The diagnostic and biological implications of laminin expression in serous tubal intraepithelial carcinoma

Elisabetta Kuhn¹, Robert Kurman¹, Robert Soslow², Guangming Han² Tian-Li Wang and Ie-Ming Shih¹

¹Pathology, Johns Hopkins Medical Institutions, Baltimore, MD, United States and ²Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, United States.

Background: Mounting evidence indicates that serous tubal intraepithelial carcinoma (STIC) is the likely precursor of most ovarian high-grade serous carcinomas (HGSCs). It has been proposed that cells from STICs are shed from the fallopian tube and implant on the ovary developing into a tumor, which simulates a primary HGSC. However, the molecular mechanisms underlying the dissemination of the cells from a STIC are not known. In order to identify the molecules that may be responsible for this critical process, we analyzed the ovarian cancer gene expression and identified several upregulated genes associated with HGSC. Among these, we selected laminin for further study because it has been shown to be involved in cell adhesion, motility and invasion.

Design: RT-PCR was used to assess the expression of different laminin isoforms (LAMA2, LAMA3, LAMC1, and LAMC2) in fresh tissue samples from 8 ovarian HGSCs, 9 ovarian cancer cell lines and 12 primary cultures of normal fallopian tube epithelium (FTE). Immunohistochemistry for LAMA3, LAMC1, p53 and Ki-67 was performed on formalin-fixed paraffin embedded tissue sections from 18 STICs, 16 of which were associated with concurrent ovarian HGSCs. LAMA3 and LAMC1 were scored based on intensity of cytoplasm (0 to 3+), and p53 and ki67 based on percentage of positive cells.

Result: RT-PCR, showed a statistically significant increase of LAMA2 (p=0.044) and LAMC1 (p=0.0006), and reduction of LAMA3 (p=0.0032) and LAMC2 (p=0.0006) in the HGSCs samples and the ovarian cancer cell lines as compared to controls. LAMA3 was expressed in normal FTE, STICs and HGSCs and was decreased in intensity in 9 (56%) of 16 HGSCs compared to STICs and FTE. Intense LAMC1 immunoreactivity (2+ and 3+) was detected in 17 (94.4%) of 18 STICs and 14 (87.5%) of 16 of the concurrent HGSCs whereas the LAMC1 staining was undetectable or weak (1+) in all FTE from the same patients. Interestingly, LAMC1 immunoreactivity was intense in 7 STICs in which p53 staining was absent and in 5 STICs with low Ki-67 index (<20%).

Conclusion: LAMC1 appears to play an important role in the development of HGSC. Since it is involved in cell adhesion, motility and invasion, upregulation of LAMC1 may facilitate shedding and dissemination of STIC cells to the ovaries and other peritoneal and abdominal structures. The presence of LAMC1 immunoreactivity in STICs, especially those with negative p53 staining and low Ki-67 labeling index, suggests that LAMC1 could be a reliable tissue biomarker to identify STICs.