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FROM MOLECULES TO CELLS AND BACK

10-14 September, 2017 | Jerusalem, Israel



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### 42nd FEBS Congress Abstracts

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## New inhibitors of ALKBH dioxygenases overexpressed in neck and head cancer

P. 4. 1-110

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AlkB protein from *E. coli* (EcAlkB) is a profoundly studied member of 2-oxoglutarate and Fe(II) - dependent dioxygenase superfamily that removes alkyl lesions from DNA bases via oxidative demethylation restoring native bases in DNA. In human cells, there are nine EcAlkB homologs, ALKBH1-8 and FTO. These dioxygenases, repair alkylation lesions to DNA and RNA but also show other biological functions. Cancerous tissues develop greater efficiency of DNA repair systems in comparison to healthy ones. Overexpression of DNA repair proteins in tumor leads to the removal of DNA lesions before they become toxic to cancer cell, in this way assuring tumor welfare and creating major mechanism of resistance to anticancer therapy. Our main approach was to determine the levels of expression of particular ALKBHs in cancer tissues by Western-blot in head and neck cancer tissues. We have demonstrated that dioxygenases ALKBH 1, 3, 4, 5, and FTO are highly expressed in these tumors. Statistical analysis allowed to create protein expression tree of ALKBHs tested. We have found that FTO and ALKBH5, and ALKBH1 and ALKBH3 show similar expression patterns in healthy and cancerous tissues. To answer the question whether ALKBHs under study form any oligomers, we performed size exclusion chromatography and observed monomeric forms of ALKBH3, 4 while ALKBH1, 5, and FTO formed protein complexes. Natural substances, rhein and emodin, show anti-cancer, anti-inflammatory, and anti-microbial activities. Rhein inhibits activity of EcAlkB, ALKBH2, ALKBH3, and FTO. We synthesized and investigated new rhein and emodin derivatives as a potential inhibitors of ALKBHs and found that chloridoemodins in the form of mono- and di-chlorides are the most active inhibitors of ALKBHs among compounds tested. Moreover, they were more selective against cancerous than healthy cells and seem to be a promising anthraquinones in anti-cancer therapy.

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