MDS Newsletter

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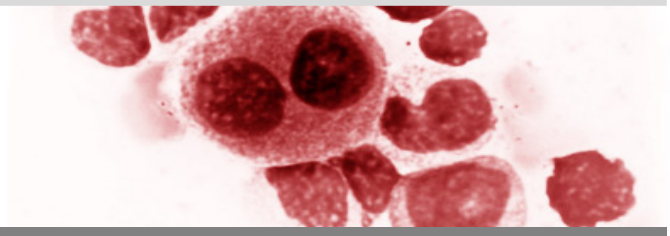
EMSCO
MYELODYSPLASTIC SYNDROMES



Motivation und Mission

The goal of the MDS Newsletter is to promote new knowledge and to support the exchange of information in the clinical research, diagnostics and therapy of myelodysplastic syndromes (MDS).

The newsletter is particularly directed towards clinicians, scientists and industry developers of therapies for MDS.

Kind regards,

Silke Gloaguen in the name of the EMSCO team

4th French-German MDS Workshop & 3rd Annual EMSCO Meeting in Marseille

For the fourth time specialists from France, Germany as well as other European countries met in Marseille on the 17th and 18th September 2015 in order to discuss the latest developments in MDS diagnosis and therapy in their respective countries. As last year's meeting had been organised by the German MDS group in Dresden, this time it was France's turn to host the event. More than 80 participants were therefore welcomed in Marseille by the three chairs Prof. Norbert Vey (Marseille), Prof. Pierre Fenaux (Paris) and Prof. Uwe Platzbecker (Dresden). Again, it was with great pleasure that we noticed that the conference continues to raise interest beyond the French and German borders and that participants from Italy, Spain, the Czech Republic, the Netherlands as well as Austria were present.

On the first day of the conference, the progress of the two commonly initiated IITs by the French and German MDS study groups were presented. These trials are coordinated under the common EMSCO label and have both started recruitment within the last year. Furthermore snapshots of clinical trials in other European countries were provided and a project related to MDS and carried out in a context of social sciences was depicted: the evaluation of a question prompt list for MDS patients. The first day finished with an educational session hosting different topics, i.e. a critical review of the 2006 IWG criteria, the statistical design of clinical trials and a short review of complex abnormal karyotype in MDS.
The second meeting day was all about clinical research and the different approaches for low-risk and high-risk >>>

Group photo of the 4th French-German MDS Workshop / 3rd Annual EMSCO Meeting

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GMIHO
Gesellschaft für Medizinische Innovation – Hämatologie und Onkologie mbH
Managing Director:
Claus-Peter Held

Address:
GMIHO mbH
Alte Jakobstraße 77
10179 Berlin
Phone:
+49 351.25933-280
Fax:
+49 351.25933-289
Email: info@gmiho.de
http://www.gmiho.de

registered at
Berlin-Charlottenburg
District Court
(Amtsgericht)
HRB 101719 B

VAT-ID
DE 250223501

Editor:
Silke Gloaguen

Layout:
Annegret Böttner

disease, as well as specific challenges associated with the therapy, as for instance iron overload or treatment failure on standard regimens, such as ESAs in low risk and azacytidine in high-risk MDS.

We are now looking forward to the next reunion in Florence where the colleagues from Italy with Prof. Valeria Santini will host the upcoming meeting on the 29th and 30th of September 2016. And last but not least a big thank you for the successful outcome of this year's event goes to all organisers, speakers and participants as well as our supporters Celgene, Novartis, Janssen, Boehringer-Ingelheim, Onconova and Amgen.

Author: Silke Gloaguen

Sponsors of the 4th French-German MDS Workshop & 3rd EMSCO Annual Meeting:

14th Annual D-A-CH MDS Meeting in Düsseldorf

On the 23rd of September 2015 the 14th Annual D-A-CH MDS Meeting took place in Düsseldorf hosted by Prof. Ulrich Germing. The purpose of this yearly reunion is to foster and further expand collaborative projects between the three countries and to discuss current and potential future projects initiated in this cross-border context.

Prof. Ulrich Germing

As every year, about 50 collaborators gathered in Düsseldorf to exchange ideas. During the first part of the day, various common initiatives presented an overview regarding their current status. First, the Düsseldorf MDS Registry commented on the number of sites involved up to date. This was followed by a status report by EMSCO, which presented the two currently recruiting collaborative trials (DACOTA and EUROPE) between the French and the German MDS study groups. Prof. Hofmann from Mannheim updated the community on the collaborative project supported by the Deutsche Krebshilfe and Prof. Gattermann from Düsseldorf presented the common biobanking programs.

Prof. Platzbecker and Dr. Wermke from Dresden then talked about selected current and planned clinical trials in MDS, including a summary of the upcoming EU regulation No 536/2014, which will impact the way European sponsors have to submit their studies in the near future. This was followed by various scientific talks. The scientific program included, among others, different topics related to molecular genetics, such as TP53 mutational status, clonal evolution during the therapy, JAK2 in CMML, associations between molecular and cytogenetic aberrations etc. Further presentations included updates on flow cytometry, dysplasia and cytopenia, anemia in del(5q), geriatric assessment, the relevance of telomere length, iron chelation and discussion of scoring systems.

Overall, the D-A-CH MDS community produced 17 common publications between September 2014 and September 2015 and Prof. Germing is now looking forward to another productive year ahead which will include the celebration of the 15th anniversary of the D-A-CH Meeting.

Author: Silke Gloaguen

The 14th MDS D-A-CH Meeting was supported by:

Innate immune and inflammatory deregulation in MDS

Myelodysplastic syndromes (MDS) are a group of clonal hematologic malignancies that are defined by the occurrence of peripheral blood cytopenias caused by defects in hematopoiesis, along with dysplasia of one or more myeloid lineages and a variable risk of progression to acute myeloid leukemia (AML). The heterogeneity of these syndromes, coupled with the lack of good experimental models, has complicated the progress of MDS research. However, the most recent efforts to characterize the specific pathogenetic mechanisms of this disease have identified some of the molecular abnormalities that contribute to the development of MDS (1).

Among the main cellular functions now known to be deregulated in MDS, the activation of innate immunity and inflammation was one of the first reported. The frequent association of MDS with chronic inflammatory disorders (in up to 30% of the cases), especially with rheumatic conditions, has been widely described in case-reports (2, 3), and more recent large-scale epidemiologic studies have confirmed the suspicions that autoimmune diseases increase the risk of MDS (4, 5). Similarly, a history of acute or chronic infections has been associated with a higher risk of developing MDS (5, 6). Taken together, these epidemiologic data strongly indicate that inflammatory and autoimmune disorders increase the predisposition of patients to MDS. It is not clear whether this is the result of a common pathogenetic mechanism or a genetic/epigenetic defect that confers sensitivity to both types of disease. However, the fact that the inflammatory disease precedes MDS in a majority of the cases (3, 6) suggests that this relationship could also be causal, perhaps through the indirect effects of sustained or unresolved inflammation on the bone marrow (BM) niche.

For instance, it is well known that the peripheral blood and BM levels of cytokines and growth factors are significantly altered in most MDS patients. This includes the overexpression of proinflammatory cytokines and chemokines such as TNF-α, IFN-γ, TGF-β, MIP-1β and MCP-1; pro-angiogenic factors such as VEGF and angiogenin; interleukins like IL-6 and IL-8; and the interleukin receptors IL-1α/β and CXCR2 (7-12). This profile is more common in MDS subtypes with low risk of progression to AML, which are characterized by high BM apoptosis rates. Similarly, TNF-α levels have been reported to be directly correlated with intramedullary cell death (7). On the other hand, immunosuppressive cytokines, such as IL-10, tend to be downregulated in low-risk MDS and upregulated in high-risk syndromes, which are characterized by autoimmune tolerance and low response rates to immunosuppressive therapies (13).

As mentioned above, the cytokine expression profiles observed in the different MDS subtypes are closely related to the activation of cell death signaling. Increased intramedullary apoptosis is thought to be one of the driving mechanisms of the BM hypocellularity and PB cytopenias observed in low-risk MDS patients and has been positively correlated with the expression of the death receptor-ligand pair Fas/Fas-L in CD34+ hematopoietic stem and progenitor cells (HSPC) (14, 15). In turn, Fas levels in patient BM appear to be associated with the expression of the pro-apoptotic TNF-α receptor TNFR1, which is more abundantly expressed in low-risk MDS, whereas the anti-apoptotic receptor TNFR2 is more frequent in high-risk patients, in whom levels of Fas are lower (16). This suggests that TNF-α -mediated signaling is both a direct and indirect regulator of apoptosis in BM HSPC. Notably, the direct effects of TNF-α on apoptosis have been ascribed to the activation of p38 MAPK, which is known to be constitutively activated in BM hematopoietic progenitor cells of low-risk patients and, as expected, positively correlated with apoptotic rates (17). Furthermore, other cytokines and growth factors known to be overexpressed in MDS BM cells, such as IFN-γ and TGF-β, also activate p38 MAPK (18), which indicates that this kinase is an important mediator of HSPC apoptosis in MDS.

Another important signaling pathway known to be hyperactivated in MDS BM cells is the toll-like receptor (TLR) pathway. TLR are innate immunity receptors capable of recognizing a variety of microbial and self-components that can be released upon cellular stress or death. Upon ligand binding, they activate different signaling pathways and induce the expression of pro-inflammatory cytokines. Several members from this receptor family, particularly TLR1, TLR2, TLR4, TLR6, TLR7 and TLR9, have been reported to be overexpressed in the BM in a significant fraction of MDS patients (19-21), and TLR4 and TLR9 appear to be correlated with higher levels of apoptosis (19) and TNF-α secretion (20), respectively. Accordingly, some TLR signaling pathway

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mediators such as MyD88, TRAF6 and IRAK1 are upregulated in MDS (22-25), which indicates that the pathway is constitutively activated.

Although the mechanism is still not fully understood, functional studies suggest that constitutive TLR activation could lead to the loss of HSPC function and induce the subsequent hematopoietic aberrations that characterize MDS (21, 24, 25). This effect can be, in part, explained by the activation of transcription factors of the NF-κB family by TLR signaling pathways. NF-κB activity is known to be significantly increased in MDS BM progenitor cells and seems to confer a survival advantage to the abnormal clone (26). Furthermore, NF-κB signaling is essential for the modulation of HSPC functions (27). However, the effects of NF-κB on hematopoietic differentiation are apparently not cell-autonomous (28), which indicates that other mechanisms are involved in the deregulation of hematopoiesis in MDS. For instance, TLR activation induces the secretion of several pro-inflammatory cytokines and some of them, such as IL-6, have been reported to be important regulators of hematopoiesis under stress and to directly affect myeloid differentiation (29). This occurs via p38 MAPK activation (17, 18) which, as previously mentioned, is also an important mediator of apoptosis in MDS BM cells. Moreover, cytokine-mediated p38 MAPK activation can also induce the release of IFN-γ, which has an inhibitory effect on progenitor differentiation and decreases the long-term stem cell-renewal capacity of HSC (30). Thus, the activation of the NF-κB and p38 MAPK signaling pathways by TLR or by their downstream cytokines seems to be one of the driving forces of the deregulation of hematopoiesis that characterizes MDS.

In addition to cytokines, other cells that coexist with HSPC in the BM niche have been shown to play relevant roles in the pathogenesis of MDS. Abnormal cellular immunity responses are typical in MDS BM, including increased numbers of myeloid-derived suppressor cells, which induce defective myeloid and erythroid differentiation (31), and high counts of cytotoxic and helper T-cells and NK cells in low-risk MDS BM (13, 32). The fact that low numbers of these cells are found in high-risk patients while the counts of T-regulatory lymphocytes, which are scarce in low-risk MDS, increase (33, 34) suggests that cellular immunity contributes to the pro-inflammatory microenvironment of low-risk MDS, but a shift toward immune tolerance is necessary for the malignant clone to progress in higher-risk subtypes. Additionally, recent studies have highlighted the relevance of mesenchymal stem cells (MSC), which may contribute to the expansion of cytotoxic T-cells in the BM of low-risk patients and exacerbate the inflammatory response (35). Furthermore, the gene expression profiles of MSC can be reprogrammed by MDS HSPC to favor their adaptation to the inflammatory microenvironment and to allow the expansion of the malignant clone (36). More mature BM cells like stromal cells and macrophages, in turn, appear to be closely involved in the induction of apoptosis in MDS HSPC expressing Fas and TNFR (16, 37).

In conclusion, accumulating evidence shows that innate immune and inflammatory pathways are constitutively activated in MDS and can affect the outcomes of hematopoiesis by inducing abnormal cytokine secretion profiles and modulating cellular immunity. In some patients, this could be the consequence of unresolved chronic inflammation related to an autoimmune or infectious disease. However, in most cases, the causes of this activation are unknown. It could be speculated that some of the genetic and epigenetic abnormalities known to be acquired with aging predispose or sensitize the cells to certain types of stress (e.g., genotoxic or oxidative stress), which can induce immune/inflammatory deregulation, but this hypothesis must be further investigated before any firm conclusions can be made. Nevertheless, the idea that innate immunity and inflammation play pivotal roles in the pathogenesis of MDS is having a significant impact on the development of new therapies for this disease. The findings discussed above have provided the biological rationale for the development of various specific inhibitors that are in different phases in clinical trials and have promising activity, such as the p38 MAPK inhibitor ARRY-614 (38), the anti-TLR2 antibody OPN-305 (39) and the TGF-β receptor kinase I-inhibitor LY-2157299 (40). These and other targeted therapies may represent a hopeful alternative for MDS patients, especially those with low-risk syndromes, in whom the improvement of hematopoiesis and the resolution of cytopenias is crucial for survival.

Authors: Irene Gañán-Gómez,
Zachary S Bohannan
and Guillermo Garcia-Manero

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Circulating miRNAs: new targets in myelodysplastic syndromes

Myelodysplastic syndromes (MDS) are a group of malignant clonal hematological disorders characterized by inefficient hematopoiesis, unilineage or multilineage dysplasia and cytopenias with life-time risk to progression to acute myelogenous leukemia (AML) *(Ades L. et al., 2014)*. The pathogenesis of MDS and the complex mechanism of disease transformation to more aggressive stage or AML is currently the topic of many studies. Molecular mechanisms and epigenetic pathways have been investigated, as well as their impact on prognosis and therapy of MDS, but there is relatively little research on microRNAs in MDS.

In recent years, numerous studies have shown aberrant expression of miRNAs in human cancers, some of which function as tumor suppressor genes or oncogenes. Due to their sample- and disease-specific expression patterns and tremendous regulatory potential, miRNAs are being identified as diagnostic and prognostic biomarkers, as well as additional therapeutic tools *(Allegra A et al. 2012; Acunzo M et al. 2015).*

MicroRNA have an important role in normal hematopoiesis due to their regulation of hematopoietic differentiation in almost every stage, but more and more studies report the relationships between miRNAs and hematologic malignancies. Its potential as novel biomarkers is growing, but one has to consider that every hematologic disorder has particular miRNA expression.

Non-coding small RNA molecules are able to regulate over 1/3 of human genes and act at the post-transcriptional level regulating protein expression by repressing translation or destabilizing target messenger RNA *(MacFarlane LA et al. 2010).*

MicroRNA expression in myelodysplastic syndromes has been studied by several groups.

Pons and colleagues examined bone marrow and peripheral blood samples from 25 MDS patients and 12 controls to provide the evidence for association between miRNAs and MDS. The authors identified 12 miRNAs overexpressed in bone marrow and 6 miRNAs overexpressed in peripheral blood compared to healthy controls *(Pons A et al. 2009).*

MiR-126, derived from a common precursor structure located within the epidermal growth factor-like domain 7 (EGFL7) gene, is frequently downregulated in a variety of malignancies and acts as a potential tumor suppressor *(Walter BA et al., 2013).*

Previous studies have demonstrated the important role of miR-126 in various cancers. Low expression of miR-126 has been found to be correlated with poor prognosis in patients with breast cancer, adult T cell leukemia, colorectal carcinoma, malignant mesothelioma, cervical cancer tissues *(Yang Y et al., 2014).*

High miR-126 expression in AML was associated with poor survival, higher chance of relapse, and expression of genes present in LSC/HSC signatures. Targeting miR-126 in LSCs and LPs reduced their clonogenic capacity and eliminated leukemic cells, again in the absence of similar inhibitory effects on normal BM cells *(de Leeuw DC et al., 2014).*

MiR-125b has multiple targets which control pro-proliferative and pro-apoptotic signaling pathways in parallel and which has to be tightly regulated under physiological conditions. If this level of regulation is lost during carcinogenesis, oncogenic or tumor suppressive pathways are activated or blocked. If miR-125b is downregulated, its tumor suppressive function is lost, oncogenic pathways are activated and pro-apoptotic cascades are repressed, resulting in malignant transformation. If the miR-125b is overexpressed due to chromosomal translocations or transcriptional activation, miR-125b promotes oncogenic signaling by for example downregulating p53 and other apoptosis-inducing pathways *(Banzhaf-Strathmann J et al., 2014).*

Aberrant expression of miR-150/miR-221/miR-222 and their designated target mRNA molecules MYB, p27 and >>>

c-KIT has been studied in a series of 52 MDS patients. An aberrant increase of miR-150 was found only in MDS with associated del(5q) ($n = 9$; $p < 0.01$). The mRNA expression of transcription factor MYB, the designated target of miR-150, was shown to correlate inversely with the miR-150 level *(Hussein K et al., 2009).*

Hussein et al. analyzed miRNAs expression in MDS by profiling 365 miRNAs in 25 MDS subsets *(Hussein K et al.,2010).* Global down-regulation of miRNAs involved in normal hematopoiesis was noted underlying the down-regulation phenomenon of miRNAs previously noted in other types of cancer *(Di Leva G et al., 2014).*

Another study used larger miRNA array consisting of 1145 various miRNAs in bone marrow cell of 39 MDS patients or patients with AML progressing from MDS. Authors found 13 up-regulated miRNAs and 9 down-regulated miRNAs compared to healthy controls. Interestingly, the majority of up-regulated miRNAs were encoded in 14q32 region with the trend for further elevation in more advanced form of disease (sAML) *(Merkerova D.M et al., 2011).*

In further analysis, the authors compared the low-risk MDS vs. high-risk MDS based on initial pathological findings. MiRNAs' expression was similar in low-risk MDS except, as in report by Husein et al., MDS with del5q had distinct expression profile (13 miRNAs elevated with 7 miRNAs reduced). Only two of the miRNAs reduced in MDS del5q were encoded in deleted region.

Merkerova and colleagues used miRNA expression profiling to investigate the effect of lenalidomide treatment on miRNA expression of peripheral blood (PB) CD14+ monocytes from patients with del(5q) MDS. In this study, miR-378 and its minor variant, miR-378*, that were induced by lenalidomide treatment actually showed also a reduced expression in pretreatment samples. On the contrary, levels of miR-143 and miR-145 were not reduced in pretreatment samples, but were increased after lenalidomide treatment. However, this increase was not correlated with the cytogenetic response but interestingly, expression levels of miR-143 correlated with those of miR-145, suggesting a common regulation.

The authors emphasized that the effects of deregulation of miRNA seems to be critical in lenalidomide response and that miRNA might be suitable candidates for molecular predictors of response. Identification of specific miRNAs that play a critical role in the mechanism of action of lenalidomide will require more comprehensive examinations of miRNA profiles in larger groups of patients taking into account cytogenetic findings as well as differential responses to therapy *(Merkerova D. M et al., 2015).*

Erdogan et al. have performed a microarray study on 44,519 miRNAs probes in low-risk MDS. They used 10 MDS patients' bone marrow sample as discovery set with further validation on 25 MDS paraffin-embedded bone marrow samples with appropriate controls. In the discovery set they discovered 13 miRNAs being deregulated. In further analysis, this set was able to specifically discriminate MDS samples in contrast to control samples. They used 8 miRNAs from the discovery set in the analysis of validation set by RT-PCR. 5 miRNAs expression was found to be statistically significant in the validation set. Three miRNAs, which target c-Myb's mRNA, were found to be down-regulated in the discovery set (microRNA-103, microRNA-150, and microRNA-342) without reaching significance in the validation set, possibly due to methodological issues *(Erdogan B et al., 2011).*

In one of the review, only five miRNAs were down-regulated and 9 miRNAs were up-regulated as shown by 2 or more studies *(Rhyasen GW et al., 2012).*

MiRNA-21 expression has been shown to be increased in MDS stem cells in contrast to healthy control *(Bhagat TD et al., 2013).*

Gomez and colleagues observed that miR-125a inhibits erythroid differentiation in leukemia and MDS cell lines and reported that miR-125a levels have been inversely connected to the survival in MDS. They have discussed that the deregulation of miR-125a expression may contribute in various ways to the disease and that this molecule is a therapeutic target of interest that should be further explored as potential prognostic marker of great utility in the clinical practice together with circulating miR-99b and let-7e *(Gomez GI et al., 2014).*

Clearly, a progress has been made in our understanding of miRNAs impact of pathogenesis of MDS, but more extensive research with several paradigms shifts is needed to clarify the role of this complex mechanism in the genetic and epigenetic MDS setting. It would also be of great interest to see what miRNAs are potential therapeutic or disease modifying targets.

Authors: Inga Mandac Rogulj &
Slobodanka Ostojić Kolonić

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Overview of event recommendations

8th MDS Colloquium
06-07 November 2015 - Berlin, Germany
More information: http://www.mds-colloquium.de/

57th Annual Meeting of the American Society of Hematology
05-08 December 2015 - Orlando, USA
More information: http://www.hematology.org/annual-meeting/

6th MDS Forum
22-23 April 2016 - Munich, Germany

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