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Commentary

Desmin dysregulation in gall bladder cancer

Desmin is a 53.5 kDa protein composed of 470 amino acids. It is a major intermediate filament (IF) protein found mainly in skeletal and smooth muscles and endothelial cells. Desmin is one of the earliest protein markers for muscle tissue in embryogenesis as it is detected in the somites[1]. In early development of muscle cells, the protein is only expressed at low levels but increases as the cell nears terminal differentiation. In skeletal and cardiac muscles, desmin is present in Z-discs, but in smooth muscle, it is located in cytoplasmic dense bodies and subplasmalemmal dense plaques[2].

Due to its muscle-specific localization, desmin is considered a specific marker for myogenic differentiation among soft-tissue tumours. Therefore, desmin is present in the majority of rhabdomyomas, leiomyomas, rhabdomyosarcomas and leiomyosarcoma (LMS). Desmin may also be co-expressed by neoplasms with divergent phenotypes, such as desmoplastic small round cell tumours, epithelioid sarcomas, malignant peripheral nerve sheath tumours and some malignant rhabdoid tumours[3].

Desmin has also been described as a marker of pericytes found in association with blood vessels from the earliest stages of capillary sprouting and throughout angiogenesis. As a result of angiogenic signals, pericytes are recruited to developing endothelial tubes and express desmin in increasing amounts as they mature and elongate to form a stable sheath around the newly formed vessels. Angiogenesis is an important characteristic of developing tumours. The mature pericytes become focally embedded within the basement membrane adjacent to the endothelial cells and are considered to be essential for angiogenesis both in normal and cancer development. In a study on colorectal cancer[4], desmin expression was significantly increased between early- and late-stage tumours. Strong focal desmin expression was found in stroma directly adjacent to carcinomatous glands and microvessels. These cells showed co-localization of desmin and vimentin in close association with cells expressing von Willebrand factor, indicating that these were pericytes. Significantly higher levels of desmin-positive pericytes were observed in late-stage tumours, which was consistent with increased angiogenesis. Pericyte coverage of vasculature is a marker of vessel maturation; hence, desmin expression may be used as a marker for microvessel maturation. Desmin staining, identifying pericyte coverage and extent of mature tumour vasculature, may be explored as a biomarker to predict the efficacy of anti-angiogenic cancer therapy in cancer patients[5].

The gall bladder is prone to the formation of gallstones which can be corrected by surgical removal of the gall bladder. However, in small percentage of population, the gall bladder becomes cancerous. Early signs and symptoms of cancer such as abdominal pain and jaundice are non-specific, and cancer is usually detected at advanced stages when it is largely uncurable. Therefore, a concerted effort is being directed to look for specific markers which can be used as biomarkers for early stages when cancer can be treated by conventional surgical and chemo-radiation approaches. In recent years, one of the common but promising tools uses proteomics to dissect out differentially regulated proteins which can be further evaluated as a biomarker in cancer diagnostics.

In the study carried out by Bhunia *et al*[6] in this issue, in gall bladder cancer (GBC) patients revealed its potential diagnostic significance in disease progression. The authors reported the epigenetic regulation of desmin protein in gall bladder cancer. Earlier, this group had carried out whole-genome methylation analysis using Human Methylation BeadChip array and showed that desmin gene is specifically hypermethylated in the promoter region in gall bladder tumours compared to

non-tumours[7]. To validate their observation based on microarray results, they employed alternate approaches. First, they used methylation-specific polymerase chain reaction (MS-PCR), which qualitatively evaluated methylated and non-methylated DNA of desmin gene in the sample. They reported that in majority of GBC samples (88%), desmin gene promoter was methylated as compared to samples from non-tumour tissues (39%). Using quantitative reverse transcription-PCR, they quantitated the desmin mRNA present in GBC and non-GBC samples and showed that the level of desmin mRNA was much lower in GBC as compared to adjacent non-tumour tissue derived from the same patient. The results of mRNA were extended to expressed protein. By Western blot study, the authors observed reduced levels of desmin present in all stages of GBC. Immunohistochemistry-based direct visualization of desmin in tumour and non-tumour samples further supported a reduction of desmin in the tumour samples[6].

The present study[6] showed a significant downregulation of desmin in tumour tissue of the gall bladder resulting from promoter methylation, suggesting epigenetic control of the desmin gene expression during tumorigenesis. Previous studies have also reported loss of expression of desmin in biliary tract and gastrointestinal stromal tumours[8]. Roles of IF-associated proteins in the dynamic remodelling of the cell during development of neoplastic phenotype and execution of apoptosis have already been proposed[8]. Desmin is a part of IF in the cell, and epigenetic silencing of desmin indicates a role of this cytoskeletal system in the carcinogenesis. Based on this and other studies, the authors proposed that desmin might be acting as a tumour suppressor gene, since hypermethylation in the promoter of any relevant gene may likely evolve novel tumour suppressor genes.

Gall bladder cancer mostly occurs in glands lining the surface of the gall bladder[9]. Immunohistochemical staining shows a diffuse pattern of desmin in the gall bladder, and the staining is considerably reduced in GBC. It is still debatable whether loss of desmin is a primary event or a bystander effect where desmin gene promoter gets methylated along with various other genes through epigenetic dysregulation.

The authors of the present study[6] have aimed to look for biomarkers for detecting gall bladder cancer in early stages. However, such a putative biomarker should be detectable in the peripheral blood. The baseline levels of desmin protein in circulation due to wear and tear of body musculature will make it difficult to follow the lower expression of desmin in gall bladder carcinogenesis. Still, the finding regarding epigenetic dysregulation of various oncogenic and tumour suppressor genes in gall bladder cancer can serve as a springboard to explore complex aetiopathogenesis of the still elusive cancer of the gall bladder.

***Conflicts of Interest*:** None.

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