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Circulating nucleosomes in hematological malignancy.

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Background:
There are over 700,000 new cases of non-Hodgkin lymphoma (NHL), acute myeloid leukaemia (AML) and acute lymphocytic leukaemia (ALL) diagnosed globally each year and approximately 415,000 deaths. The non-specific symptoms of lymphoma and leukemia often delay diagnosis. We investigated the circulating levels of intact nucleosomes containing the histone H3.1 isoform (Nu.Q-H3.1) in a variety of solid tumors, NHL, AML, ALL, and in healthy subjects.

Methods:
We measured levels of Nu.Q-H3.1 in plasma samples taken from 62 healthy volunteers (mean age = 45 yrs) and 329 patients diagnosed with cancer (mean age = 56 yrs), including 25 patients diagnosed with each of cancer of the bladder, bone, brain, oesophagus, cervix, skin, head & neck or melanoma, 21 patients diagnosed with uterine cancer as well as with NHL (n = 25), AML (n = 25) and ALL (n = 8). The cohort included samples taken from patients at diagnosis and at relapse. Whole blood samples were collected in EDTA plasma tubes, double-centrifuged at 1500 rcf for 15 minutes within 2 hrs of blood draw, after which plasma was transferred to a cryotube and frozen immediately until analysis. Plasma samples (20µl) were analyzed in duplicate for Nu.Q-H3.1 using an ELISA method developed and validated to CLSI guidelines.

Results:
We observed elevated levels of Nu.Q-H3.1 in the patients diagnosed with various cancers. Only 14 of 271 patients with a solid tumor had levels > 200ng/ml. In contrast the median Nu.Q-H3.1 levels

observed for NHL, AML and ALL were 276, 284 and 585ng/ml respectively. The median nucleosome level in 62 healthy subjects was 40ng/ml; the highest level was 198ng/ml. The AUC for all patients diagnosed with NHL, AML or ALL (n = 54) vs healthy volunteers was 91% with a sensitivity of 74% at 95% specificity. The AUC for the subset of patients newly diagnosed with NHL, AML or ALL (n = 31) vs healthy volunteers was 92% with a sensitivity of 81% at 95% specificity.

Conclusions:

Elevated nucleosome levels have been reported for a number of diseases. Our early results indicate that levels of Nu.Q-H3.1 are particularly elevated in haematological malignancies and may be a useful diagnostic tool warranting further study.

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