

involves unwinding of the siRNA duplex and remodelling of the complex to create an active form of RISC. Only one of the two strands, which is known as the guide strand, binds the argonaute protein and directs gene silencing. The other anti-guide strand or passenger strand is degraded. This process is ATP-independent and performed directly by the protein components of RISC. The strand selected as the guide tends to be the one whose 5' end is less stably paired to its complement. The R2D2 protein may serve as the differentiating factor by binding the more-stable 5' end of the passenger strand. The phosphorylated 5' end of the RNA strand enters a conserved basic surface pocket and makes contacts through a divalent cation and by aromatic stacking between the 5' nucleotide in the siRNA and a conserved tyrosine residue.

4. Cleavage of mRNA: The final step includes the recognition and cleavage of mRNA complementary to the siRNA strand present in RISC (guide strand of siRNA), (44,45) by exoribonucleases. In some organisms (*C. elegans*, *Arabidopsis thaliana*) an additional step in the RNAi pathway has been described involving a population of secondary siRNAs derived from the action of a cellular RNA-dependent RNA polymerase (RdRp). Eukaryotic cells possess two major means for regulating the turnover of mRNAs. In one pathway they utilize the 3'-5' exonuclease, exosome, to degrade the message in the cytoplasm (46). The other pathway is thought to occur in specialized centers known as processing (P) bodies/cytoplasmic bodies/mRNA decay centers (38,39). These centers contain decapping enzymes Dcp1 and 2 and the 5'-3' exonucleases Xrn1(39). It is thought that transcripts are transported to these centers to be degraded by the 5'-3' exonuclease, Xrn1. Ago2 was found to be localized to the cytoplasm, with most of the Ago2 concentrated in discrete cytoplasmic bodies, the mammalian equivalent of yeast P-bodies (25,40).

FUNCTIONAL ASPECTS AND APPLICATIONS OF RNAi

Defence

RNA interference acts as a defense mechanism against viruses and other foreign genetic material, especially in plants. It may also prevent the self-propagation of transposons. Apart from plants there is significant debate over the ability of siRNAs and longer dsRNAs to induce innate immune response (47,48). In mammalian cells molecules less than 30 bp in length are generally believed to avoid induction of interferon pathways (47-49). Long (27-29 bp) dsRNAs and shRNAs provide more efficient gene silencing than shorter, *Dicer*-independent substrates (48,49). Some plant genomes also express endogenous siRNAs in response to infection by specific types of bacteria. These effects may be part of a

generalized response to pathogens that downregulates any metabolic processes in the host that aid the infection process. In both juvenile and adult *Drosophila*, RNA interference is important in antiviral innate immunity and is active against pathogens such as *Drosophila X virus*. A similar role in immunity may operate in *C. elegans*, as argonaute proteins are upregulated in response to viruses and worms that over express components of the RNAi pathway are resistant to viral infection.

Down and up-regulation of genes

Endogenously expressed miRNAs, including both intronic and intergenic miRNAs, are most important in translational repression. The roles of endogenously expressed miRNA in downregulating gene expression were first described in *C. elegans* in 1993. In plants, the majority of genes regulated by miRNAs are transcription factors thus miRNA activity is particularly wide-ranging and regulates entire gene networks during development by modulating the expression of key regulatory genes, including transcription factors as well as F-box proteins. RNA sequences (siRNA and miRNA) that are complementary to parts of a promoter can increase gene transcription, a phenomenon dubbed RNA activation. Here, *dicer* and argonaute play major role, possibly via histone demethylation. They have also been proposed to upregulate their target genes upon cell cycle arrest.

Development

Mutations in *dcr-1* and *ego-1* lead to complete sterility, (50,52) indicating importance of RNAi in germline development. In plants also RNAi-like processes have a crucial role in development (53,54). It is seen to be involved in maturation of endogenously encoded miRNAs, (51,55) some of which are involved in development, but most of which have no known function at present.

Gene function analysis

Double-stranded RNA is artificially synthesized, complementary to a gene of interest and introduced into a cell where it is recognized as exogenous genetic material and activates the RNAi pathway. Using this mechanism, researchers can cause a drastic decrease in the expression of a targeted gene which can show the physiological role of the gene product. Functional analysis of almost all the ~19,000 genes of *C. elegans* has been carried out with the siRNA-directed knockdown approach (56).

To determine gene function

- RNAi is sequence-specific and thus can be targeted, requiring only a few transformants per target gene.
- RNAi is dominant, so phenotypes can be observed in the T1 generation.
- RNAi often leads to partial knockdown and thus to a range of phenotypes of differing severity; this facilitates the study of essential genes whose inactivation would lead to lethality or extremely severe pleiotropic phenotypes.
- RNAi can be controlled in a tissue-specific or time-dependent manner RNAi can be quickly and easily used in a wide range of genotypes or even species, whereas insertion mutant collections are limited to just a few due to the effort involved.
- RNAi can be used to reduce the expression of several related genes in parallel by targeting conserved regions of the genes, facilitating the study of redundant gene functions.

Heterochromatin formation

There is derepression of the centromeric outer-transposon repeats in RNAi mutants deficient for RNAi components. This led to the proposal that small RNAs function as guides to target the chromatin modifications that are typical of heterochromatin (57). There is reduced amounts of H3K9 methylation and repeat-associated Swi6 in the RNAi mutants. Second evidence was that a transgene that is located in the centromeric repeats, which would usually be silenced, was activated in RNAi mutants. Apart from centromeric heterochromatin formation, RNAi pathway is also implicated in the targeting of non-centromeric, interstitial sites in euchromatin for silencing. In *D. melanogaster*, dispersed transgenes that are inserted at several sites in euchromatin are silenced at the transcriptional level through association with the POLYCOMB COMPLEX(58)through histone modifications which is dependent on components of RNAi pathway. The Polycomb-dependent silencing involves histone modifications and is known to keep the chromatin in the closed or compact conformation. Heterochromatin formation requires that histone H3 of the chromatin is first deacetylated and then methylated at lysine 9. This methylated lysine is subsequently bound by a heterochromatin binding protein, HP1 in highly specific manner and with a very high affinity (59).

RNA INTERFERENCE AS A THERAPEUTIC TOOL**In Animals**

RNAi is having a lot of applications in biomedical research and health care and has begun to produce a paradigm shift in the process of drug discovery (60). Presently, many dsRNA molecules are being designed for silencing specific genes in humans and animals as shown in Table 1. It may be possible to exploit RNA interference in therapy. Although it is difficult to introduce long dsRNA strands into mammalian cells due to the interferon response, the use of ds RNAs shorter than ~30 nts are proving to be successful. The very first application of RNAi were mainly in the treatment of macular degeneration and respiratory syncytial virus knockdown of host receptors and coreceptors for HIV, the silencing of hepatitis A and hepatitis B genes, silencing of influenza gene expression, and inhibition of measles viral replication. Potential treatments for neurodegenerative diseases have also been proposed, with particular attention being paid to the polyglutamine diseases such as Huntington's disease. Despite the proliferation of promising cell culture studies for RNAi-based drugs, some concern has been raised regarding the safety of RNA interference, especially the potential for "off-target" effects in which a gene with a coincidentally similar sequence to the targeted gene is also repressed. A computational genomics study estimated that the error rate of off-target interactions is about 10%.

In Plants

This RNAi technology has proven to be an eco-friendly technique for crop improvement. Through this technique the genes which are responsible for inducing various stresses in plants are silenced and novel traits like disease resistance are incorporated into plants. It has emerged as a method of choice for gene targeting in fungi,(61) viruses,(62,63) bacteria(64) and plants (65). It has been used for applications in biotechnology, particularly in the engineering of food plants that produce lower levels of natural plant toxins as shown in Table 2. Other plant traits that have been engineered in the laboratory include the production of non-narcotic natural products by the opium poppy, resistance to common plant viruses, and fortification of plants such as tomatoes with dietary antioxidants.

DISADVANTAGES OF RNA INTERFERENCE**Off-target effect**

In large-scale screens in animals it was observed that the silencing effects were also seen in genes that were

not the predicted targets of RNAi. The major difficulty is the limited sequence specificity of siRNAs, as few as seven nucleotides of sequence complementarity between a siRNA and an mRNA can lead to the inhibition of expression.

A second specificity problem can occur via 'transitive silencing', whereby RNAi against a gene-specific sequence 'spreads' into neighbouring sequences conserved between the target mRNA and mRNAs from related genes, which become silenced in turn.

Inefficacy and instability

RNAi inhibition can have widely varying effects depending on the target gene, the region of the transcript that is targeted and even between sibling plants carrying identical RNAi constructs. The instability can result from silencing of the transgene long hairpin transgenes appear to be particularly sensitive to transcriptional silencing leading to a loss of RNAi phenotypes over several generations.

Conclusion and Future Prospects

RNA interference is an area of intense, upfront basic research and holds the key to various technological applications in future due to their higher silencing efficiency and shorter time requirements for screening and to analyses functions of wide variety of genes in different organisms. The RNA silencing technology apart from being highly sequence specific is also technologically facile and economical. Therefore, this technique has great potential in agriculture specifically for nutritional improvement of plants and the management of various plant diseases. Future directions will focus on developing finely tuned RNAi-based gene

silencing vectors that are able to operate in a temporally and spatially controlled manner. In coming years better and comprehensive understanding of RNAi would allow the researchers to work effectively and efficiently in order to work more on improvement of crop plants nutritionally and in managing various diseases of crop plants. Finally, the discovery of RNAi has not only provided us with a powerful new experimental tool to study the function of genes but also raises expectations about future applications of RNAi in medicine.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

REFERENCES

1. Agrawal N, Dasaradhi PVN, Mohmmmed A, Malhotra P, Bhatnagar RK, Mukherjee SK. RNA Interference: Biology, Mechanism, and Applications. *Microbiology and Molecular Biology Reviews*. 2003; 67: 657-685.
2. Bernstein E., Caudy AA., Hammond SM., and Hannon GJ. *Role for a bidentate ribonuclease in the initiation step of RNA interference*. *Nature*. 2001; 409: 363-366.
3. Zamore PD. RNA Interference: big applause for silencing in Stockholm. *Cell*. 2006; 127: 1083-1086.
4. Tan FL. and Yin JQ. Application of RNAi to cancer research and therapy. *Front. Biosci*.

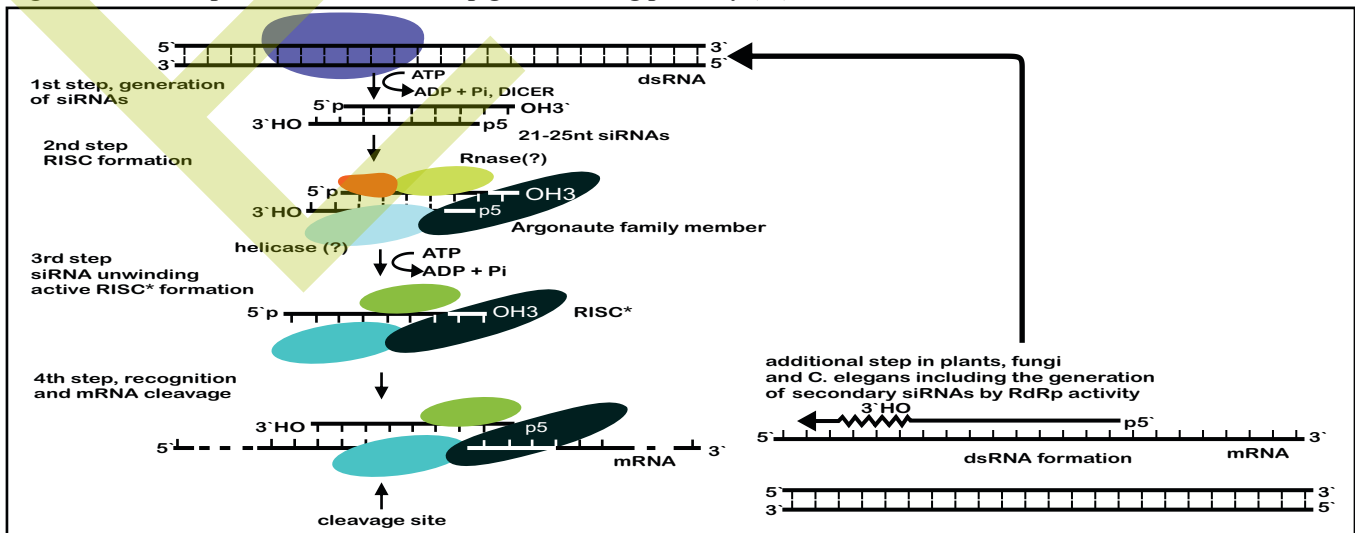
Table1. Application of RNAi in treating human disease (66)

Disease	Case study
Lymphoblastic leukemia	Using siRNA's specific for the BCR - ABL transcript to silence the oncogenes
Bladder cancer	Treatment by miRNA's as biomarkers
HIV	Downregulation of cellular cofactors required for HIV infection by RNAi
Viral hepatitis	Inhibition of Fas expression by siRNA
Ocular diseases	Shutting down production of VEGF by siRNA
Metabolic disease and neurodegenerative disorders	Treatment of these diseases by miRNA's as potential therapeutic targets.
Cardiovascular and cerebrovascular diseases	Used to reduce damage to heart tissues and brain cells
Pancreatic and colon carcinomas	Use of retroviral vectors to introduce interfering RNAs specific for an oncogenic variant of K -Ras

Table 2. Application of RNAi in plants (67)

Application	Case study
Increasing the level of lysine	Reduction of lysine catabolism and improving seed germination generating a dominant high-lysine maize variant by knocking out the expression of the 22-kD maize zein storage protein
Barley and Rice	Resistance of barley to BYDV and producing a rice variety called LGC-1 (low glutenin content 1)
Banana	Production of banana varieties resistant to the Banana Bract Mosaic Virus (BBrMV)
Cotton	Transgenic cotton plants expressing a RNAi construct of the d-cadinene synthase gene of gossypol synthesis fused to a seed-specific promoter caused seed-specific reduction of Gossypol
Wood and fruit quality	-Down regulation of lignin biosynthesis pathways. -Producing transgenic hypoallergenic apples and a possible solution for the undesirable separation of juice into clear serum and particulate phase
Coffee	RNAi technology has enabled the creation of varieties of <i>Coffee</i> that produces natural coffee with low or very low caffeine content
Healthier oil	Using RNAi to silence the gene in cotton which codes for the enzyme that converts oleic acid into a different fatty acid
Tomato	RNAi-mediated suppression of DET1 expression under fruit-specific promoters has recently shown to improve carotenoid and flavonoid levels in tomato fruits with minimal effects on plant growth
Gentian	Producing white-flowered transgenic gentians by suppressing the chalcone synthase (<i>CHS</i>) gene .
Blue Rose	Producing blue transgenic rose by knock down the cyanidin genes in rose and carnation .
Pest control	Combining Bt technology with RNAi would both enhance product performance and further guard against the development of resistance to Bt proteins

Fig1. Schematic representation of four-step gene silencing pathway (68)



- 2005: 10” 1946–1960.
5. Lee YS, Nakahara K, Pham JW, Kim K, He Z, Sontheimer EJ, Carthew RW. Distinct roles for *Drosophila* Dicer-1 and Dicer-2 in the siRNA/miRNA silencing. *Cell*. 2004: 117(1)” 69-81.
 6. Deleris A, et al. Hierarchical action and inhibition of plant Dicer-like proteins in antiviral defense. *Science*. 2006: 313” 68–71.
 7. Blevins T, Rajeswaran R, Shivaprasad PV, et al. Four plant Dicers mediate viral small RNA biogenesis and DNA virus induced silencing. *Nucleic Acids Res*. 2006: 34(21)” 6233-46.
 8. Xie Z, Allen E, Wilken A, Carrington JC. Dicer-like 4 functions in trans-acting small interfering RNA biogenesis and vegetative phase change in *Arabidopsis thaliana*. *Proc Natl Acad Sci USA*. 2005: 102(36)” 12984 - 9.
 9. Hammond SM, Boettcher S, Caudy AA, Kobayashi R, Hannon GJ. Argonaute2, a link between genetic and biochemical analyses of RNAi. *Science*. 2001: 293” 1146-1150.
 10. Caudy AA., Myers M., Hannon GJ. and Hammond SM. Fragile X-related protein and VIG associate with RNA interference machinery. *Genes Dev*. 2002: 16” 2491–2496.
 11. Cerutti L, Mian N, Bateman A. Domains in gene silencing and cell differentiation proteins: the novel PAZ domain and redefinition of the Piwi domain. *Trends Biochem. Sci.* 2000: 25” 481–82
 12. Okamura K, Ischizuka A, Siomi H, Siomi MC. Distinct roles for Argonaute proteins in small RNA- directed RNA cleavage pathways. *Genes Dev*. 2004: 18(14)” 1655–66.
 13. Zheng X, Zhu J, Kapoor A, Zhu JK. Role of *Arabidopsis* AGO6 in siRNA accumulation, DNA methylation and transcriptional gene silencing. *EMBO J*. 2007: 26(6)” 1691-701.
 14. Katiyar-Agarwal S, Gao S, Vivian-Smith A, Jin H. A novel class of bacteria-induced small RNAs in *Arabidopsis*. *Genes Dev*. 2007: 21(23)” 3123-34.
 15. Cogoni C. and Macino G. *Conservation of transgene-induced post-transcriptional gene silencing in plants and fungi*. *Trends Plant Sci*. 1997: 2” 438-443.
 16. Cogoni, C., and G. Macino. *Gene silencing in Neurospora crassa requires a protein homologous to RNA-dependent RNA polymerase*. *Nature*. 1999: 399” 166-169.
 17. Elbashir S. M., Lendeckel W., and Tuschl T. *RNA interference is mediated by 21- and 22-nucleotide RNAs*. *Genes Dev*. 2001: 15” 188-200.
 18. Yang D., Lu H., and Erichson J. W. *Evidence that processed small dsRNA may mediate sequence specific mRNA degradation during RNAi in Drosophila embryos*. *Curr. Biol*. 2000: 10” 1191-1200.
 19. Talmor-Neiman M, Stay R, Klipcan L, Kobi B, Baulcombe DC, Arazi T. Identification of trans-acting siRNAs in moss and an RNA-dependent RNA polymerase required for their biogenesis. *Plant J*. 2006: 48(4)” 511-21.
 20. Fahlgren N, Montgomery TA, Howell MD, et al. Regulation of AUXIN RESPONSE FACTOR3 by TAS3 ta-siRNA affects developmental timing and patterning in *Arabidopsis*. *Curr Biol*. 2006: 16(9)” 939-44.
 21. Montgomery TA, Howell MD, Cuperus JT. Specificity of ARGONAUTE7-miR390 interaction and dual functionality in TAS3 trans-acting siRNA formation. *Cell*. 2008: 133(1)” 128-41
 22. Liu J, Carmell MA, Rivas FV, Marsden CG, Thomson JM, et al. Argonaute2 is the catalytic engine of mammalian RNAi. *Science*. 2004: 305” 1437–41.
 23. Grad Y, Aach J, Hayes GD, Reinhart GD, Church GM, Ruvkun G, et al. Computational and experimental identification of *C. elegans* microRNAs. *Mol Cell*. 2003: 11(5)” 1253-63.
 24. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell*. 2004: 116(2)” 281-97
 25. Pillai, RS, Bhattacharyya SN, Artus CG, Zoller T, Cougot N, Basyuk E, et al. Inhibition of translational initiation by let-7 MicroRNA in human cells. *Science* 2005: 309” 1573–1576.
 26. Aukerman, M.J. and Sakai, H. Regulation of

- flowering time and floral organ identity by a microRNA and its APETALA2-like target genes. *Plant Cell*. 2003: 15” 2730–2741
27. Okamura K, Hagen JW, Duan H, Tyler DM, Lai EC. The mirtron pathway generates microRNA-class regulatory RNAs in *Drosophila*. *Cell*. 2007: 130(1)” 89–100
 28. Ruby JG, Jan CH, Bartel DP. Intronic microRNA precursors that bypass Drosha processing. *Nature*. 2007: 448(7149)” 83-6.
 29. Llave C, Xie Z, Kasschau KD and Carrington JC. *Cleavage of Scarecrow-like mRNA targets directed by a class of Arabidopsis miRNA*. *Science*. 2002: 297” 2053-2056.
 30. Rhoades MW, Reinhart BJ, Lim LP, Burge CB, Bartel B et al. Prediction of plant microRNA targets. *Cell*. 2002: 110(4)” 513-20.
 31. Kasschau K, Xie Z, Allen E, Llave C, Chapman E, Krizan K et al. P1/HC-Pro, a viral suppressor of RNA silencing, interferes with Arabidopsis development and miRNA function. *Dev. Cell*. 2003: 4” 205-217.
 32. Tang G, Galili G. Using RNAi to improve plant nutritional value: from mechanism to application. *TRENDS in Biotechnology*. 2003: 22(9)” 463-469.
 33. Lewis B, Burge C, Bartel D. Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. *Cell*. 2005: 120(1)” 15-20.
 34. Brennecke J, Stark A, Russell RB, Cohen SM. Principles of microRNA- target recognition. *PLoS Biol*. 2005: 3(3)” 85.
 35. Reinhart BJ, Weinstein EG, Rhodes MW, Bartel B and Bartel DP. MicroRNAs in plants. *Genes Dev*. 2002: 16” 1616-1626.
 36. Blow MJ, Grocock RJ, van Dongen S. RNA editing of human microRNAs. *Genome Biol*. 2006: 7(4)” R27.
 37. Wakiyama M, Takimoto K, Ohara O, Yokoyama S. Let-7 microRNA- mediated mRNA deadenylation and translational repression in a mammalian cell-free system. *Genes & Dev*. 2007: 21(15)” 1857-62.
 38. Sheth U, and Parker R. Decapping and decay of messenger RNA occur in cytoplasmic processing bodies. *Science*. 2003: 300” 805–808.
 39. Cougot N, Babajko S, Seraphin B. Cytoplasmic foci are sites of mRNA decay in human cells. *J Cell Biol*. 2004: 165(1)” 31-40.
 40. Liu J, Valencia-Sanchez MA, Hannon GJ, Parker R. MicroRNA-dependent localization of targeted mRNAs to mammalian P-bodies. *Nat Cell Biol*. 2005: 7(7)” 719-23.
 41. Bhattacharyya SN, Habermacher R, Martine U, Closs EI, Filipowicz W. Relief of microRNA mediated translational repression in human cells subjected to stress. *Cell* 2006: 125(6)” 1111-24.
 42. Song L, Han MH, Lesicka J, Fedoroff N. Arabidopsis primary microRNA processing proteins HYL1 and DCL1 define a nuclear body distinct from the cajal body. *Proc Natl Acad Sci USA*. 2007: 104(13)” 5437-42.
 43. Hamilton AJ, Baulcoumbe DC. A species of small antisense RNA in posttranscriptional gene silencing in plants. *Science*. 1999: 286(5441)” 950–952.
 44. Nykanen A, Haley B, Zamore PD. ATP requirements and small interfering RNA structure in the RNA interference pathway. *Cell* 2001: 107” 309–21.
 45. Hutvagner G, Zamore PD. RNAi: nature abhors a double-strand. *Curr Opin Genet Dev*. 2002: 12” 225–32.
 46. Anderson J. S. and Parker R. P. The 3’ to 5’ degradation of yeast mRNAs is a general mechanism for mRNA turnover that requires the SKI2 DEVH box protein and 3’ to 5’ exonucleases of the exosome complex. *EMBO J*. 1998: 17” 1497–1506
 47. Manche L, Green SR, Schmedt C. and Mathews MB. Interactions between double-stranded RNA regulators and the protein kinase DAI. *Mol. Cell. Biol*. 1992: 12” 5238–5248.
 48. Kim DH, Behlke MA, Rose SD, Chang MS,

- Choi S. and Rossi JJ. Synthetic dsRNA Dicer substrates enhance RNAi potency and efficacy. *Nat. Biotechnol.* 2004; 23” 222–226.
49. Siolas D, Lerner C, Burchard J, Ge W, Linsley PS, Paddison PJ. Synthetic shRNAs as potent RNAi triggers. *Nat. Biotechnol.* 2004; 23” 227–231.
50. Smardon A, Spoerke JM, Stacey SC, Klein N, Mackin ME, and Maine EM. *EGO-1 is related to RNA-directed RNA polymerase and functions in germ-line development and RNA interference in C. elegans.* *Curr. Biol.* 2000; 10” 169-178.
51. Ketting RF, Fischer SE, Bernstein E, Sijen T, Hannon GJ, and Plasterk RHA. *Dicer functions in RNA interference and in synthesis of small RNA involved in developmental timing in C. elegans.* *Genes Dev.* 2001; 15” 2654-2659
52. Knight SW, Bass BL. A role for the RNase III enzyme DCR-1 in RNA interference and germ line development in *Caenorhabditis elegans.* *Science* 2001; 293” 2269–71.
53. Bohmert K, Camus I, Bellini C, Bouchez D, Caboche M, and Benning C. *AGO 1 defines a novel class of Arabidopsis controlling leaf development.* *EMBO J.* 1998; 17” 170-180.
54. Jacobsen SE, Running MP and Meyerowitz EM. Disruption of an RNA helicase/RNaseIII gene in *Arabidopsis* causes unregulated cell division in floral meristems. *Development* 1999; 126” 5231-5243.
55. Grishok A, Pasquinelli AE, Conte D et al. *Genes and mechanisms related to RNA interference regulate expression of the small temporal RNAs that control C. elegans developmental timing.* *Cell.* 2001; 106” 23-34.
56. Dykxhoorn DM, Novina CD, and Sharp PA. *Killing the messenger: short RNAs that silence gene expression.* *Nat. Rev. Mol. Cell. Biol.* 2003; 4” 457-467.
57. Volpe TA. Regulation of heterochromatic silencing and histone H3 lysine-9 methylation by RNAi. *Science* 2002; 297” 1833–1837.
58. Fire A. *RNA triggered gene silencing.* *Trends Genet.* 1999; 15” 358-363.
59. Bannister AJ, Zegerman P, Partridge JF, Miska EA et al. *Selective recognition of methylated lysine 9 on histone H3 by the HP1 chromo domain.* *Nature.* 2001; 410” 120-124.
60. Hannon GJ and Rose JJ. Unlocking the potential of the human genome with RNA interference. *Nature* 2004; 431” 371-378.
61. Nakayashiki. *RNA Silencing in Fungi: Mechanisms and Applications.* *Federation of European Biochemical Societies Letters.* 2005; 579” 5950-5970.
62. Baulcombe DC. RNA silencing in Plants. *Nature.* 2004. 431” 356-363.
63. Wani SH. and Sanghera GS. *Genetic Engineering for Viral Disease Management in Plants.* *Notulae Scientia Biologicae.* 2010; 2” 20-28.
64. Escobar MA, Civerolo EL, Summerfelt KR. and Dandekar AM. RNAi-Mediated Oncogene Silencing Confers Resistance to Crown Gall Tumorigenesis. *Proceedings of the National Academy of Sciences USA.* 2001; 68(23)” 13437-42.
65. Brodersen P and Voinnet O. The Diversity of RNA Silencing Pathways in Plants. *Trends in Genetics* 2006; 22” 268-280.
66. Angaji SA, Hedayati SS, Poor RH et al. Application of RNA interference in treating human diseases. *J. Genet.* 2010; 89” xx–xx
67. Angaji SA, Hedayati SS, Poor RH. et al. Application of RNA interference in plants. *POJ* 2010; 3(3)” 77-84.
68. Zofia Szweykowska-Kulińska, Artur Jarmolowski and Marek Figlerowicz. RNA interference and its role in the regulation of eucaryotic gene expression. *Acta Biochimica Polonica.* 2003; 50(1/2003)” 217–229

