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Evaluation of 5-methylcytosine and 5-hydroxymethylcytosine as potential biomarkers for characterisation of chemical allergens

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Running Head: Chemical sensitization and DNA methylation biomarkers

Abstract

Epigenetic regulation of gene expression plays a pivotal role in the orchestration of immune responses. Chemical allergens form two categories: skin sensitizing chemicals associated with allergic contact dermatitis, and chemicals that cause sensitization of the respiratory tract and occupational asthma. In mice these are characterized by different T helper (Th) cell responses. Changes in DNA methylation in particular have been implicated in the *in vivo* responses to chemical allergy. As such it was hypothesised that differentially methylated regions (DMR) may provide candidates biomarkers of chemical allergy. To examine this, mice were exposed to 2,4-dinitrochlorobenzene (DNCB; a contact allergen) or trimellitic anhydride (TMA; a respiratory allergen). DNA from draining lymph nodes was processed for methylated (5mC) and hydroxymethylated (5hmC) DNA immunoprecipitation (MeDIP/hMeDIP) then selected DMR analysed by qPCR. We describe a number of DMRs which, by combined analysis of 5mC and 5hmC, differentiate between responses induced by DNCB and those by TMA. Furthermore, these changes in methylation are specific to the draining lymph node. The *Gmpr* DMR is suggested as a possible biomarker for contact allergen-induced immune responses; it is characterised by divergent levels of 5mC and 5hmC DNCB-treated mice only. In contrast, the *Nwc* DMR was characterised by divergent 5mC and 5hmC specifically in response to TMA, highlighting its possible utility as a biomarker for responses induced by chemical respiratory allergens. These data not only represent novel analysis of 5hmC in response to chemical allergy *in vivo*, but with further investigation, may also provide a possible basis for differentiation between classes of chemical allergens.

Abbreviations

5hmC, 5-hydroxymethylcytosine; 5mC, 5-methylcytosine; AOO, acetone:olive oil; DMR, differentially methylated region; DNCB, 2,4-dinitrochlorobenzene; hMeDIP, hydroxymethylated DNA immunoprecipitation; IFN, interferon; IL, interleukin; IP, immunoprecipitated; LLNA, local lymph node assay; MeDIP, methylated DNA immunoprecipitation; Tc, cytotoxic T cell; Tet, ten eleven translocation; Th, T helper; TMA, trimellitic anhydride.

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