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Taking Genomics to Reality with Microbial and Synthetic Products

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Drug discovery is the product of concerted effort of diverse technical areas ranging from bench to bed. Innovative genomic and proteomic researches have unveiled numerous new genes and proteins with close relationship to various human diseases. Thanks to this progress, the bottleneck in new drug discovery is rapidly moved from "target discovery" to "lead discovery", and much effort is being made to speed up the translation from the basic discovery in bench to clinical application. In this presentation, a few examples will be addressed that link basic genomic research to drug development. We have been studying the functional importance of "sub-proteome" mediated by human aminoacyl-tRNA synthetases (ARSs) and their interacting factors (recent reviews 1-3), and trying to find pathological relationship of these factors to various human diseases such as cancer, autoimmune and metabolic diseases. Interestingly, ARSs are not only the enzyme essential for protein synthesis but also play crucial regulatory roles in diverse biological processes such as apoptosis[4], ribosome biogenesis[5], angiogenesis[6] and inflammation[7] (Table 1). In addition, ARS-interacting factors showed pleiotropic activities. Among these factors, we have identified that AIMP1 (also known as p43) is secreted to work as a cytokine with complex activities. Since AIMP1 induces

Table. 1 Diverse activities mediated by human aminoacyl-tRNA synthetases and their interacting factors

Name	Activities	References
QRS (Glutaminyl-tRNA synthetase)	Anti-apoptosis	4
MRS (Methonyl-tRNA synthetase)	rRNA synthesis	5
KRS (Lysyl-tRNA synthetase)	Inflammatory cytokine	7
KRS (Lysyl-tRNA synthetase)	HIV assembly	12
KRS (Lysyl-tRNA synthetase)	Transcription control	13
YRS (Tyrosyl-tRNA synthetase)	Pro-angiogenic cytokine	14
EPRS (Glu-prolyl-tRNA synthetase)	Translational silencing	15
WRS (Tryptophanyl-tRNA synthetase)	Anti-angiogenic cytokine	16
AIMP1 (p43)	Angiogenesis	8
AIMP1 (p43)	Inflammation	17
AIMP1 (p43)	Wound healing	9
AIMP2 (p38)	Lung cell differentiation	10
AIMP3 (p18)	Tumor suppressor	11

apoptosis on endothelial cells, it is being developed as anti-angiogenic cancer drug (ref. 8 and data not shown). In contrast, it stimulates proliferation on fibroblasts, which is useful for wound healing therapy[9]. We also found AIMP2 (known as p38) as a novel tumor suppressor, especially playing a critical role in lung cancer (ref 10 and submitted). AIMP3 was also determined to be a tumor suppressor involved in DNA repair process responding to DNA damage[11]. The aberrant expression pattern or loss of activities was frequently detected in various cancer patients. Using these factors as the target, drug screening systems were designed to select the compounds that could restore their normal expression or activities, and nearly 10,000 different microbial and synthetic products were screened. Some of these compounds restored the target tumor suppressor activities and suppressed the tumor progression in vivo with no cellular or systemic toxicity. The selected compounds are modified to optimize their drug efficacy and pharmacological behavior.

References

1. Lee, S.W. et al. (2004) Aminoacyl-tRNA synthetase complexes: beyond translation. *J. Cell Sci.* 117, 3725-3734.
2. Han, J.M. et al. (2003) Molecular network and functional implications of macromolecular tRNA synthetase complex. *Biochem. Biophys. Res. Commun.* 303, 985-993.
3. Ko, Y.G. et al. (2002) Novel regulatory interactions and activities of mammalian tRNA synthetases. *Proteomics* 2 (9), 1304-1310.
4. Ko, Y.-G., Kim, E.-Y., Kim, T., Park, H., Park, H.-S., Choi, E.-J., and Kim S. (2001) Glutamine-dependent antiapoptotic interaction of human glutaminyl-tRNA synthetase with apoptosis signal-regulating kinase 1. *J. Biol. Chem.* 276, 6030-6036.
5. Ko, Y.G. et al. (2000) Nucleolar localization of human methionyl-tRNA synthetase and its role in ribosomal RNA synthesis. *J. Cell Biol.* 149, 567-574.
6. Kise, Y. et al. (2004) A short peptide insertion crucial for angiostatic activity of human tryptophanyl-tRNA synthetase. *Nat. Struct. Mol. Biol.* 11, 149-156.
7. Park, S.G., Kim, H. J., Min, Y. H., Choi, E. C., Shin, Y. K., Park, B. J., Lee, S. W., Kim, S. (2005) Human lysyl-tRNA synthetase is secreted to trigger pro-inflammatory response. *Proc. Natl. Acad. Sci. U S A* in press.
8. Park, S.G. et al. (2002) Dose-dependent biphasic activity of tRNA synthetase-associating factor, p43, in angiogenesis. *J. Biol. Chem.* 277, 45243-45248.
9. Park, S.G. et al. (2005) The novel cytokine p43 stimulates dermal fibroblast proliferation and wound repair. *Am. J. Pathol.* 166, 387-398.
10. Kim, M.J., Park, B.-J., Kang, Y.-S., Kim, H. J., Park, J.-H. Kang, J. W., Lee, S. W., Han, J. M., Lee, H.-W., Kim, S. (2003) Downregulation of fuse-binding protein and c-myc by tRNA synthetase cofactor, p38, is required for lung differentiation. *Nat. Genet.* 34, 330-336.
11. Park, B.J. et al. (2005) The Haploinsufficient tumor suppressor p18 upregulates p53 via interactions with ATM/ATR. *Cell* 120, 209-221.

12. Halwani, R. et al. (2004) Cellular distribution of lysyl-tRNA synthetase and its interaction with Gag during human immunodeficiency virus type 1 assembly. *J. Virol.* 78, 7553-7564.
13. Lee, Y.N. et al. (2004) The function of lysyl-tRNA synthetase and Ap4A as signaling regulators of MITF activity in FcepsilonRI-activated mast cells. *Immunity* 20, 145-151.
14. Wakasugi, K. and Schimmel, P. (1999) Two distinct cytokines released from a human aminoacyl-tRNA synthetase. *Science* 284, 147-151.
15. Sampath, P. et al. (2004) Noncanonical function of glutamyl-prolyl-tRNA synthetase: gene-specific silencing of translation. *Cell* 119, 195-208.
16. Wakasugi, K. et al. (2002) A human aminoacyl-tRNA synthetase as a regulator of angiogenesis. *Proc. Natl. Acad. Sci. U S A* 99, 173-177.
17. Ko, Y.-G., Park, H., Kim, T., Lee, J.-W., Park, S. G., Seol, W., Kim, J. E., Lee, W.-H., Kim, S.-H., Park, J. E., and Kim, S. (2001) A cofactor of tRNA synthetase, p43, is secreted to up-regulate proinflammatory genes. *J. Biol. Chem.* 276, 23028-32303.