Colorectal cancer (CRC) is the third most common cancer type in both genders and arises from intestinal-epithelial cells (IECs), a cellular monolayer separating the gut lumen from the body. While only a minority of new diagnosed patients carries genetic predispositions, the major risk factors for CRC are age, inflammatory bowel diseases, and obesity.

In this study, IEC-specific deficiencies of the insulin receptor (IR) and insulin-like growth factor receptor 1 (IGF1R) have been analyzed, allowing for the investigation whether IEC-specific insulin resistance affects colitis-associated cancer (CAC) development and IEC integrity. Upon chemical CAC induction, IR/IGF1RIEC-KO mice exhibited accelerated tumor burden as a consequence of impaired gut barrier restoration. The compromised epithelial integrity in insulin resistant colons was caused by a decreased expression of the cell junction molecule Desmocollin 3 (Dsc3) that was directly controlled via insulin-regulated FoxO1 transcription factors. Consistently, IEC-specific expression of an insulin insensitive FoxO1ADA construct and IEC-specific Dsc3 deficiency recapitulated the increased CAC development as a consequence of gut barrier defects like observed in IR/IGF1RIEC-KO mice. As part of the Desmosomes, DSC3 interconnects the IEC monolayer and conveys strength against mechanical forces. Thus, it facilitates the strict separation between gut lumen and underlying tissues, avoiding an inflammatory immune response. These findings demonstrate that the development of insulin resistance impacts on CAC development via impaired transcriptional control of Dsc3, resulting in compromised desmosome formation and impaired gut barrier restoration.