Author's response to reviews

Title: Remodeling of extracellular matrix by normal and tumor-associated fibroblasts promotes cervical cancer progression

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Version: 2 Date: 20 November 2014

Author's response to reviews: see over
Dear Ms Solera,

Please find enclosed our manuscript entitled “Remodeling of extracellular matrix by normal and tumor-associated fibroblasts promotes cervical cancer progression”. The highlights of the manuscript are as follows:

Immunohistochemical analysis of tissue microarray from cervical cancer specimens revealed the profound rearrangement of extracellular matrix of tumor tissue. To dissect the events responsible for this remodeling normal and cancer-associated fibroblasts were isolated from human cervical specimens and their matrix secretion has been compared in monoculture and co-culture with CSCC7 cervical cancer cell line.

We discovered that:

**Normal fibroblasts** promote the proliferation of cancer cells, stimulate the production of TGF-β1 and MMP-7 of cancer cells. These fibroblasts synthesize mainly the components of fibrillar matrix.

**Cancer-associated fibroblasts** are implicated in the degradation of fibrillar matrix by producing MMP-1, and basement membrane by producing MMP-2. They synthesize laminin-1 and perlecan, but down regulate the synthesis of type IV collagen, replacing normal fibrillar matrix with an abortive basement membrane-like matrix which promotes the invasion of cancer cells.

**CSCC7 cervical cancer cells** express α6β4 integrin, a laminin receptor promoting the migration of cancer cells on laminin-1 matrix. In invasion assay laminin-1 proved to be the strongest chemoattractant of cancer cells. We could detect CD151, a protein known to facilitate the interaction of laminin-1 with its receptor both in the fibroblasts and tumor cell membrane.

According to the request of the Editorial Office

1. We adjusted the manuscript with line numbering
2. We stated that we do not have competing interest.
3. We tried to delineate more precisely the contribution of authors in the establishment of the manuscript.

We do hope that our manuscript meets the standards of your journal!

Best regards,

Ilona Kovalszky MD, Ph.D, DSc.
Professor of pathology