Abstract (in English)

Colorectal cancer (CRC) is one of the most prevalent cancer types. Patients suffering from inflammatory bowel disease (IBD) have an increased risk of CRC development. IBD is manifested by extensive intestinal inflammation, associated with perturbations in the intestinal epithelial barrier (IEB). Functional IEB relies on intestinal epithelial cells (IECs) and its integrity is dependent on cellular cohesion secured by cell-cell junctions such as adherens junctions (AJs) and desmosomes (Ds). IECs thus form epithelial sheets, which are integrated into a structural and functional continuum with subjacent dense extracellular matrix (ECM), also called basement membrane (BM), through cell-ECM adhesions called hemidesmosomes (HDs). The formation of functional Ds and HDs relies on the association of their transmembrane constituents with keratin filaments (KFs). Anchorage of KFs to junctions is mediated by plectin, a versatile cytolinker protein that integrates intermediate filaments (IFs) with cellular junctions and other cell structures, including the nucleus, thus providing mechanical stability to cells and tissues. Although mutations in plectin have previously been shown to negatively impact the integrity of skin tissue, its precise function in intestinal homeostasis has not been documented. Using a mouse model carrying constitutive ($Ple^{\Delta IEC}$) or inducible ($Ple^{\Delta IEC\text{-}ERT2}$) IEC-specific plectin deletion, we characterized the role of plectin in cytoskeletal architecture of IECs and IEB homeostasis. Moreover, our data reveal higher propensity of $Ple^{\Delta IEC}$ mice for development of colitis and colitis-associated CRC (CA-CRC). We also determined how altered cytoarchitecture impacts colorectal carcinogenesis and how mechanical forces threaten genome integrity, driving the oncogenic potential of plectin-deficient cells.

Our results reveal that plectin expression negatively correlates with the severity of inflammation in ulcerative colitis (UC) patients. $Ple^{\Delta IEC}$ mice spontaneously develop colitis characterized by extensive detachment of IECs from the BM, increased intestinal permeability, hyperproliferation, and inflammatory lesions. Such compromised epithelial barrier integrity, coupled with chronic inflammation, promotes spontaneous CRC development in $Ple^{\Delta IEC}$ mice. Mechanistically, plectin deficiency leads to disorganized KF networks, dysfunctional HDs, and intercellular junctions. Strikingly, expression profiling of UC patients reveals significant downregulation of plectin, KFs, and components of associated junctions. Consistent with these

findings, plectin knock-out (KO) Caco-2/RPE cells exhibit reduced mechanical stability and adhesion capacity. Spontaneous carcinogenesis in *Ple*$^{\Delta IEC}$ mice is associated with increased susceptibility to DNA damage. In cell monolayers, plectin deletion is associated with delayed adaptation to mechanical stress, resulting in increased nuclear deformability, DNA damage, and chromosomal instability, which together increases susceptibility to oncogenic transformation. Plectin-controlled architecture thus protects the genome from damage induced by mechanical stress.

Our study demonstrates that plectin-controlled cytoarchitecture is essential for maintaining the mechanical homeostasis of IECs, thereby protecting intestinal epithelia against DNA damage and carcinogenesis.