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OPINION

miR-17–92 cluster: ups and downs in cancer and aging

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Abstract The miR-17–92 cluster encoding 6 single mature miRNAs was identified a couple of years ago to contain the first oncogenic miRNAs. Now, one of these 6 miRNAs, miR-19 has been identified as the key responsible for this oncogenic activity. This in turn reduces PTEN levels and in consequence activates the AKT/mTOR pathway that is also prominently involved in modulation of organismal life spans. In contrast, miR-19 and other members of the miR-17–92 cluster are found to be commonly downregulated in several human replicative and organismal aging models. Taken together, these findings suggest that miR-19 and the other members of the miR-17–92 cluster might be important regulators on the cross-roads between aging and cancer. Therefore, we here briefly summarize how this cluster is transcriptionally regulated, which target mRNAs have been confirmed so far and how this might be linked to modulation of organismal life-spans.

Keywords miRNA · miR-17–92 · Aging · TOR · PTEN · miR-19

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Aging, cancer and miR-17–92

It is not long ago that the first miRNA cluster has been identified with oncogenic potential and was therefore termed oncomiR-1 (He et al. 2005). Now, two recent reports have been able to pin down miR-19 as the key oncogenic miRNA of this cluster containing 6 miRNA members (Mu et al. 2009; Olive et al. 2009). Furthermore, the idea that miRNAs also play a role in aging is increasingly substantiated (Grillari and Grillari-Voglauer 2010; Bates et al. 2009). Recently, a large scale microRNA microarray analysis of 4 different cell types in replicative senescence and 3 different tissue types *ex vivo* representing organismal aging was performed (Hackl et al. 2010). Thereby, a common down-regulation of miR-17, 19b, 20a and miR-106a, members of the miR-17–92 and paralogous cluster, was found (see Table 1 for an overview of the clusters, their members, and their seed sequences). This indicates that this cluster represents one additional important player not only in the complex regulatory network of cell cycle and tumorigenesis, but also in aging, emphasising that these processes are intricately interwoven (Campisi 2003). Even more so, as miR-19 upregulation in cancer activates the AKT-mTOR pathway via PTEN silencing (Olive et al. 2009). It is tempting to speculate therefore, that decrease of miR-19 might lead to increased PTEN and in consequence repress AKT-mTOR, a pathway that has been clearly linked with modulation of life-span in a variety of

Table 1 Overview on the miRNAs of the miR-17–92 cluster as well as of its paralogous clusters miR-106a–32 and miR-106b–25

microRNA	Seed family	Genomic location	Seed sequence	Mature miRNA sequence
hsa-miR-17	miR-17	miR-17–92	AAAGUG	CAAAGUGCUUACAGUGCAGGUAG
hsa-miR-20a		miR-17–92	AAAGUG	UAAAGUGCUUAUAGUGCAGGUAG
hsa-miR-106a		miR-106a–363	AAAGUG	AAAAGUGCUUACAGUGCAGGUAG
hsa-miR-20b		miR-106a–363	AAAGUG	CAAAGUGCUCAUAGUGCAGGUAG
hsa-miR-106b		miR-106b–25	AAAGUG	UAAAGUGCUGACAGUGCAGAU
hsa-miR-93	miR-18	miR-106b–25	AAAGUG	CAAAGUGCUGUUCGUGCAGGUAG
hsa-miR-18a		miR-17–92	AAGGUG	UAAGGUGCAUCUAGUGCAGAUAG
hsa-miR-18b		miR-106a–363	AAGGUG	UAAGGUGCAUCUAGUGCAGUUAG
hsa-miR-19a	miR-19	miR-17–92	GUGCAA	UGUGCAAAUCUAUGCAAAACUGA
hsa-miR-19b		miR-17–92	GUGCAA	UGUGCAAAUCCAUGCAAAACUGA
hsa-miR-25	miR-25	miR-106b–25	AUUGCA	CAUUGCACUUGUCUCGGUCUGA
hsa-miR-92a		miR-17–92	AUUGCA	UAUUGCACUUGUCCCGGCCUGU
hsa-miR-363		miR-106a–363	AUUGCA	AAUUGCACGGUAUCCAUCUGUA

model organisms (Kapahi et al. 2004; Blagosklonny 2007; Schieke and Finkel 2007) and even in mouse, where the mTOR inhibitor rapamycin leads to a life-span extension (Harrison et al. 2009).

Thus, understanding the regulatory network of this cluster might well increase our knowledge on why advancing age is the largest single risk factor to develop cancer. Therefore, we here want to briefly summarize the current knowledge on the regulation loops of this cluster (Fig. 1) especially in regard to senescence that has been largely accepted as tumor suppressor mechanism in vivo (reviewed in Hornsby 2007; Sedivy 2007) and aging.

Transcriptional regulation of the miR-17–92 cluster

So far, c-MYC (O'Donnell et al. 2005), E2F1 and 3 (Petrocca et al. 2008b), as well as STAT3 (Brock et al. 2009) have been identified to transcriptionally activate the miR-17–92 cluster and paralogous clusters, while p53 represses it (Yan et al. 2009). However, MYC does not seem to change in senescence (Chang and Chen 1988; Seshadri and Campisi 1990), even though tumour cells enter senescence upon MYC inactivation (Wu et al. 2007). Similarly, STAT3 seems not to be involved, even if it might be

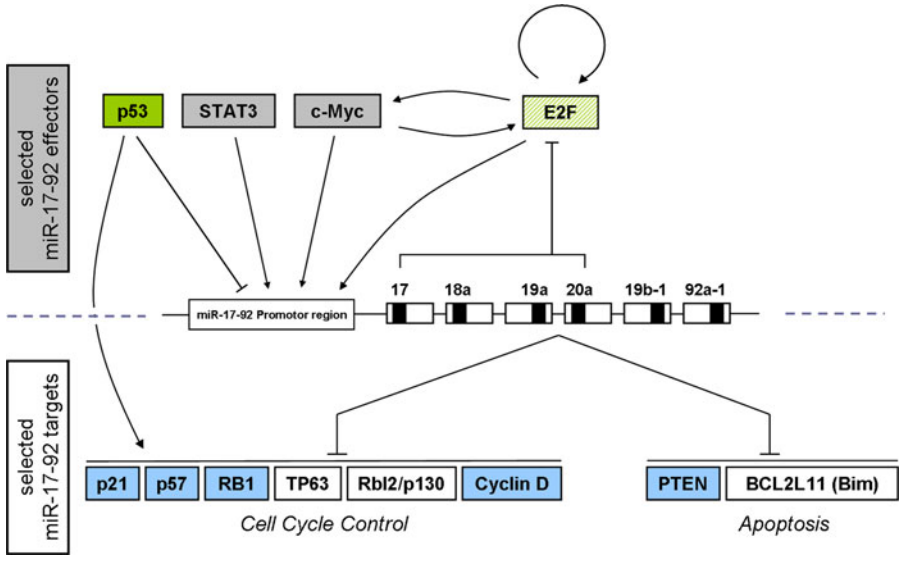

Fig. 1 Overview on transcriptional regulation and target mRNAs of the miR-17–92 cluster

expected to rise with senescence in response to the senescence-dependent increase of secreted IL-6 and IL-8 (Acosta et al. 2008) which are upstream activators of STAT3. Why in turn the miR-17–92 cluster is decreased instead of activated is unclear. STAT3 might be blocked at the post-translational level, since it is very susceptible to oxidation and is easily S-glutathionylated. In consequence of this modification, it is not activated by JAK anymore and does not translocate to the nucleus (Xie et al. 2009). High levels of S-glutathionylated, and thus inhibited STAT3 might be possible due to high levels of S-glutathione transferase P that are known to be present in senescent cells (Chang et al. 2005).

Thus, two responsible transcriptional regulators remain to most probably account for less miR-17–92 in senescence. Less E2F family members have been observed in senescent cells (Dimri et al. 1994), and p53, which is a decisive switch in aging and tumorigenesis (Rodier et al. 2007; Schmid et al. 2007) is increasingly active in senescence (Atadja et al. 1995; Kulju and Lehman 1995) and might thus contribute by actively repressing miR-17–92 (Yan et al. 2009).

Table 2 Published mRNA targets of the miR-17–92 cluster members

Target Gene Symbol	MicroRNA	Refs
APP	miR-106a	Patel et al. (2008)
BCL2L11 (Bim)	miR-17	Cloonan et al. (2008)
CCND1	miR-17, miR-20a	Yu et al. (2008)
CDKN1A (p21)	miR-106a, miR-106b, miR-17	Cloonan et al. (2008), Li et al. (2009), Ivanovska et al. (2008)
CDKN1C (p57)	miR-92b	Sengupta et al. (2009)
CTGF	miR-18a	Cloonan et al. (2008), Ohgawara et al. (2009)
E2F1	miR-106b, miR-20a	Petrocca et al. (2008a, b), O'Donnell et al. (2005), Pickering et al. (2009)
GAB1	miR-17	Cloonan et al. (2008)
HIF-1α	miR-17-92	Taguchi et al. (2008)
HIPK3	miR-92a	Landais et al. (2007)
IRF1	miR-17	Cloonan et al. (2008)
ITCH	miR-106b	Sampath et al. (2009)
MAPK9	miR-17	Cloonan et al. (2008)
MAPK14	miR-17, miR-20a, miR-106b	Carraro et al. (2009)
MYLIP	miR-92a	Landais et al. (2007)
NCOA3	miR-17	Cloonan et al. (2008), Hossain et al. (2006)
NR4A3	miR-17	Cloonan et al. (2008)
p63	miR-92	Manni et al. (2009)
PCAF	miR-17, miR-20a	Cloonan et al. (2008)
PKD1, PKD2	miR-17	Cloonan et al. (2008)
PPARA-C	miR-17	Cloonan et al. (2008)
PTEN	miR-19a	Cloonan et al. (2008), Lewis et al. (2003)
RB1	miR-106a	Volinia et al. (2006), Cloonan et al. (2008)
RB2/p130	miR-17-92	Wang et al. (2008)
RUNX1	miR-106a, miR-17, miR-20a	Fontana et al. (2007), Cloonan et al. (2008), Yu et al. (2008)
SOCS-1	miR-19a, miR-19b	Pichiorri et al. (2008)
STAT3	miR-17, miR-20a, miR-106b	Carraro et al. (2009)
TGFBR2	miR-17, miR-20a	Cloonan et al. (2008), Volinia et al. (2006)
THBS1	miR-19a	Cloonan et al. (2008)
TSG101	miR-17	Cloonan et al. (2008)
VEGFA	miR-106a, miR-106b, miR-17, miR-20a	Ye et al. (2008)

Targets of the miR-17–92 cluster

Around 30 mRNA targets have been experimentally confirmed so far (Table 2), among them BCL2L11 (Bim), IRF, JNK2/MAPK9, MYCN, PKD1, PKD2, GAB1, RBL1, TSG101 (Cloonan et al. 2008), p63 (Manni et al. 2009), STAT3 and p38/Mapk14 (Carraro et al. 2009), the TGFβ signal pathway (Petrocca et al. 2008a), HIF-1α (Taguchi et al. 2008), or Rbl2/p130 (Wang et al. 2008), p57, p27 and p21 all involved in tumorigenesis and cell cycle control. Especially p21 transcription is well correlated with miR-17, 19b, 20a and miR-106a in the replicative and organismal aging model systems described above (Hackl et al. 2010).

Indeed, miR-17–92 suppression induces complete growth arrest in an anaplastic thyroid cancer cell model (Takakura et al. 2008). In contrast, overexpression of one of its members in mouse embryonic fibroblasts, miR-20a, induces senescence by reducing Leukemia/lymphoma Related Factor (LRF) levels (Poliseno et al. 2008), indicating that cell type specific responses are possible in response to miR-17–92. This is consistent with the notion that overexpression of miR-106a that derives from a paralogous cluster, targets p21 in human fibroblasts and trabecular meshwork cells (Li et al. 2009). Finally, overexpression of miR-17–92 inhibits generation of ROS and DNA damage in RB mutated tumor cells (Ebi et al. 2009).

It will be exciting to see if the opposite, reduction of miR-17–92 will result in more ROS and DNA damage, as well as block of tissue repair by inhibition of stem cell self renewal. All of these are well accepted driving forces of age-related functional decline.

Conclusion

It is still unclear, how and why miR-17–92 is downregulated during aging and senescence. Future work will have to reveal if it is cause or consequence and to what extent its downregulation functionally contributes to aging or even to tumor suppression during aging. In any case, members of this cluster might represent novel biomarkers of aging and the link between miR-17–92 and AKT/mTOR via PTEN might provide a novel regulatory loop of life span modulation.

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