FISH banding methods: applications in research and diagnostics

Thomas Liehr†, Anita Heller, Heike Starke and Uwe Claussen

Recently, several chromosome banding techniques based on fluorescence in situ hybridization (FISH) have been developed for the human and the mouse genome. In contrast to the standard chromosome banding techniques presently used, giving a protein-related banding pattern, those FISH techniques are DNA-specific. Currently the FISH banding methods are still under development and no high resolution banding technique is available that can be used for a whole genome in one hybridization. Nevertheless, FISH banding methods were used successfully for research in evolution- and radiation-biology, as well as for studies on the nuclear architecture. Moreover, their suitability for diagnostic purposes has been proven in prenatal, postnatal and tumor cytogenetics, indicating that they are an important tool with the potential to partly replace the conventional banding techniques in future.

The availability of simple, rapid and reliable methods for chromosome characterization is a main interest in human and animal cytogenetics. Even though the G-bands by Trypsin using Giemsa (GTG-banding) technique (FIGURE 1) is still the gold standard of all cytogenetic approaches, its technical restrictions are well known. As not more than chromosome morphology combined with a black and white banding pattern can be evaluated, only changes within the normal pattern, size variations in a chromosomal band or the chromosome itself and changes of the centromere index can be detected. However, the origin of additional material in a structurally altered chromosome remains often questionable (FIGURE 1). Moreover, not well-spread and condensed chromosomes, such as those present in tumor cell preparations or cell lines, as well as the acrocentric mouse chromosomes, are often hardly distinguishable from each other by GTG banding [1–2]. As demonstrated recently by chromosome stretching, the GTG banding technique has its limit of resolution at about 4 Mb [3], thus microdeletion or microduplication syndromes below 2 Mb cannot be resolved as well. To overcome such limits fluorescence in situ hybridization (FISH) approaches have been introduced into cytogenetics in the 1980s. Thus, microdeletion or microduplication events are easily detected in situ by locus-specific probes [4], under the prerequisite to the corresponding clinical suspicion. However, the main progress of the recent years was the introduction of multicolor-FISH (mFISH) in molecular cytogenetics. The first successful mFISH experiment was performed by Nederlof et al. in 1989 [5]. Staining of each of the 24 different human chromosomes in another color at the same time using whole chromosome painting (wcp) probes [5-6] was introduced in 1996 by two different groups as multiplex-FISH (M-FISH) [7] and spectral karyotyping (SKY) [8]. In the same year, a SKY approach for the 22 murine wcp probes was developed [9], wcp probes specific for the chicken genome followed in 1999 [10]. For an overview of the M-FISH developments and literature see [2,10,101].

M-FISH methods using wcp probes reach their limits when exact localization of a translocation are required, in case of intrachromosomal rearrangements, such as small interstitial
deletions or duplications and inversions without change of the centromeric index. Thus, different approaches were developed to overcome these limitations, such as the use of chromosome arm-specific probes additionally to the wcp probes or the development of FISH banding methods [12,13,14].

What are FISH banding methods?

For this discussion FISH banding methods are defined as any kind of FISH technique, which provide the possibility to characterize simultaneously several chromosomal subregions smaller than a chromosome arm (excluding the short arms of the acrocentric chromosomes). FISH banding methods fitting that definition may have quite different characteristics but share the ability to produce a DNA-specific chromosomal banding. This review will not exclusively focus on FISH banding methods that have been used in diagnostics but as well on such, which have been used only in research, up to present.

Different FISH banding methods

The different possibilities to obtain a FISH-based chromosome banding are listed in the following. Their applications, advantages and limitations are scheduled in Table 1 (1,2) and discussed later.

A banding pattern simultaneous to M-FISH has been described for the so-called IPM-FISH approach [34]. IPM stands for IRS-PCR multiplex FISH and IRS means interpersed PCR. Human WCP probes are amplified using IRS-PCR primers according to [32] and labeled with five different fluorochromes by nick translation. The resulting painting probes show an R-band like pattern concurrent to 24 M-FISH colors. A banding pattern similar to GTG-banding can be achieved, which is rather protein- than DNA-specific, even though the GTG-dark bands are known to consist of AT-richer sequences than GTG-light ones [35]. Its resolution is mainly dependent on the quality of the chromosome preparation.

The cross-species color banding (Rs-FISH) set is derived from chromosomes of two gibbon species, which have been flow sorted, split in three portions and labeled with three different fluorochromes [34]. With Rs-FISH a resolution of 80–90 bands per haploid human karyotype can be achieved (Figure 1B) [32,35]. A set of 110 human-hamster somatic cell hybrids, which were split into two pools are labeled in two different fluorochromes [34]. As this produces a limited number of bars on the chromosomes of two gibbon species, which have been flow sorted, split in three portions and labeled with three different fluorochromes [34]. As this produces a limited number of bars on each chromosome this pattern has been called (somatic cell hybrid-based) ‘chromosome barcode’. A combination of the 110 somatic cell hybrid probes with the Rs-FISH probe set mentioned before results in ‘160 positive bands’ in human karyotypes according to [34].

A chromosome can be identified also by a specific signal pattern produced by region-specific yeast artificial chromosomes (YAC) clones. The first attempts to label each chromosome by subregional DNA probes in different colors were performed by the groups of Peter Lichter [35] and Thomas Cremer [36,37]. A YAC-based chromosome barcode (Figure 5) has been elucidated especially for chromosome 12 [38,39].

According to the definition of a FISH banding method used in this article, another type of approach, not defined as chromosome banding by the authors has to be mentioned: mFISH approaches using subtelomeric probe sets [20,38]. Apart from the FISH approach, mentioned previously no chromosome barcode for the entire human genome has been presented up to now. However, there are three such approaches published for the mouse genome [28–32].

One more technique has been developed to avoid the missing of substantial portions of inter- and intrachromosomal aberrations in human. It is a high-resolution multicolor-banding (MCB) technique based on three to five different fluorochromes. MCB was first described for example of chromosome 5 in 1999 [30], allowing the differentiation of chromosome region-specific areas at the band and sub-band level at a resolution of 550 bands per haploid karyotype. It is based on changing fluorescence intensity ratios along the chromosomes, which are used to assign different pseudocolors to specific chromosomal regions, i.e., the pseudocolors are DNA- and band-specific [30,34,36]. The MCB technique provides moreover the possibility to analyze chromosomes irrespective of their condensation. As the number of pseudocoded bands per chromosome can freely be assigned using the Mcm software (MetaSystems) a resolution even higher than that of GTG banding of the corresponding chromosome can be achieved, e.g., up to 10 MCB bands for chromosome 22, equals 800 bands per total haploid karyotype [30].

This is a unique possibility provided only by the MCB technique, to change the resolution simply by application of a software, without additional sophisticated chromosome preparations and repetition of a staining technique. Meanwhile, a complete set of approximately 140 region-specific microdissection libraries covering the entire human genome has been created (Figure 4) [24,25]. Moreover, YAC/BAC-based MCB-sets for the chromosomes 2, 13 and 22 have been established in parallel, which, in comparison to the microdissection-based ones, turned out to be of lower quality (Lichter et al., unpublished data). On the other hand, a combination of microdissection based MCB probe sets with locus or breakpoint specific probes is very promising [32].

Finally, an approach called spectral color banding (SCAN) has been described, where eight microdissection libraries have been created along chromosome 10 with the goal to obtain a banding pattern similar to the MCB-banding [34].

Applications, advantages & limitations of FISH banding methods

FISH banding methods have been applied to a different extent, each for the characterization of markers and derivative chromosomes in clinical genetics and tumor cytogenetics, for studies to clarify the intranuclear structure, for analysis of cell lines, in radiation research and in comparative cytogenetics (Table 1). It has to be stated that until now, applications of the FISH banding methods have only been reported for the human chromosome specific probe sets and not for the mouse probes sets.

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As mentioned in Table 2, the FISH banding approaches are based on different types of DNA probes. Techniques such as the chromosome barcode technique using YACs (17–22), region-specific human-hamster somatic cell hybrids (16) or nonoverlapping microdissection libraries (26) have per definition the disadvantage that unstained and thus noninformative gaps are left along the chromosome. Such gaps can cause problems, as breakpoints in the unstained gaps cannot be determined exactly (11). Conversely, especially the techniques based on locus-specific probes (such as YACs, BACS or cosmids) would theoretically provide the advantage that chromosomal breakpoints could be defined very exactly by the corresponding breakpoint-spanning or flanking clones. However, the coverage of the human genome by available nonchimeric clones seems to be too low for such a molecular cytogenetic approach (Liehr et al., unpublished data). The IPM-FISH approach (12), Rx-FISH technique (14), Rx-FISH combined with the somatic cell hybrids (15) and the MCB method (23–25) provide the advantage of leaving no noninformative gaps.

With regard to the possible resolution of the corresponding FISH banding methods, those are quite different (Table 2). IPM-FISH is an elegant approach connecting GTG banding and M-FISH (12). However, IPM-FISH does not seem to have the potential to help enhance banding resolution when applied on condensed, contracted and highly rearranged tumor chromosomes. For the latter case the orientation of smaller chromosomal fragments can hardly be determined. The chromosome barcodes technique using region-specific human-hamster somatic cell hybrids (16) or Rx-FISH (14) have the lowest resolution of about 100 bands per human haploid karyotype. This resolution is lower than that of chromosomes in (solid) tumourcytogenetic preparations. Moreover, the Rx-FISH bands have only seven different colors, which easily leads to ambiguous results. Rx-FISH combined with the somatic cell hybrid has 160 molecular landmarks corresponding a resolution of ~400, according to (22). In this approach five fluorochromes are used, which help overcome in part the problem mentioned previously for Rx-FISH, however, still only up to 33 pseudocolor combinations can be achieved for the whole karyotype. The resolution of SCAN- (26) and YAC-based chromosome barcode (17–22) is somewhere around 300–400 bands per haploid karyotype, while for MCB resolutions between 383 (23) up to 550 (24) or even 800 bands per haploid karyotype (25) have been described.

All probe sets created for FISH banding of the human karyotype are complete, apart from the YAC-based chromosome barcode and the SCAN approach (Table 2). Considering the mouse, only YAC-based approaches with a maximum resolution of about 300 bands per haploid genome (22) are existing. All completely available FISH banding methods can be used simultaneously for the corresponding genome, excluding the MCB approach (Table 2). At least eight to ten fluorochromes applicable in parallel would be necessary to use the complete human MCB probe set in one single hybridization. Thus, maximum MCB probe sets specific for three different chromosomes can be used simultaneously (2, LIEHR ET AL., UNPUBLISHED DATA). The decision as to which MCB probe set to apply has to be performed according to the results of GTG-banding and/or nMISH using WCP probes.

In conclusion, seven different FISH banding methods are available for the human and one for the mouse genome. All of them have potential for further developments. However, no high resolution banding technique with a resolution >450 bands per haploid karyotype is available, which can be used for a whole genome in one single FISH experiment up to present.
Using standard banding approaches (GTG-, Q-, R-banding), the dependence on chromosomal preparation and its quality is high. FISH techniques in general and FISH banding techniques in special have proven to be the methods of choice to analyze each possible kind of chromosomal rearrangement in detail [5,16,20,23,24,27,28,31,32,35–41,44–50,52,53,55–62]. This is in contrast to the DNA array technologies, which are mainly focussed on the detection of chromosomal imbalances and which are still not available for the whole genome [64]. However, this and other molecular genetic approaches, such as detection of single nucleotide polymorphisms (SNP) [65] or multiplex amplifiable probe hybridization (MAPH) [66,67] should be integrated in the analysis of studies designed to illuminate complex human diseases.

With optimized banding resolution and the possibility for the simultaneous hybridization of all human chromosomes, FISH banding assays could be performed routinely on clinical material. This would be reasonable especially in cases in which GTG-banding is known to be unable to resolve any possible kind of cryptic chromosomal alteration. This is a known problem in rhabdomyosarcoma, where in 50% of cases with MDS and in 40% of cases with acute leukemia no chromosomal alterations can be detected by GTG-banding cytogenetics [46]. FISH banding methods have the potential for bringing high impact of new diagnostic information as well for the analysis of clinical cases with mental retardation. Even though the use of subtelomeric probe sets [2,11,20,69–70,101] were quite straightforward in the last 5 years, by far not all unresolved clinical cases could be clarified by these approaches.

**Future applications**
For almost every one of the FISH banding methods, pilot studies have been performed using the presently available probes. Even though not completely developed to the desirable resolution the obtained results are extremely promising.

**Expert opinion**
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FISH banding methods can be successfully applied in routine diagnostics of leukemia [75] or for the detection of microdeletion and microduplication syndromes in interphase nuclei without the need of cell culture at all [76]. As demonstrated, FISH banding methods can be successfully applied in interphase cytogenetics, to study interphase architecture, as well as for chromosomal rearrangements [24,48,51, CLAUSSEN interphase cytogenetics, to study interphase architecture, as well as for chromosomal rearrangements [24,48,51]. This field is likely to expand in the future.

In 30 studies on mouse cell lines and mouse strains, the mFISH using the 22 WCP probes for the mouse simultaneously have been applied up to present [76]. Thus, apart from the FISH banding studies on human specimen, investigations on animal – especially on mouse models of human diseases – have the potential to be enhanced in the next 5 years. The Rx-FISH approaches resulting in various different fluorescence profiles along the studied chromosomes are uninformative for分析 for the human eye, even when translated into pseudocolors, for example, as done in MCB or in Rx-FISH, recently [42]. Thus, computer-aided evaluation is necessary, which highlights only potentially aberrant FISH banding patterns. With such computer-assisted evaluation, the FISH banding methods will have the potential to revolutionize the cytogenetic analysis and novel horizons will be opened for further interphase FISH banding routine applications.

Key issues

• FISH-banding methods allow the simultaneous characterization of several chromosomal subregions smaller than a chromosome arm.
• Several different FISH-banding methods for the human genome are available at present. Resolutions between 100–800 bands per haploid karyotype are available.
• Cross species color banding (Rx-FISH) and high-resolution multicolor banding (MCB) are the most promising developments in the current field.
• Cross species banding methods were successfully applied to diagnostics in preclinical, postnatal and tumor cytogenetics as well as in research of evolution- and radiation-biology, as well as for studies on the nuclear architecture.
• FISH-bandung methods will be applicable to diagnostics and in research for the analysis of metaphases and interphases under the presupposition for appropriate computer-assisted evaluation systems.

Figure 1. Inverted DAPI-banding result, corresponding to GTG-banding result, of a highly complex altered and rearranged karyotype. The chromosomes were prepared from bone marrow cells of a patient with leukemia. While for this special case the numerical aberrations (i.e., trisomy 3, 7, 8) could be characterized by GTG-banding, the question of which chromosomes were involved into structural rearrangements could only be answered by M-FISH. The M-FISH result is only shown for those structurally altered chromosomes – yellow numbers indicate the chromosomes involved into formation of derivatives. However, the breakpoints and orientation, at least of the smaller chromosomal fragments could only be revealed by FISH-banding methods.

Figure 2. Rx-FISH analysis of a metaphase from peripheral blood of a normal male. Due to a cultural artifact a double inversion appeared in one chromosome 7 (arrowhead). For a detailed description see as well [77]. The figure was kindly provided by Dr Fengtang Yang and Dr Malcolm Ferguson-Smith, University of Cambridge, UK.

Figure 3. Results of the chromosome barcode technique of chromosome 13 applied to a leukemia case with a shortened chromosome 13. The used YACs are presented each. Notify, that at present only one up to three chromosomes can be stained simultaneously by MCB. The breakpoints are located between 13q13 and 13q14 and between 13q31 and 13q32.

Figure 4. Multicolor banding (MCB) para dichlor tower for all 24 human chromosomes as an in summary 356 band level. Two homologous chromosomes are presented each, Notify, that at present only one to three chromosomes can be stained simultaneously by MCB.

Figure 5. MCB result on a case with familial inversion in one chromosome 5. For the normal chromosome 5 (at 5) and the derivative chromosome (at 5ID) the MCB para dichlor tower as well as the fluorescent profiles along the chromosomes are depicted. The pseudocolors are not more than a computer-based translation of the profiles, which are difficult to evaluate for the human eye. The labeling scheme for chromosome 5 using region-specific overlapping restriction probes is given.
References

Papers of special note have been highlighted as:

- of considerable interest

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8. MiniFISH staining with in situ hybridization.


12. Initial work describing IPM-FISH technique.


15. Initial work describing Rx-FISH technique.


18. Initial work describing microFISH for human chromosomes.


20. Initial work describing multiplex FISH.


23. Multicolor spectral karyotyping.

24. Initial work describing co-indexed FISH probes.


27. Initial work describing Rx-FISH technique.


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Overview on DNA-array technologies.


Websites

101 Multicolor FISH (m-FISH) Literature Database
http://mti-n.mti.uni-jena.de/~huwww/MOL_ZYTO/mFISHlit.htm

Overview on all multicolor FISH techniques and applications, updated regularly.

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