Nefertiti El-Nikhely, Hereditary Genet Curr Res 2018, Volume 7
DOI: 10.4172/2161-1041-C1-003

Metastasis-associated protein 2 (MTA2) as a regulator of NF-kB in lung cancer

Nefertiti El-Nikhely
Institute of Graduate Studies and Research—Alexandria University, Egypt

Statement of the Problem: Lung cancer is a multifactorial disease with poor prognosis and survival. Inflammation is an important aspect in tumorigenesis that is gaining increasing attention in many studies. A key player of variant processes in tumour growth is the transcription factor nuclear factor kappa B (NF-kB) which shows aberrant expression in several cancers and plays a role in drug resistance. As NF-kB is a pleiotropic agent, it is tightly regulated on several levels.

Methodology: A transgenic animal model was used, where IKK2, the key kinase activating NF-kB, was altered (downregulated IKK2, IKK2^{DN} or activated IKK2; IKK2^{CA}) in CRaf BxB-induced tumor in alveolar epithelial type-II cells (Sftpc/CRaf/IKK2^{DN} and Sftpc/CRaf/IKK2^{CA}). Xenograft model was used with LLC1 cells for subcutaneous tumours whose immune cell repertoire was analysed by flow cytometry.

Findings: We could observe impaired tumour growth when IKK2 was downregulated. Using several lung cancer cell lines, we revealed that NF-kB is regulated by metastasis-associated protein 2 (MTA2). NF-kB activity was decreased when MTA2 was overexpressed in A549 cells. Moreover, knockdown of MTA2 by shMTA2 in LLC1 cells lead to increased subcutaneous tumours in a xenograft model. The tumours with lower MTA2 levels included macrophages showing rather type 1 markers which are pro-tumorigenic and thus contributing to the increased tumour sizes.

Conclusion: This study sheds more light into the epigenetic regulation of NF-kB signalling pathway. The interaction between NF-kB and MTA2 can be subject of novel therapy modalities.

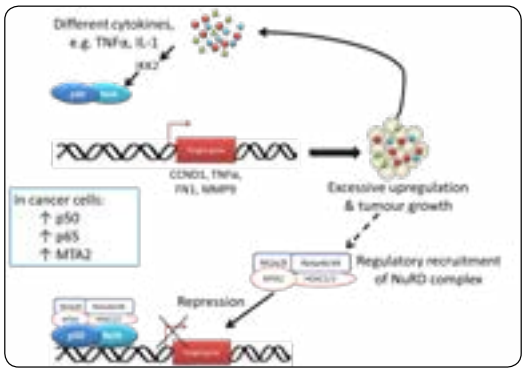

Figure 1: Mechanism of feedback regulation of NF-kB by MTA2/NuRD complex.

Recent Publications:

1. Soni Savai Pullamsetti, Baktybek Kojonazarov, Samantha Storn, Henning Gall, Ylia Salazar, Janine Wolf, Andreas Weigert, Nefertiti El-Nikhely, Ardeschir Ghofrani, Gabriele A Krombach, Ludger Fink, Stefan Gattenlöhner, Ulf R Rapp, Ralph Theo Schermuly, Friedrich Grimminger, Werner Seeger and Rajkumar Savai (2017) Lung cancer–associated pulmonary hypertension: role of micro-environmental inflammation based on tumor cell-immune cell crosstalk. Sci Transl Med. 9(416).
2. Kiehl S, Herkt S C, Richter A M, Fuhrmann L, El-Nikhely N, Seeger W, Savai R and Dammann R H (2014) ABCB4 is frequently epigenetically silenced in human cancers and inhibits tumor growth. Sci Rep. 4:6899.
3. Kopp F, Hermawan A, Oak P S, Ulaganathan V K, Herrmann A, El-Nikhely N, Thakur C, Xiao Z, Knyazev P, Ataseven B, Savai R, Wagner E and Roidl A (2014) Sequential salinomycin treatment results in resistance formation through clonal selection of epithelial-like tumor cells. Transl Oncol. 7(6):702-11.

4. Zanucco E, El-Nikhely N, Götz R, Weidmann K, Pfeiffer V, Savai R, Seeger W, Ullrich A and Rapp U R (2014) Elimination of B-RAF in oncogenic C-RAF-expressing alveolar epithelial type II cells reduces MAPK signal intensity and lung tumor growth. J Biol Chem. 289(39):26804- 16.

5. Larzabal L, El-Nikhely N, Redrado M, Seeger W, Savai R, Calvo A (2013) Differential effects of drugs targeting cancer stem cell (CSC) and non-CSC populations on lung primary tumors and metastasis. PLoS One 8(11):e79798.

Biography

This work was part of the PhD thesis and the work was done at the Max Planck Institute for Heart and Lung Research, Bad Nauheim, Germany. Nefertiti El-Nikhely was working there as PhD graduate student and then as a postdoc. This study is novel in elucidating new epigenetic regulation mechanisms for NF-kB in lung cancer. NF-kB is a crucial inflammatory factor that is often aberrant in many caners. Several studies attempted to use its inhibitors as adjunct therapy to conventional cancer therapies. A better understanding of its underlying regulatory mechanisms is needed. This study paves the way for developing new therapy interventions by addressing the interaction between NF-kB and its regulators.