Filling the gaps: need for research on cell-specific xenobiotic metabolism in the skin

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The removal and metabolism of organic molecules is a pivotal body function, usually performed by phase I and phase II enzymes. While detoxification is beneficial and necessary, at the same time, the metabolic intermediates and breakdown products generated in the process can have immunogenic, cancerogenic or apoptogenic potential, which differs from the respective parental chemical. Whether and which adverse health effects ensue depends on the affected cell types and tissue. For instance, if damage caused by a chemical induces apoptosis, easily regenerating tissues may cope better than slowly proliferating or rare precursor cells. On the other hand, potential extent of damage is conceivably dependent on the xenobiotic metabolizing activity of cell types, which in turn might be governed by exposure, that is, tissues with high exposure could be more competent in xenobiotic metabolism. There is, however, a surprising lack of research to identify cell-specific xenobiotic metabolism. Research on the molecular activity of xenobiotic metabolizing enzymes (XME) has traditionally a strong focus on the liver as the main metabolizing and detoxifying organ of the body. The skin is less well studied, albeit it forms a major barrier against the environment (including the chemical environment) and is a target of occupational, accidental and intended-use (i.e., cosmetics and pharmaceuticals) chemical exposure. Risks of exposure are irritation, inflammation, allergies and cancer. Conceivably, skin cells may possess yet underestimated strategies to balance XME-mediated danger.

In a recent paper, the team around Michael Girardi (Modi et al. 2012) presented the exciting finding that differential expression of phase I enzymes CYP4501A1 and 1B1 in skin Langerhans cells versus keratinocytes leads to generation of DNA-modifying metabolites from the carcinogen 7,12-Dimethylbenz[a]anthracene (DMBA) in the skin and eventually non-melanoma skin cancer. They found that skin Langerhans cells efficiently metabolize DMBA to DMBA-3,4-diol which leads to oncogenic Hras mutations. Mice lacking skin Langerhans cells had fewer skin tumours upon DMBA treatment. They conclude “*Thus, tissue-associated dendritic cells can enhance chemical carcinogenesis via PAH metabolism, highlighting the complex relation between immune cells and carcinogenesis.*” While the paper of Girardi and colleagues looks at chemical-induced (DMBA-induced) cancer, it has also important implications for understanding skin physiology and skin toxicology.

Sun light, that is, its UV radiation component, is the most important stressor of skin (Fritsche et al. 2007) and has long been known to be genotoxic and a major risk factor in skin cancer (Narayanan et al. 2010). UV and UV-induced DNA damage are the primary cause not only for melanoma with increasing incidence and new cases worldwide every year (Little and Eide 2012), but also of skin basal cell carcinoma, squamous cell carcinoma, Kaposi’s sarcoma and others. Recent studies confirmed that UV radiation sensitizes keratinocytes to polycyclic aromatic hydrocarbons (PAH)-mediated DNA adduct formation (Nair et al. 2009), and therefore, the physiological interplay of UV radiation and chemical inducers should not be neglected. Both DMBA and UV are targeted toward the transcription factor AhR (aryl hydrocarbon receptor), which represents the chemical sensor in the skin and controls the transcription of genes for phase I and phase II

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enzymes. AhR can be activated both by DMBA and by amino-acid dimers generated by UV-light. AhR is highly expressed in all skin cell types, that is, in keratinocytes, Langerhans cells, dendritic epidermal T cells, melanocytes and fibroblasts, albeit differentially inducing XMEs. Intriguingly, some skin cells, but not all, appear to keep AhR activation in check by concomitantly expressing the AhR repressor (Jux et al. 2009; Tigges et al. 2012). Beyond orchestrating detoxification of chemicals, AhR plays an important role in skin cell homeostasis and the skin immune system (Esser 2012). This raises the question to what extent the expression levels of AhR and its activation by small chemical compounds is skin protective (by quickly removing dangerous chemicals) or genotoxic (by conversion of inert chemicals into toxic metabolites). The epidemiological connection between skin cancer and exposure to AhR-activating substances in workers (e.g., coal miners), or by lifestyle (in smokers!), or via UV radiation are well known. The results by Modi et al. are a dire warning to avoid this exposure.

Some important questions remain. Compared to liver, skin has historically been much less investigated or even considered as an actively metabolizing organ in toxicological studies. The situation is now changing. There is increasing interest to understand skin metabolism particularly in regard to chemical registration. The 7th amendment to the European Cosmetics Directive, for example, demands replacement methods for animal testing (Pauwels and Rogiers 2004). This requires, in consequence, better information on XME and their regulation for any proposed test model and for the target organ skin. Previous publications indicate that skin of various species is indeed well equipped with a broad range of xenobiotic metabolizing enzymes (for reviews see Gibbs et al. 2007; Oesch et al. 2007; Svensson 2009). Work from our own institute recently has proven that human whole skin as well as human keratinocytes, the main cell type of the epidermis, are equipped with both Phase I and II XME (Götz et al. 2012a, b). Interestingly, the CYP450 monooxygenase family 1, which is an integral part of the publication of Modi et al., is neither expressed nor active in human keratinocytes without stimulus, but strongly reacts toward AhR ligands leading to physiologically relevant substrate turnover rates (Götz et al. 2012a) which have the potential to convert CYP1 from a protective to a detrimental XME activity. Almost nothing is known for XME profiles in human Langerhans cells compared to other skin dendritic cells and on the possibility of their differential expression levels upon chemical exposure or UV radiation (both could be mediated by AhR).

Apart from the above-discussed Langerhans cells, skin comprises a variety of specialized cells like keratinocytes, fibroblasts, stem cells, melanocytes, Merkel cells and

others where there is still more need for information on xenobiotic metabolism and its regulation. Particularly, the latter two cell types are known to be involved in the development of aggressive skin tumors, melanoma (with UV radiation a major cause) and Merkel cell carcinoma (Andea et al. 2008), respectively. The involvement of metabolic processes in the formation of immuno-reactive compounds from xenobiotics, for example, via *N*-acetylation (Aeby et al. 2009) or via functional loss of glutathione *S*-transferase activity (Lutz et al. 2001), is again of relevance in the context of the development of allergic reactions. Moreover, in human AhR polymorphisms exist some of which reduce AhR activity and conceivably XME balance, but whose relevance in skin cancer and skin health is entirely unexplored. Another important aspect is the likelihood of species specificity regarding xenobiotic metabolism (Gassmann et al. 2010). XME expression, specificity, tissue distribution and regulation or AhR activity might differ from human XME which must be considered in toxicological studies. Finally, the surprising finding of differential expression of XMEs between skin cells could be mirrored by differential expression of DNA repair enzymes (needed to repair damage from genotoxic chemicals). This is largely unexplored, albeit some evidence suggests that DNA repair enzymes are not uniformly expressed in all cells of the body (Bauer et al. 2011).

Taken together, there is a high demand to understand human skin xenobiotic metabolism on a cell- and species-specific level. Any such knowledge would also be welcome for preventive or therapeutic considerations, involving any disbalance of XME enzymes and eventually tipping the scale from protection to genotoxicity.

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