Toxicogenomic effect of nickel and beyond

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Abstract

Nickel is widely applied in industrial settings and Ni (II) compounds have been classified as group one human carcinogens. The molecular basis of Ni (II) carcinogenicity has proved complex, for many stress response pathways are activated and yield unexpected Ni (II) specific toxicology profile. Ni (II) induced toxicogenomic change has been associated with altered activity of HIF, p53, c-MYC, NFκB and iron and 2-oxoglutarate dependent dioxygenases. Advancing high-throughput technology has indicated the toxicogenome of Ni (II) involves crosstalk between HIF, p53, c-MYC, NFκB and dioxygenases. This paper is intended to review the network of Ni (II) induced common transcription-factor-governed pathways by discussing transcriptome alteration, its governing transcription factors and the underlying mechanism. Finally, we propose a putative target network of Ni (II) as a human carcinogen.

Keywords

nickel; gene expression profile; microarray; next generation sequencing; p53; HIF; dioxygenase

Introduction

Nickel (Ni) is widely employed in industrial applications due to its corrosion resistance, physical strength, and special magnetic electronic properties. Ni (II) compounds have been classified as group one human carcinogens and metallic nickel has been listed as group 2b possible human carcinogens by the International Agency for Research on Cancer (IARC) (IARC 1990). The molecular basis of Ni (II) carcinogenicity has proved complex, for many stress response pathways are activated and yet yield unexpected Ni (II) specific toxicology profile.

Gene expression profiling has revealed a comprehensive image of differentially expressed genes (DEG) in cells after various stresses including Ni (II). The picture has become daunting with the advancing technology of microarray and next generation sequencing, turning the candidate gene pool from several thousands of genes to more than 30 thousands

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genes (Affimetrix). It is a useful strategy to focus on identification of modules (transcription factors, chromatin modifiers) that may regulate a set of genes involved in a biological process, and to work down the regulatory hierarchy to identify specific effectors. Toxins usually induce similar toxicogenomic change through common transcription-factor-governed pathways (Jennings et al. 2013). This paper is intended to review the crosstalk of Ni (II) induced common transcription-factor-governed pathways by discussing transcriptome alteration, its governing transcription factors and the underlying mechanism. Finally, we propose a putative target network of Ni (II) as a human carcinogen.

HIF governed DEG in Ni (II) exposed cells

An early study utilizing Affymetrix platform mouse U74 Genechip array to profile DEG in mouse embryonic fibroblast exposed to Ni (II) has found increased expression of genes involved in glucose metabolism including glycolytic enzymes and genes responsible for glucose transport (Salnikow et al. 2003). A comparison of DEG induced by Ni (II) and hypoxia revealed a significant role of hypoxia inducible factors (HIF) in altered transcription profile in both cases. Indeed, HIF has been found accumulated in various cell lines exposed to Ni (II) (Chen and Costa 2009; Yao et al. 2014). Glycolytic enzymes are among the genes that are inducible by HIF. A careful examination of DEG in Ni (II) exposed cells revealed that hexokinase I and glucose 6-phosphate dehydrogenase were two glycolytic enzymes that were not induced by nickel, and neither were they induced by hypoxia (Salnikow et al. 2003). In consistence with this, Ni (II) failed to induce glucose metabolism genes expression in HIF-1α deficient mouse fibroblast (Salnikow et al. 2002; Salnikow et al. 2003); indicating Ni (II) exerts its effect through up regulating HIF protein levels and their activities.

Ni (II) reportedly down regulates xenobiotic-response element containing genes, including CYP1B1, NQO1, UDP-glucuronyltransferase1A6, glutathione S-transferases, and aldehyde dehydrogenases (ALDH)(Davidson et al. 2003). These genes are regulated by aryl hydrocarbon receptor (AHR), a transcription factor that shares the same heterodimerization partner, ARNT/HIF-1β, with hypoxia inducible factors. It is conceivable that these two pathways might interact via competing ARNT/HIF-1β. However, evidence indicates this might not be true. Although the AHR protein amount is 4 to 10 fold higher than ARNT/HIF-1β *in vivo* and *in vitro*, the vast majority of liganded AHR is rapidly degraded, and only about 15% of the ARNT/HIF-1β pool is used when the AHR-signaling pathway is saturated (Pollenz 1996). Similarly, only about 12 to 15% of the ARNT/HIF-1β pool is sequestered in cells cultured under 1% oxygen tension for up to 16 hours (Pollenz et al. 1999). On the other hand, Ni (II) was capable of reducing AHR regulated genes' expression to similar extent in the absence of HIF-1α (HIF-1α deficient mouse fibroblast); indicating HIF activity is dispensable to the suppression of AHR regulated genes induced by Ni (II) (Davidson et al. 2003).

Iron homeostasis and dioxygenase activity

The association of Ni (II) and HIF has been linked to iron homeostasis by further studies (Davidson et al. 2005). Iron homeostasis has to be meticulously balanced in cells to provide sufficient iron to achieve cellular functions, and to eliminate excessive accumulation of iron

to avoid toxicity. Cells sequester extraneous iron by storing it in ferritin molecules (Nadadur et al. 2008). Ni (II) was found to block transferrin-dependent and -independent iron uptake, suggesting Ni (II) exerts its effects via perturbing iron homeostasis (Davidson et al. 2005). The prolyl hydroxylase PHD family hydroxylates the oxygen dependent disruption (ODD) domain of HIF. The hydroxylated proline residues in the ODD domain of HIF proteins can be recognized by E3 ligase Von Hippel-Lindau protein (VHL) and targeted for degradation. The PHD family is one of numerous members of iron and 2-oxoglutarate dependent dioxygenase family that also require oxygen and ascorbic acid for enzymatic activity. When the prolyl hydroxylases are not functional, no hydroxylation of the proline residues in the ODD domain occurs and VHL will not bind to it. This phenomenon was found inducible by Ni (II) in A549 cells (Davidson et al. 2005); indicating Ni (II) stabilizes HIF proteins via perturbing hydroxylation at ODD domain.

Iron and 2-oxoglutarate dependent dioxygenase is also a major component of histone demethylases. These jumonji C (JmjC)-domain containing enzymes can catalyze the oxidization of methyl groups on histones, and the resultant hydroxymethyl group is spontaneously lost in the form of formaldehyde, to remove one methyl group from the modified lysine(Labbe et al. 2013).

Ni (II) has been found to inhibit demethylase activity of KDM3A (JMJD1A) *in vitro*, and in turn led to an accumulation of dimethylation at histone H3 lysine 9 (H3K9me2) (Chen et al. 2010a). The same study also showed that the activity of DNA repair enzyme ABH2 was inhibited by Ni (II). Extended X-ray absorption fine structure showed that the best fit for iron binding ABH2 consists of five oxygen/nitrogen donor ligands of which two are histidine ligands; and when nickel binds to ABH2, the binding site is indistinguishable from the iron-binding site (Chen et al. 2010a). Isothermal titration calorimetry analysis suggested that Ni (II) binds to ABH2 with higher affinity than Fe (II). It is likely that dioxygenases such as PHD family, JmjC-domain containing histone demethylases and ABH DNA repair enzymes use the same iron coordinating motif (His-Asp-His) to bind ferrous iron at their active sites, and Ni(II) competes with Fe(II) and replaces it at the iron-binding site (Chen et al. 2010a; Gorres et al. 2009).

Histone mark governed DEG in Ni (II) exposed cells

The inhibition of JmjC-domain containing histone demethylases activity by Ni (II) was further evidenced by accumulation of other methylation modifications on histones in Ni (II) exposed cells, both *in vivo* and *in vitro*. H3K9me2 (substrate of JmjC-domain containing KDM3A, KDM4A, etc.), a mark of transcriptional repression; and H3K4me3 (substrate of JmjC-domain containing KDM2B, KDM5A, etc.), a mark of transcriptional activation, were found increased in gene promoter regions in cells exposed to Ni (II) (Chen et al. 2006; Chen et al. 2010b; Tchou-Wong et al. 2011). Human peripheral blood mononuclear cells (PBMC) from healthy subjects treated with Ni (II) *ex vivo* showed an increase in global levels of H3K4me3 and H3K9me2 (Arita et al. 2012b). On the other hand, *in vivo* study of PBMC of subjects with occupational exposure to high levels of nickel at a nickel refinery in China has found elevated global level of H3K4me3 ($p = 0.0004$) when compared to referent subjects(Arita et al. 2012a). In an independent *in vivo* study of workers in a steel plant,

H3K4me2 (substrate of JmjC-domain containing KDM5A, KDM5B, etc.) were found increased in association with the years of steel plant employment of the study subjects. The increased H3K4me2 level was found associated with nickel exposure but not aluminum, manganese, zinc, lead exposure (Cantone et al. 2011). It is noticeable that H3K4me2 is also a substrate of a second group of histone demethylase, amine oxidase domain-containing flavin dependent enzymes KDM1A and KDM1B (Wojcieszynska et al. 2012). Whether Ni (II) exerts its effects through this group of enzyme needs to be investigated.

A high throughput screening of KDM3A (JMJD1A) targeted genes in human bronchial epithelial BEAS-2B cells exposed to Ni (II) using ChIP-on-Chip Affymetrix GeneChip® Human Promoter 1.0R Array revealed 620 potential genes that are in close association with KDM3A (supplemental table 1 in Chen et al. 2010b), 67 of which were repressed more than two-fold when siRNA against KDM3A was used to knockdown the histone demethylase expression in BEAS-2B cells (supplemental table 2 in Chen et al. 2010b), indicating these 67 genes are most likely to be affected by Ni (II) through inhibiting KDM3A activity. We cross-referenced the list of genes that were down regulated in nickel refinery workers *in vivo* when compared to referent subjects (supplemental table 1 in Arita et al. 2012a), and found 10 genes were repressed in both cases (Table 1). Given these two independent studies were conducted in different systems (*in vitro* and *in vivo*) and different cell types (bronchial epithelial cells and PBMC), we argue that this observation suggests *in vitro* research of Ni (II) provides valuable information to help understand the consequences of human exposure to Ni (II) and their underlying mechanism.

Ni (II) exposure has been shown to induce accumulation of histone marks of both repressive and active transcription. While decreased gene transcription levels probably result from accumulation of H3K9me2 at gene promoter regions, the increased transcription levels might be caused by an increase of H3K4me3 at gene transcription starting sites (TSS) (Barski et al. 2007). Despite the dramatic increase of global H3K4me3 in Ni (II) exposed human lung adenocarcinoma A549 cell line (detected by Western Blot) (Zhou et al. 2009), the global H3K4me3 profile at TSS wasn't affected by Ni (II) in A549 cells (detected by ChIP-Seq) (Tchou-Wong et al. 2011). It was rather the post-TSS peak of nickel-treated cells remained higher than that of control cells over a broader region spanning over 4,000 bp downstream of TSS of the genes that were up-regulated in nickel-treated cells (Tchou-Wong et al. 2011).

P53 and MYC governed DEG in Ni (II) exposed cells attenuated by HIF

Increased gene expression of p53 (Salnikow et al. 2002), and its downstream CDK inhibitor p21 (*CDKN1A*) (Arita et al. 2012a; Green et al. 2013; Salnikow et al. 2002; Wong et al. 2013), GADD45 (Arita et al. 2012a; Arita et al. 2012b; Salnikow et al. 2002; Wong et al. 2013) has been reported in Ni (II) exposed cells, which includes *in vitro* studies on human lung cell lines BEAS-2B, H460, and *in vivo* study on PBMC from nickel exposed human subjects, indicating the activation of p53 is a highly reproducible phenomenon from nickel exposure. However, p53 transcription factor binding site was not over-represented in the genes that had elevated expression in nickel refinery workers (Yao et al. unpublished data), this is consistent with an early report that nickel (both soluble and insoluble form) did not

induce p53 driven reporter gene (Huang et al. 2001). Moreover, no change has been found in expression of BCL2, BCL-XL, and MCL1 (transactivated by p53) in Ni (II) exposed cells (Arita et al. 2012a; Green et al. 2013).

The activity of p53 is regulated at multiple layers, including the phosphorylation at Ser15 and protein levels, which have been found up-regulated and coordinated with an increase of p21 expression in cells exposed to Ni (II) (Ding et al. 2009; Green et al. 2013; Wong et al. 2013). The induction of p21 has been found to be p53-dependent and HIF-independent in Ni (II) exposed cells (Salnikow et al. 2002; Wong et al. 2013). On the other hand, the induction of GADD45 has been found to be independent of p53 and HIF (Salnikow et al. 2002; Wong et al. 2013).

Interestingly, p53 is activated under hypoxia but its activity is usually attenuated at the same time (Achison and Hupp 2003; Crowder et al. 2013; Koumenis et al. 2001). Hypoxia environment induced p53 accumulation and caused an enhanced interaction of p53 with mSin3A transcription co-repressor complex but not p300 transcription activator complex (Koumenis et al. 2001). It was later proven that HIF and p53 indeed compete for p300 for their transactivation activity, ectopic expression of p300 could relieve the competition (Schmid et al. 2004). We propose that the seemingly contradictory phenomena of p53 activation (accumulated p53 protein level versus transactivation of limited p53 binding genes) observed in Ni (II) exposed cells was rather due to limited amount of p300 occupied by dramatically elevated HIF protein, which led to limited transactivation of p53 binding genes (Figure 1).

Similar activation-attenuation phenomena have been observed in c-MYC pathway in Ni (II) exposed cells, but through different mechanism. Ni (II) induced c-MYC protein as well as mRNA transcription in BEAS-2B cells while HIF (both HIF-1α and HIF-2α) attenuates c-MYC activity by promoting proteasomal degradation of c-MYC in lung carcinoma A549 cells (Li et al. 2009a; Li et al. 2009b). Ubiquitin specific peptidase 28 (USP28) is a deubiquitinating enzyme bound to c-MYC that prevent salvaging signal to be accumulated on the protein (Wasylishen et al. 2013). Ni (II) and hypoxia increased the levels of the gene silencing mark H3K9me2 (substrate of iron dependent dioxygenase) at USP28 promoter region, which suppressed USP28 gene expression (Li et al. 2009a). The decreased level of USP28 in Ni (II) exposed cells further led to enhanced proteasomal degradation of c-MYC (Figure 1). Although both HIF-1α and HIF-2α have been found essential for c-MYC degradation in A549 cells, no evidence support HIF regulates the expression of USP28 (Li et al. 2009a). Interestingly, MYC and p53 activation in Ni (II) exposed cells is known to lead to cell apoptosis, the attenuation of both pathways by HIF presumably would help cells to bypass apoptosis.

Reactive oxygen species (ROS) governed DEG and pathways

Nickel induces weak oxidative stress that depletes glutathione and activates nuclear factor kappa B (NF-κB) and other oxidatively sensitive transcription factors (Salnikow et al. 1994). However, induced ROS is a very common phenotype in cells that encounter various toxins, so we chose to discuss ROS governed DEG and pathway alterations induced by Ni

(II). ROS have been implicated in a wide array of cellular processes by mediating signal transduction. ROS induced by Ni (II) was able to promote phosphorylation of AKT (protein kinase B). The activated AKT in turn activates apoptosis signal-regulating kinase 1 (ASK1) by promoting the phosphorylation at threonine 838 residue, this association is specific in Ni (II) exposed cells but not in unexposed cells (Pan et al. 2010). The signal is then relayed to downstream kinase p38, which activates AP-1 and NFAT, leading to a p53 independent G2-M growth arrest (Ding et al. 2009; Huang et al. 2001).

The activated NF-κB by Ni (II) serves as a transcription repressor, leading to decreased expression of key regulators of the interferon-dependent transcriptional cascade, IRF3, IRF7 and IKKε. The activated NF-κB also results in a down-modulation of N-terminal truncated (N) p63, which lacks the transactivation domain (Zhang et al. 2011). A supplement of Np63 suppressed p21 induction by Ni (II), indicating there is crosstalk between p53 and NF-κB pathways in Ni (II) exposed cells (Zhang et al. 2011). Ni (II) up-regulates p21 through p53 and NF-κB pathways. A direct activation of p53 as well as an inhibition of p21 negative regulator Np63 via NF-κB lead to decreased proliferation in cells exposed to Ni (II). It was proposed that the inhibitory effect of Np63 on p21 promoter may be either through p53 binding site or other sites beyond p53 (Zhang et al. 2011). The cell cycle arrest and apoptosis induced by activation of p53, NF-κB and c-MYC might be critical and serve as a selection force during Ni (II) carcinogenicity, because only the cells have compromised p53, NF-κB and c-MYC will be selected for during long term Ni (II) exposure. This hypothesis has been supported by a selection for Ni (II) resistant cells in mouse fibroblast, only those with lower NF-κB, AP-1 DNA binding capacity were selected and an altered oxidative stress response was found in these cells, which provided a possible mechanism of cell transformation (Salnikow et al. 1994). Nevertheless, it is critical for cancer cells to arrest their growth and survive in secondary organs as micrometastases until suitable environmental conditions are present to reactivate tumor cell outgrowth (Tran et al. 2011).

Conclusion remark

Ni (II) modulates an intricate network containing several modules including transcription factors and histone modifiers through perturbing iron homeostasis, oxidative stress; ultimately resulting in early transformation, as elaborated in Figure 1. Ni (II) promotes proliferation and cell survival by increasing the accumulation of HIF, and hence HIF governed gene expression. HIF directly inhibits transactivation of p53 by competing p300 transcription activator, further down-regulating the expression of p53 governed gene expression and apoptosis. Nickel treatment leads to an accumulation of c-MYC, however, the accumulation is attenuated by Ni (II) induced H3K9me2 driven transcription repression of USP28. Oxidative stress generated by Ni (II) activates NFκB, p53 and c-MYC pathway, promoting cell cycle arrest and apoptosis, which might serve as a selection force to shift the population to one with impaired tumor suppressor genes as well as keeping the cells as dormant micrometastases until suitable microenvironment presents.

Acknowledgments

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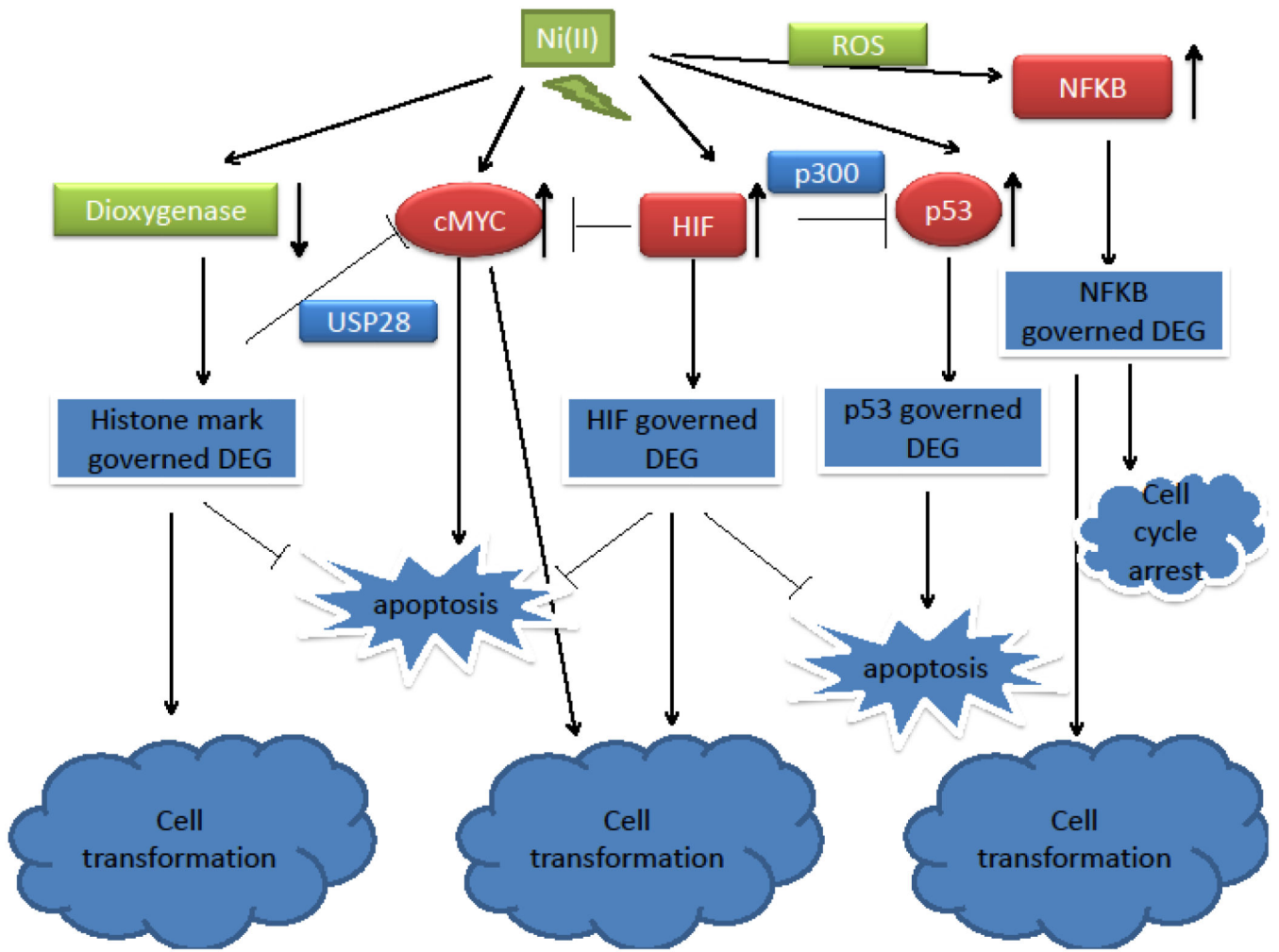
Figure 1.
Putative target network of nickel carcinogenicity.

Table 1

KDM3A target genes that were repressed in nickel refinery workers.

Gene Symbol	Expression				Description
	Control RNAi	KDM3A RNAi	Referents	Nickel refinery workers	
IL6R	1	0.37	1	0.61	Interleukin 6 (IL6) receptor
TAF1	1	0.2	1	0.81	TATA box binding protein (TBP)-associated factor
ITGB2	1	0.28	1	0.77	Integrin, beta 2
FAM48A	1	0.28	1	0.68	Family with sequence similarity 48, member A
AMACR	1	0.33	1	0.83	Alpha-methylacyl-CoA racemase
EXOSC2	1	0.34	1	0.78	Exosome component 2
EDEM3	1	0.41	1	0.65	ER degradation enhancer, mannosidase alpha-like 3
SMC2	1	0.45	1	0.67	Structural maintenance of chromosomes 2
MTAP	1	0.47	1	0.84	Methylthioadenosine phosphorylase
C10orf57	1	0.49	1	0.66	Also known as TMEM254, transmembrane protein 254