Maastricht University

Metabolic reprogramming and redox perturbations

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CHAPTER 8: SUMMARY

The goal of this PhD thesis was to understand how changes in redox biochemistry affect cellular metabolism and whether this plays a role in the biology of lung epithelial cells and allergic lung diseases. We started our investigations by examining the importance of metabolic reprogramming in allergic airways disease, before linking these changes with the redox environment. Work herein highlights glycolytic reprogramming and redox perturbations as contributors in the pathophysiology of allergic airways disease (in mice) and in asthma. In addition, we describe a new complex mechanism by which glutathione, a major determinant of redox homeostasis, regulates its own synthesis with relevance to inflammatory allergic lung diseases, notably asthma.

After the introduction of key players investigated in this thesis along with the supportive background and the study questions (**chapter 1 and 2)**, we first explored the importance of metabolic alterations in the development of allergic airway disease in mice. In **chapter 3**, we reported the critical role played by enhanced glycolysis in house dust mite-induced allergic airways disease, an asthma model that we used in our studies. We additionally described IL1B signaling as the driver for the aforementioned glycolytic reprogramming and demonstrated its contribution to the pro-inflammatory responses in epithelial cells. Moreover, we confirmed our results in human samples where we showed that both sputum and nasal cells derived from asthmatics exhibited higher lactate levels, indicative of elevated glycolysis, compared to healthy controls. This higher lactate levels correlated positively with IL1B but negatively with lung function. We therefore suggested the potential use of elevated lactate and IL1B as non-invasive biomarkers in asthmatics.

Results from chapter 3 demonstrated increases in expression of PKM2, a key enzyme in glycolysis pathway, levels in nasal epithelial cells derived from asthmatics as well as in mice with HDM-induced allergic airways disease. Therefore, in **chapter 4**, we designed our experiments to study a potential role played by PKM2 in asthma pathogenesis. Here, we showed that PKM2 indeed promoted the allergic response in HDM-induced allergic airways disease and in epithelial cells, contributing to the disease pathogenesis. In addition, activating the PKM2 tetramer, using TEPP46, decreased mucus metaplasia, attenuated collagen deposition, and dampened IL-1B-induced proinflammatory cytokines in mice. As a result, we highlight the possibility that targeting PKM2 might be of significant value in asthma therapeutics.

After confirming the involvement of metabolic alterations in the development and pathogenesis of allergic airways disease, we moved to investigate the involvement of redox perturbations in this regulation. Utilizing an unbiased multi-omics approach in **chapter 5**, we first confirmed the IL1B contribution to the enhanced glycolysis. Secondly, we demonstrated a role played by S-glutathionylation chemistry in regulating glycolysis in epithelial cells. This result stemmed from the correlation between overall increases in S-glutathionylation and elevated glycolysis. In addition, multiple glycolytic genes were targets for S-glutathionylation, further linking metabolic reprogramming with redox biochemistry. Interestingly, we also showed the impact of the higher S-glutathionylation on inflammatory signal in epithelial cells, notably the increases in TSLP and GM-CSF. This further emphasize the link between redox perturbations and inflammatory cytokines in asthma.

Our multi-omics analysis in chapter 5 unraveled an interesting observation whereby GSH, the mainstay of redox homeostasis, is increased in response to IL1B. In **chapter 6**, we sought to better understand the molecular mechanism underlying this GSH upregulation and whether this have any impact on IL1B-induced inflammatory signaling and therefore is relevant to asthma. In this chapter we identified a new mechanism by which GSH, through S-glutathionylation of the deubiquitinase OTUB-1, positively regulated its own synthesis. This mechanism involved the upregulation of system x_c^-, a cystine transporter that have implications in multiple diseases. In addition, we demonstrated the contribution of GSH (and system x_c^-) in IL1B-induced proinflammatory responses, specifically TSLP. The outcome of this chapter highlights the role played by S-glutathionylation biochemistry in metabolic reprogramming and its contribution to inflammatory events. In addition, in this chapter we identify a new paradigm important in GSH regulation that may translate to better therapeutics in multiple inflammatory conditions involving GSH, including asthma.

In **chapter 7**, we discussed the main findings of the thesis and elaborated on connecting the dots between metabolic reprogramming, redox homeostasis and their relevance in asthma pathogenesis. Overall, work in this thesis broaden our current knowledge on the crosstalk between glycolytic reprogramming and redox perturbation and their implications in asthma pathogenesis