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Quantification and localization of matrix metalloproteinases (MMP15 and MMP19) in human colorectal carcinogenesis

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Matrix metalloproteinases (MMPs) are capable of degrading all kinds of extracellular matrix proteins, but they also can process a number of other bioactive molecules. They are well known to be involved in the cleavage of cell surface receptors, the release of apoptotic ligands (as FAS ligand) and chemokine/cytokine activation/de-activation. MMPs are also thought to play a pivotal role on cell processes like proliferation, migration (adhesion/dispersion), differentiation, apoptosis and host defence; thus they have been extensively studied to elucidate their involvement in both tumour development and progression. In the present study the attention was focused on two members of MMP family, i.e. MMP-15 and MMP-19, not jet well investigated as far as their role is concerned in the onset of colorectal neoplastic pathologies.

The expression profile of MMP-15 and MMP-19 was assayed from samples of: a) normal mucosa, b) microadenomas and c) cancer, using confocal analysis, Western blotting and quantitative reverse transcription polymerase chain reaction (qRT-PCR). Western blot and qRT-PCR showed that MMP-15 expression level increases from normal mucosa to microadenomas, with a reduced level in cancer respect to microadenomas. The semiquantitative immunofluorescence analysis correlate with these data showing a localization exclusively at the stromal level of this protein, suggestive of an important role of stromal compartment, especially in the early phases of neoplastic transformation.

Increasingly amount of MMP-19 mRNA and protein levels were instead recorded in the progression of colon lesions both in epithelial and stromal compartments. MMP-19 staining increases in parallel to normal mucosa ® microadenoma® carcinoma sequence; in particular this protein was showed to be expressed at the epithelial level only at the end of the sequence, indicating an intriguing epithelial involvement of MMP-19 production only in the late stages of carcinogenesis.

In conclusion, MMP-15 and MMP-19 appear to be up-regulated during tumorogenesis, with different expression patterns, which in turn are probably due to the different roles played by these two molecules. The results reported up to now in literature show conflicting data regarding the specific role of these proteins in tumour progression so that the improved understanding of the biological roles of MMPs in colorectal cancer suggests a re-evaluation of the use of MMP inhibitors and highlights the importance of integrated translational studies on the MMP expression patterns.

Keywords: Matrix metalloproteinases (MMPs), colorectal carcinogenesis, quantitative reverse transcription polymerase chain reaction (qRT-PCR).