



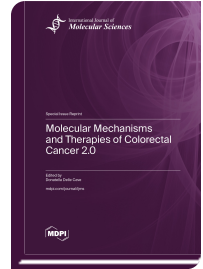
*Special Issue Reprint*

## Molecular Mechanisms and Therapies of Colorectal Cancer 2.0

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Colorectal cancer (CRC) is currently the third leading cause of cancer-related mortality. Transforming growth factor beta (TGF- $\beta$ ) signaling has been associated with CRC growth and metastasis due to its involvement in proliferation, epithelial-to-mesenchymal transition (EMT), and angiogenesis. The TGF- $\beta$  superfamily contains over forty members, including TGF- $\beta$ s, Nodal, Activin, and bone morphogenetic proteins (BMPs). Three types of TGF- $\beta$  receptors (TGF- $\beta$ Rs) have been identified: types 1, 2, and 3. After ligand binding, TGF- $\beta$ R2 recruits and phosphorylates TGF- $\beta$ R1, which, in turn, phosphorylates downstream SMAD (small mother against decapentaplegic) proteins. Phosphorylated SMAD4 translocates into the nucleus, where it activates the transcription of numerous target genes (including *SERPINE1*, *LTBP2*, *CDKN1A*, *ARID3B*, *ATXN1*, *PTPRK*, *RAB6A*, *SMAD7*, *EHBP1*, etc.), acting predominantly as a tumor suppressor gene. Interestingly, alterations in *SMAD4* are frequent in metastatic CRC and, together with *TGF- $\beta$ R2* gene mutations, have been reported as late events able to promote CRC progression. The study of the TGF- $\beta$  pathway in metastatic CRC is challenging because of the great genetic heterogeneity of CRC. However, the increasing availability of targeted and whole-exome DNA sequencing techniques makes it possible to identify genetic mutations in complex, dynamic, and heterogeneous clinical contexts and make correlations with clinical outcomes.



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