Methods: By using immunohistochemistry, we studied the pattern of histone H4 modifications in a series of 100 primary non small cell lung tumors comprising 51 squamous carcinoma and 49 adenocarcinoma. Specific antibodies recognizing acetylated histone H4 at positions K5, K8 and K16 and trimethylated histone H4 at position K20 were used on frozen tissue sections with an automated immunostainer Ventana to standardize the staining. Normal lung epithelial cells (alveolar and bronchial basal cells) were taken as internal controls and their score used for determination of the cut off score to discriminate between positive (score at least equal to normal) and negative (score lower than normal) cases.

Results: Our data show that, as compared to normal lung, lysines 5 and 8 of histone H4 are hyperacetylated in 48% and 40% of all tumors respectively, more frequently in squamous carcinoma than in adenocarcinoma (p=0.009 and p=0.0002 respectively). In contrast, acetylation at Lys16 and trimethylation at Lys20 are lost in 52% and 47% of the tumors respectively. Across histological types loss of trimethylation at Lys20 is more frequent in squamous carcinoma than in adenocarcinoma (p=0.0002), is associated with advanced stage (p=0.018) and nodal metastasis (p=0.01) and correlates with a poor survival among stage I (p=0.026). Importantly, in adenocarcinoma, loss of trimethylation at Lys20 is associated with advanced stage (p=0.006) and correlates with a poor survival among stage I-III (p=0.0001) and N0 versus N1-2 (p=0.013) tumors. Furthermore, the double loss of acetylation at Lys16 and trimethylation at Lys20 is associated with a shorter survival in these patients as compared to the presence of either one or none of these alterations.

Conclusions: Retrospective analysis of trial data suggests that PSALC is a reliable, valid, and responsive scale for measuring SCLC symptoms. If feasible in SCLC population, a prospective validation study could be used to further evaluate the validity of this symptom scale.

Session B7: BSTB: Molecular Diagnostics & Pathology
Tuesday, September 4

B7-01 BSTB: Molecular Diagnostics & Pathology, Tue, 13:45 - 15:30

Aberrant pattern of histone H4 modification in human lung carcinoma
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Background: Post-translational modifications in the tails of nucleosomal core histones are emerging as important signalling processes controlling a wide variety of functions. Indeed they play a crucial role in chromatin packaging, gene expression and genome stability. Therefore, perturbation of this epigenetic information is likely to be involved in the development of cancer. Although some studies identified an altered activity of histone-modifying enzymes in tumors, little is known about the post-translational modifications of histones in these malignancies.

Methods: To study the pattern of histone H4 modifications in a series of 100 primary non small cell lung tumors comprising 51 squamous carcinoma and 49 adenocarcinoma, specific antibodies recognizing acetylated histone H4 at positions K5, K8 and K16 and trimethylated histone H4 at position K20 were used. On frozen tissue sections with an automated immunostainer Ventana in order to standardize the staining. Normal lung epithelial cells (alveolar and bronchial basal cells) were taken as internal controls and their score used for determination of the cut off score to discriminate between positive (score at least equal to normal) and negative (score lower than normal) cases.

Results: Our data show that, as compared to normal lung, lysines 5 and 8 of histone H4 are hyperacetylated in 48% and 40% of all tumors respectively, more frequently in squamous carcinoma than in adenocarcinoma (p=0.009 and p=0.0002 respectively). In contrast, acetylation at Lys16 and trimethylation at Lys20 are lost in 52% and 47% of the tumors respectively. Across histological types loss of trimethylation at Lys20 is more frequent in squamous carcinoma than in adenocarcinoma (p=0.0002), is associated with advanced stage (p=0.018) and nodal metastasis (p=0.01) and correlates with a poor survival among stage I (p=0.026). Importantly, in adenocarcinoma, loss of trimethylation at Lys20 is associated with advanced stage (p=0.006) and correlates with a poor survival among stage I-III (p=0.0001) and N0 versus N1-2 (p=0.013) tumors. Furthermore, the double loss of acetylation at Lys16 and trimethylation at Lys20 is associated with a shorter survival in these patients as compared to the presence of either one or none of these alterations.

Conclusion: These data provide the first evidence of a global aberrant pattern of histone H4 modification in lung tumors with hyperacetylation of Lysines 5 and 8 and loss of acetylation of lysine 16 and of trimethylation of Lysine 20. The frequent loss of lysine 20 trimethylation in squamous carcinoma, independently of the stage, suggests that it could be an early event in the carcinogenesis of this tumor type. In contrast, loss of lysine 20 trimethylation is less frequent in adenocarcinoma but correlates with a poor prognosis suggesting a role in the progression of these tumors.