FEATURES

VOLUME 116 • NUMBER 6

Thiol Redox Chemistry: Role of Protein Cysteine Oxidation and Altered Redox Homeostasis in Allergic Inflammation and Asthma

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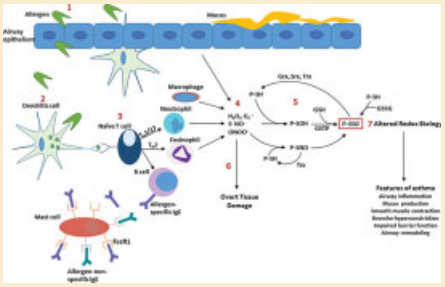
ACCEPTED MANUSCRIPT ONLINE 7 JANUARY 2015

Asthma is a pulmonary disorder, with an estimated 300 million people affected worldwide. While it is thought that endogenous reactive oxygen species (ROS) and reactive nitrogen species (RNS) such as hydrogen peroxide and nitric oxide, are important mediators of natural physiological processes, inflammatory cells recruited to the asthmatic airways have an exceptional capacity for producing a variety of highly reactive ROS and RNS believed to contribute to tissue damage and chronic airways inflammation. Antioxidant defense systems form a tightly regulated network that maintains the redox environment of the intra- as well as extracellular environment. Evidence for an oxidant-antioxidant imbalance in asthmatic airways is demonstrated in a number of studies, revealing decreased total antioxidant capacity as well as lower levels of individual antioxidants. Thiols in the form of GSH and sulfhydryl groups of proteins are among the most susceptible oxidant-sensitive targets, and hence, studies investigating protein thiol redox modifications in biology and disease have emerged. The perspective offers an overview of the combined efforts aimed at the elucidation of mechanisms whereby cysteine oxidations contribute to chronic inflammation and asthma, as well as insights into potential cysteine thiol-based therapeutic strategies.



Epigenetic States of Nephron Progenitors and Epithelial Differentiation

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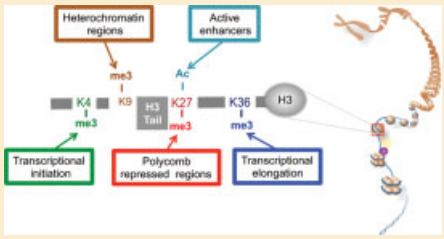
ACCEPTED MANUSCRIPT ONLINE 5 JANUARY 2015

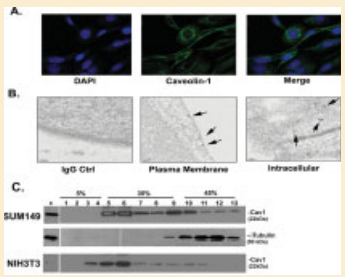
In the following article, the authors summarize current knowledge and gaps in the epigenomic landscape of the developing kidney. It is now known that Pax2/PTIP/H3K4 methyltransferase activity provides the initial epigenetic specification signal to the metanephric mesenchyme. During nephrogenesis, the cap mesenchyme housing nephron progenitors is enriched in bivalent chromatin marks; as tubulogenesis proceeds, the tubular epithelium acquires H3K79me2. The latter mark is uniquely induced during epithelial differentiation. Analysis of histone landscapes in clonal metanephric mesenchyme cell lines and in Wilms tumor and normal fetal kidney has revealed that promoters of poised nephrogenesis genes carry bivalent histone signatures in progenitors. The use of small cell number ChIP-Seq should facilitate the characterization of the chromatin landscape of the metanephric mesenchyme and various nephron compartments during nephrogenesis. Only then will it be known if stem and somatic cell reprogramming into kidney progenitors recapitulates normal development.



Journal of Cellular Biochemistry

ACCEPTED MANUSCRIPT ONLINE 5 JANUARY 2015

With a propensity to invade the dermal lymphatic vessels of the skin overlying the breast and readily metastasize, inflammatory breast cancer (IBC) is arguably the deadliest form of breast cancer. The authors previously reported that caveolin-1 is overexpressed in IBC and that RhoC GTPase is a metastatic switch responsible for the invasive phenotype. RhoC-driven invasion requires phosphorylation by Akt1. Using a reliable IBC cell line the authors set out to determine if caveolin-1 expression affects RhoC-mediated IBC invasion. Caveolin-1 was down regulated by introduction of siRNA or a caveolin scaffolding domain. The ability of the cells to invade was tested and the status of Akt1 and RhoC GTPase examined. IBC cell invasion is significantly decreased when caveolin-1 is down regulated. Activation of Akt1 is decreased when caveolin-1 is down regulated, leading to decreased phosphorylation of RhoC GTPase. Thus, the authors report that caveolin-1 overexpression mediates IBC cell invasion through activation Akt1, which phosphorylates RhoC GTPase.



ACCEPTED MANUSCRIPT ONLINE 23 DECEMBER 2014

The 1,25-dihydroxyvitamin D_3 (1,25D) hormone is derived from vitamin D generated in skin or obtained from the diet, and binds to and activates the vitamin D receptor (VDR) in target tissues including kidney, colon/small intestine, and bone/muscle. The authors tested resveratrol for its ability to modulate VDR signaling, using vitamin D responsive element (VDRE) and mammalian 2-hybrid (M2H) transcriptional system technology. Via VDRE-based assays in kidney, colon and myoblast cells, VDR-mediated transcription was activated by resveratrol, and a cooperative effect on transactivation was observed with resveratrol plus 1,25D. The M2H assay revealed a modest, resveratrol-induced dimerization of VDR with its retinoid X receptor (RXR) heteropartner. Cells treated with both resveratrol and 1,25D displayed synergistic stimulation of VDR–RXR heterodimerization, while resveratrol antagonized rexinoid-mediated RXR-RXR homodimerization. Increased transactivation in response to resveratrol was also observed with a subset of other nuclear receptors and respective cognate responsive elements. Evaluation of wild-type versus a ligand-binding domain mutant VDR revealed that hormone-responsiveness to 1,25D was severely depressed, while the response to resveratrol was only moderately attenuated. Moreover, radiolabeled 1,25D-displacement assays demonstrated an increase in VDR-bound 1,25D in the presence of resveratrol. Thus, resveratrol may affect VDR and other nuclear receptors indirectly, likely via the ability of resveratrol to: (1) potentiate 1,25D binding to VDR; (2) activate RXR; and/or (3) stimulate SIRT1, an enzyme known to deacetylate nuclear receptors. The results of the study elucidate a possible pathway for crosstalk between two nutritionally derived lipids, vitamin D and resveratrol, both of which converge on VDR signaling.