Abstract

Colorectal cancer (CRC) is one of the most common lethal cancers in USA and Europe. Studies have mainly focused on either older patients (≥60 years) or younger patients (≤50 years) with a familial predisposition. Several recent reports have indicated an increase in the proportion of young sporadic CRC patients in India, as compared to USA and Europe, and account for a significant proportion of the total CRC patients (up to 45% in our study). There appear to be several indications to suggest that the tumors occurring in the young may be distinct from similar tumors occurring in the elderly.

Two genetic instability pathways viz. deregulated canonical Wnt signaling causing chromosomal instability (CIN) or mismatch repair (MMR) inactivation driven microsatellite instability (MSI) have been shown to propel a majority of colorectal tumors, especially in late-onset CRC in the West. However our understanding of early-onset non-familial CRC is comparatively limited.

The current study included a comprehensive comparative characterization of sporadic CRCs occurring in the young with those occurring in the elderly, from India, using both fresh and archived tumor samples.

Our results reveal the absence of Wnt signaling and MMR defects in a significant proportion (35%) of Indian CRC patients, especially in early-onset CRC. In addition, KRAS2 mutation frequency was significantly lower in early-onset (as against late-onset) CRC indicating thereby the absence of seminal tumorigenesis pathways previously validated to drive the adenoma to carcinoma transition in CRC. Comparative analysis of gene expression profiles from tumors with or without canonical Wnt signaling revealed the possible presence of non-canonical Wnt signaling signature in latter. Further, non-canonical Wnt pathway genes were confirmed to be elevated using RT-Q-PCR and at the protein expression level using Immunohistochemistry targeted to NFATc1, a target of non-canonical Wnt pathway, using Tissue Microarray (TMA).

Our study for the first time reveals the existence of non-canonical Wnt signaling in early onset sporadic CRC.