP [51]. Of note, this family had no oligodontia or ectodermal dysplasia phenotype. The AXIN2 mutation in this third family was a missense mutation in exon 5 with possible deleterious effects. However, the role for this AXIN2 mutation in tumorigenesis seems quite uncertain, as the mutant allele was lost in adenomas and polyps from the proband and his sister. The three reported germline mutations were heterozygous, suggesting that AXIN2 mutation in tumorigenesis seems quite uncertain.

AXIN2 sequence alterations reported in association with GI cancers. (A) Diagram of the location of germline and somatic AXIN2 variants implicated in GI cancers. The locations of important functional domains in AXIN2 are indicated. Missense and nonsense variants and deletions are shown above the diagram, frameshifts are shown below. Note the density of frameshifts in the exon 7 mononucleotide repeats region. (B) Amino acid conservation of the missense variants. Conservation designated by Gonnet [56] PAM 250 scores: > 1.5 (+), 0.5 to 1.5 (;), 0.5 to –0.5 (–), < –0.5 (−).

Colorectal cancer – somatic mutations in AXIN1/2

Shortly after the identification of a role for AXIN1 in the β-catenin destruction complex, screening of AXIN1 for mutations in selected patient samples and cell lines from various cancers was undertaken [40]. Two missense alterations were seen in the CRC cell lines studied. The first was S215L, found in the LS513 cell line, which also exhibited loss of heterozygosity (LOH) of the wild type AXIN1 allele. The second variant, L396M, was found in three cell lines: HCT-8, HCT-15, DLD-1, and the authors chose to follow up on this alteration because of the conservation of the affected amino acid and its location in the GSK3β binding domain (see Fig. 2). Expression of a fragment of the mouse Axin1 gene with an analogous mutation indeed showed reduced binding to GSK3β, suggesting this variant allele may have functional consequences on the ability of the AXIN1 protein to regulate β-catenin. Because these variants were identified in cell lines, with no matched normal DNA, it was unclear if the AXIN1 variants are somatic mutations or germline polymorphisms. Both The S215L and L396M variants have since been listed in dbSNP, likely suggesting that these variants represent germline sequence variants, and not somatically acquired mutations.

A 2002 report comparing CRCs harboring mismatch repair pathway (MMR) defects (so-called microsatellite instability-high or MSI-H CRCs) versus CRCs with intact MMR (microsatellite-stable or MSS CRCs) suggested that AXIN1 mutations may be important in MSI-H CRCs [57]. Out of 33 MSI-H CRC samples studied, eight somatic, missense mutations in AXIN1 were found in seven tumors. No somatic mutations predicted to alter AXIN1 protein encoding sequences were found in the MSS samples. In the MSI-H CRCs with Polyphen analysis: T510T and N412S [50]. Both the T510T and N412S AXIN2 alleles are now included in dbSNP.

AXIN2 mutation was found in a family with an apparently milder form of familial polyposis, known as attenuated FAP [51]. Of note, this family had no oligodontia or ectodermal dysplasia phenotype. The AXIN2 mutation in this third family was a missense mutation in exon 5 with possible deleterious effects. However, the role for this AXIN2 mutation in tumorigenesis seems quite uncertain, as the mutant allele was lost in adenomas and polyps from the proband and his sister. The three reported germline AXIN2 mutations are heterozygous, suggesting that AXIN2 mutation could perhaps predispose to cancer via a classical tumor suppressor model, where the second allele is inactivated during tumor formation. However, loss of the wild-type allele was not seen in the missense mutation family (third family) [51], and the state of the wild type AXIN2 alleles has not been studied in cancer tissues from individuals carrying the two different AXIN2 nonsense mutations [54,55]. It is also possible that the nonsense alleles could produce truncated proteins with dominant or haplo-insufficient effects.

A 2005 paper aimed to counter prior reports suggesting that constitutional AXIN2 sequence variants play an important role in CRC development. Specifically, the paper reported that analysis of 82 probands from families with hereditary CRC revealed 20 AXIN2 sequence variants in 19 individuals [49]. Silent and intronic mutations were ruled non-pathogenic and none of the identified missense mutations were enriched in patient populations when compared to controls. The authors thus concluded that germline AXIN2 mutations are not associated with an increased CRC risk. While the findings in this 2005 paper do not support a role for germline AXIN2 mutations in CRC risk, the collection of familial CRC cases studied was moderate in size and none of the probands had oligodontia. Another paper reporting on analysis of 31 patients with multiple adenomas or CRC found two notable AXIN2 germline variants in a single patient, but neither variant was clearly pathogenic based on...
AXIN1 somatic mutations, no LOH analysis was done. But, one tumor did show two different AXIN1 mutations, potentially representing selection for AXIN1 bi-allelic defects, perhaps akin to the situation seen for some tumor suppressor genes. Another study of AXIN1 mutations in 54 CRC samples reported five missense mutations and one nonsense mutation [58]. No matching normal tissue or blood samples were available to determine if these were somatic or germline changes. AXIN2 was not assessed in either study [57,58].

A study by Liu et al. reported that 11 of 45 MSI-H CRCs tested had somatic mutations in AXIN2 [45]. All of the mutations were frameshifts in exon 7 mononucleotide tracts that were predicted to lead to premature stop codons in the frameshifts in exon 7 mononucleotide tracts. In 310 CRCs with intact MMR, none contained an axon 7 AXIN2 transcript with premature stop codons. Of some interest, they did show that overexpression of a truncated AXIN2 protein, predicted to result from the frameshifts, promoted β-catenin accumulation in cells in culture, consistent with a possible gain-of-function role for the truncated AXIN2 protein.

Fig. 2. Location and amino acid conservation of AXIN1 sequence alterations reported in association with GI cancers. (A) Diagram of the location of germline and somatic AXIN1 variants implicated in GI cancers. The locations of important functional domains in AXIN1 are indicated. Missense and nonsense mutations are shown above the diagram, insertions and deletions are shown below. (B) Amino acid conservation of the reported missense variants. Conservation designated by Gonnet [56] PAM 250 scores: >1.5 (+), 0.5 to 1.5 (;), 0.5 to -0.5 (−), <−0.5 (−).
mutations in seven tumors, all of which were MSI-H. Four of the seven tumors also had APC mutations, perhaps raising some uncertainties about whether the AXIN2 frameshift mutations were functionally significant in CRC development or just a potential marker of the MMR-defective phenotype. Finally, a survey of AXIN2 sequence alterations in sporadic CRCs and some CRC cell lines identified several silent mutations, one 12-bp in frame deletion (del2013–2024), and potentially pathogenic frameshift mutation (1993del1G), which led to a premature stop at L688X [43]. This frameshift was seen in tumors with or without APC mutation, but only in MSI-H cancers, as reported previously [45]. The 12-bp deletion occurred in a MSS tumor and resulted in the in-frame loss of four amino acids, including two potential phosphorylation sites [43].

A study of a Kashmiri population looking for AXIN1/2 mutations in CRCs found two previously reported AXIN2 single nucleotide polymorphisms and a novel missense variant A695S [53]. The three patients with this sequence variant were diagnosed at ages 50, 57, and 65 and all presented with well-differentiated tumors with LOH of the DCC region. While the authors reported using adjacent normal tissue in their analysis, this variant has since been included in dbSNP, and because it was found in 6% of the patients, it is likely a germline polymorphism.

In addition to somatic sequence changes, changes in AXIN2 expression have been proposed as a potential contributing factor in CRC progression [48]. In a study of gene expression data, AXIN2 expression was significantly reduced in MSI-H CRCs compared to MSS cases. Of note, the AXIN2 gene is directly regulated by the Wnt/β-catenin pathway, and elevated AXIN2 expression is observed in most CRCs with APC mutations or other canonical Wnt pathway defects. Consistent with the gene expression data, the AXIN2 promoter was found to be hypermethylated in 10 out of 27 MSI-H samples, but in none of the MSS samples. Additionally one of the nine MSI-H CRCs with AXIN2 promoter hypermethylation had a frameshift leading to a premature stop codon (L688X). Ectopic expression of AXIN2 in an MSI-H CRC cell line with low levels of endogenous protein resulted in inhibition of cell growth, suggesting that AXIN2 may act as a tumor suppressor in MSI-H CRCs [48]. A second study also found AXIN2 methylation and reduced expression in MSI-H CRCs [60]. The authors reported that AXIN2 expression was correlated with certain clinical and pathological features of sessile serrated adenomas, a colon cancer precursor lesion distinct from typical adenomas. These studies suggest that the level of AXIN2 protein may indeed have consequences for cancer development.

**Hepatocellular carcinoma (HCC) and hepatoblastoma (HB)**

Germline mutations in APC are associated with an increased risk of HB, suggesting other components of the Wnt pathway may be important in HB tumorigenesis [61]. Sequencing of the AXIN1 gene in 22 HBs revealed eight exon variants, seven of which were silent [62]. The eighth variant, T387M, was also found in peripheral blood, so it may be a potentially benign polymorphism. A second study of sporadic HB tumors and HB cell lines found two large, out of frame deletions (52-bp and 1624-bp) and one somatic, missense mutation (S762N) in AXIN2 [42] that has since been added to dbSNP. HCCs frequently display activated Wnt signaling, but often lack mutations in CTNNB1 or APC; hence, the AXIN1 gene was screened for mutations. Out of 100 primary HCCs studied, six AXIN1 alterations were found in five tumors, including three deletions and three premature stop codons [63]. In three of the four AXIN1-mutant tumors that could be fully analyzed, LOH of the wild type AXIN1 allele was seen. Out of six HCC cell lines, two were found to contain deletions in both AXIN1 alleles. The authors then investigated the AXIN1 alterations in HCC lines for dysregulated Wnt signaling and/or cell proliferation. One of the two AXIN1-mutant HCC cell lines showed increased β-catenin reporter activity, and, in all six cell lines, overexpression of AXIN1 was growth suppressive. The authors therefore concluded that AXIN1 may act as a tumor suppressor in HCC.

Further analysis of HCC and HB has revealed some additional alterations in AXIN1 and AXIN2 [52]. While no AXIN2 variants were seen in 27 HBs, two AXIN1 missense variants were found (G650S and R841Q). Both of these sequence variants have since been added to dbSNP with minor allele frequencies of 0.0147 and 0.0101, respectively. Even though the authors stated that they used matched normal samples to specifically identify somatic alterations, it is possible that the reported variants were just germline polymorphisms. In a study of 73 HCCs, seven somatic variants were found in AXIN1: five missense alterations, one 12-bp insertion, and a 1-bp deletion leading to a premature stop codon. LOH of the wild type AXIN1 allele was seen in four of the five AXIN1-mutant HCCs tested, further supporting a role for AXIN1 as a tumor suppressor in HCC. In this same collection of 73 HCCs, two AXIN2 sequence changes were identified, both in exon 7: a missense mutation (R659W) and a 12-bp deletion (del2013–2024). The 12-bp deletion has since been identified in many other cancer types, and the missense allele has been included in dbSNP.

**Gastric carcinoma**

Because of the highly mutable mononucleotide repeats present in AXIN2, one study looked for exon 7 AXIN2 alterations in gastric cancers with MSI [47]. Nine of the 60 cancers had an AXIN2 frameshift mutation, and all of the cancers with an AXIN2 mutation were MSI-H.

**Discussion**

The potential tumor suppressor function of the AXIN1 and AXIN2 proteins has long been hypothesized, based largely on their roles in the β-catenin destruction complex. However, the importance of the AXIN proteins, in vivo, for the inhibition of tumor development or progression is not well established, and the functional consequences of AXIN1 or AXIN2 mutations in cancer remain largely undefined. While many of the reported AXIN2 mutations cluster in one region of the gene, AXIN1 mutations are more dispersed with no clear preference for certain sequence features or functional domains. Maps of the AXIN1 and AXIN2 mutations discussed above are shown in Figs. 1 and 2, along with a prediction of the functional conservation for the missense alleles. Some reported AXIN1/2 mutations can be deemed non-contributory in cancer development, based on the lack of a clear link to familial cancer predisposition or because the variants are present at similar frequencies in controls. As noted in Table 2, many of the AXIN1 mutations reported in cancers have since been added to the dbSNP database or identified in the 1000 Genomes Project. Further studies to compare allele frequencies in control and patient populations could shed light on whether these polymorphisms have any cancer significance. Other reported mutations need to be more thoroughly tested in clinical samples, human populations, and in cell culture and animal models to determine if they are functionally significant. Studies that address the loss of both alleles of AXIN1 or AXIN2 versus mutation of one allele in patient samples or animal models could help to clarify if AXINs function as classic “two-hit” tumor suppressor genes, or if the mutant alleles have a dominant effect in cancer development. A recent study found that complete loss of AXIN1 has a role in predisposition to liver cancer in a mouse model [64]. Combined with AXIN1 somatic inactivating mutations and LOH in HCCs, these data strongly support a role for AXIN1 as a tumor suppressor in HCC.

In addition to the many AXIN2 mutations reported in various cancer types, a few reports have linked AXIN2 SNPs to the disease risk in breast and lung cancers [65–67]. Further efforts may support...
the role of AXIN2 variant alleles in cancer predisposition and perhaps might uncover some value for the variants in informing approaches for the prevention or early diagnosis of cancer. The vast majority of the AXIN2 mutations in cancer have been found in exon 7 and many are frameshifts, as highlighted in Fig. 1. Because the frameshift mutations are present in highly mutable mononucleotide tracts and because the mutations arise in MMR-defective CRCs, it is difficult to determine whether these frameshifts, which lead to premature stop codons, play a role in cancer development or progression, or whether they are passenger mutations. The association with a major tooth phenotype and a very strong predisposition to colon and perhaps other cancers in some individuals carrying heterozygous, germline truncating AXIN2 mutations strongly suggests that these variant alleles may have major contributing roles in development and in cancer predisposition. Because the tooth phenotype is constitutional, it could inform on the function of these germline, truncating mutations. However, the role of the Wnt pathway in tooth development is complex and the tooth defect in these two families affects the development of a subset of secondary teeth, which cannot be easily modeled in the mouse. Nonetheless, it is interesting to note that some FAP patients (carrying heterozygous APC germline mutations) will develop extra teeth and benign odontomas [68]. If we assume that the APC mutations lead to activation of Wnt signaling, then the reduction in teeth in AXIN2 mutation carriers suggests that the AXIN2 mutant alleles might not be simple loss of function alleles, or perhaps AXIN2 plays an important role outside the β-catenin destruction complex. Further studies of the function of the wild type and mutant AXIN2 proteins may yield important clues into AXIN2 function in development and cancer.

If the AXIN proteins are indeed important suppressors of cancer development or progression, then small molecules that stabilize these proteins, such as the tankyrase inhibitor XAV939, could be valuable treatment strategies [25]. While some findings suggest that increased levels of AXIN proteins inhibit colon cancer cells that are dependent on β-catenin signaling, a recent mouse study suggests the opposite: that high levels of AXIN2 actually promote cancer cell invasion and perhaps metastasis [69]. Additionally, the AXIN proteins have been reported to be involved in multiple non-canonical signaling pathways, including the Ras/ERK pathways [70,71], so it will also be valuable to assess if any of the reported mutations in AXIN1/2 could promote tumorigenesis via a non-β-catenin dependent mechanism. Without clear evidence of the pathogenicity of the mutations identified to date or strong evidence from animal models, the importance of AXIN1 and AXIN2 as tumor suppressor genes or oncogenes in cancer and the potential role of the variants in non-Wnt pathway functions remain unresolved issues of keen interest.

In closing, many AXIN1/2 sequence variants in cancer have been reported. The evidence for AXIN1 as a possible tumor suppressor gene in a subset of HCCs is generally convincing, based on sequence analyses, tissue culture work, and mouse model studies. However, evidence supporting the functional significance of AXIN1 mutations in other human cancer types is inconclusive or lacking at this point. The rare germline AXIN2 mutations that have been associated with oligodontia and predisposition to colon and possibly other cancers provide intriguing evidence of a role for AXIN2 mutations in CRC development. The causal significance of the somatic AXIN2 frameshift mutations in mononucleotide repeats seen in a
subset of MSI-H cancers is unclear as the mutations may simply reflect the MSI-H phenotype. Further functional studies are needed to define the roles of the AXIN1 and AXIN2 proteins in regulating the Wnt and other signaling pathways in context- and tissue-dependent fashions, as well as to define the means by which mutant AXIN1 and AXIN2 alleles may contribute to cancer development and progression via classic loss-of-function (“two-hit”) mechanisms, dosage-dependent mechanisms, and potentially even dominant gain-of-function mechanisms.

Conflict of interest

The authors declare that they have no financial interests or other conflicts of interest associated with this manuscript.

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Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.canlet.2014.09.018.

References


